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Massachusetts General Hospital

HANDBOOK OF GENERAL HOSPITAL PSYCHIATRY

Theodore A. Stern

Gregory L. Fricchione

Ned H. Cassem

Michael Jellinek

Jerrold F. Rosenbaum

EDITION 6

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Massachusetts General Hospital

Handbook of General Hospital Psychiatry

SIXTH EDITION

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Theodore A. Stern, M.D.
Endowed Professor of Psychiatry in the Field of
Psychosomatic Medicine/Consultation
Harvard Medical School;
Professor of Psychiatry, Harvard Medical School;
Psychiatrist and Chief, Psychiatric Consultation Service
Massachusetts General Hospital
Boston, Massachusetts

Gregory L. Fricchione, M.D.
Professor of Psychiatry, Harvard Medical School;
Associate Chief of Psychiatry and Director, Division of Psychiatry and Medicine
Massachusetts General Hospital
Boston, Massachusetts

Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.
Professor of Psychiatry, Harvard Medical School;
Psychiatrist
Massachusetts General Hospital
Boston, Massachusetts

Michael S. Jellinek, M.D.
Professor of Psychiatry, Harvard Medical School;
President, Newton Wellesley Hospital
Newton Lower Falls, Massachusetts;
Chief, Child Psychiatry
Massachusetts General Hospital
Boston, Massachusetts

Jerrold F. Rosenbaum, M.D.
Stanley Cobb Professor of Psychiatry, Harvard Medical School;
Psychiatrist-in-Chief
Massachusetts General Hospital
Boston, Massachusetts

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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To our patients, our students, our colleagues,
and our mentors . . .

Contributing Authors

Annah N. Abrams, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Associate Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Menekse Alpay, M.D.
Instructor in Psychiatry, Harvard Medical School; Clinical Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Jonathan E. Alpert, M.D., Ph.D.
Joyce R. Tedlow Associate Professor of Psychiatry, Harvard Medical School; Associate Chief of Psychiatry for Clinical Services, Associate Director, Depression Clinical and Research Program, Massachusetts General Hospital, Boston, Massachusetts

BJ Beck, M.S.N., M.D.
Assistant Clinical Professor, Harvard Medical School; Psychiatrist, Robert B. Andrews Unit, Massachusetts General Hospital, Boston, Massachusetts; Vice President for Medical Affairs, Beacon Health Strategies, Woburn, Massachusetts

Anne E. Becker, M.D., Ph.D., Sc.M.
Associate Professor of Social Medicine, Department of Global Health and Social Medicine; Associate Professor of Psychiatry, Harvard Medical School; Vice Chair, Department of Global Health and Social Medicine, Harvard Medical School; Director, Eating Disorders Clinical and Research Program, Massachusetts General Hospital, Boston, Massachusetts

Eugene V. Beresin, M.A., M.D.
Professor of Psychiatry, Harvard Medical School; Director of Child and Adolescent Psychiatry Residency Training, Massachusetts General Hospital/McLean Hospital; Co-Director, Massachusetts General Hospital Center for Mental Health and Media; Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Mark A. Blais, Psy.D.
Associate Professor of Psychology in Psychiatry, Harvard Medical School; Associate Chief of Psychology, Massachusetts General Hospital, Boston, Massachusetts

Ilana M. Braun, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Director of Cancer-Related Fatigue Clinic, Massachusetts General Hospital, Boston Massachusetts

Rebecca W. Brendel, M.D., J.D.
Assistant Professor of Psychiatry, Harvard Medical School; Assistant Director for Forensic Psychiatry Fellowship Program, Massachusetts General Hospital, Boston, Massachusetts

Megan Moore Brennan, M.D.
Instructor in Psychiatry, Harvard Medical School; Clinical Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

George Bush, M.D., M.M.Sc.
Associate Professor of Psychiatry, Harvard Medical School; Director of Neuroimaging Research, Benson-Henry Institute for Mind-Body Medicine at Massachusetts General Hospital; Assistant Director of Psychiatric Neuroimaging Research, Massachusetts General Hospital, Boston, Massachusetts

Jason P. Caplan, M.D.
Chief of Psychiatry, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; Vice-Chair of Psychiatry, Creighton University School of Medicine, Omaha, Nebraska

Paolo Cassano, M.D., Ph.D.
Instructor in Psychiatry, Harvard Medical School; Clinical Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.
Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

T. Atilla Ceranoglu, M.D.
Instructor in Psychiatry, Harvard Medical School; Clinical Assistant in Psychiatry, Massachusetts General Hospital; Child and Adolescent Psychiatry, Massachusetts General Hospital, Shriners Hospitals for Children, Boston, Massachusetts

Lee S. Cohen, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Director, Perinatal and Reproductive Psychiatry Clinical Research Program, Massachusetts General Hospital, Boston, Massachusetts

M. Cornelia Cremens, M.D., M.P.H.
Assistant Professor of Psychiatry, Harvard Medical School; Geriatric Psychiatrist, Massachusetts General Hospital Senior Health Practice, Geriatric Psychopharmacology, Massachusetts General Hospital, Boston, Massachusetts

Cristina Cusin, M.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Resident in Psychiatry, Massachusetts General Hospital/ McLean Hospital, Boston, Massachusetts

Abigail L. Donovan, M.D.
Instructor in Psychiatry, Harvard Medical School; Assistant Psychiatrist and Associate Director, Acute Psychiatry Service, Massachusetts General Hospital, Boston, Massachusetts

Daniel H. Ebert, M.D., Ph.D.
Instructor in Neurobiology, Harvard Medical School; Clinical Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Lucy A. Epstein, M.D.
Assistant Professor of Clinical Psychiatry, Columbia University, New York, New York

William E. Falk, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Director, Outpatient Geriatric Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Maurizio Fava, M.D.
Professor of Psychiatry, Harvard Medical School; Executive Vice-Chair Department of Psychiatry and Director of the Depression Clinical and Research Program, Massachusetts General Hospital, Boston, Massachusetts

Carlos Fernandez-Robles, M.D.
Instructor in Psychiatry, Harvard Medical School; Attending Psychiatrist, Psychiatry Oncology Service, Psychiatry Consult Service, and Somatic Therapies Service, Massachusetts General Hospital, Boston, Massachusetts

Christine T. Finn, M.D.
Assistant Professor of Psychiatry, Dartmouth Medical School; Director of Emergency Services, Dartmouth Medical School; Assistant Clinical Geneticist, Harvard-Partners Center for Genetics and Genomics, Massachusetts General Hospital, Boston, Massachusetts

Marlene P. Freeman, M.D.
Lecturer in Psychiatry, Harvard Medical School; Psychiatrist, Perinatal and Reproductive Psychiatry, Clinical Research Program, Massachusetts General Hospital, Boston, Massachusetts

Oliver Freudenreich, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Director, First Episode and Early Psychosis Program, Massachusetts General Hospital, Boston, Massachusetts

Gregory L. Fricchione, M.D.
Professor of Psychiatry, Harvard Medical School; Associate Chief of Psychiatry and Director, Division of Psychiatry and Medicine, Massachusetts General Hospital, Boston, Massachusetts

David R. Gastfriend, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Donald C. Goff, M.D.
Professor of Psychiatry, Harvard Medical School; Director, Schizophrenia Program, Massachusetts General Hospital, Boston, Massachusetts

Christopher Gordon, M.D.
Assistant Clinical Professor of Psychiatry, Harvard Medical School; Assistant Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts; Medical Director and Vice President, Clinical Services, Advocates, Inc., Framingham, Massachusetts

Donna B. Greenberg, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Program Director, Psychiatric Oncology, Director, Medical Student Education, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Anne F. Gross, M.D.
Clinical Fellow, Department of Psychiatry, Harvard Medical School; Resident, Department of Psychiatry, Massachusetts General Hospital/McLean Hospital, Boston, Massachusetts

James E. Groves, M.D.
Associate Clinical Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

†Thomas P. Hackett, M.D.
Former Eben S. Draper Professor of Psychiatry, Harvard Medical School; Chief of Psychiatry, Massachusetts General Hospital (1976–1988), Boston, Massachusetts

Stephan Heckers, M.D.
James G. Blakemore Professor in Psychiatry, Chairman, Department of Psychiatry, Vanderbilt University; Psychiatrist-in-Chief, Vanderbilt Psychiatric Hospital, Nashville, Tennessee

David C. Henderson, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Director, Chester M. Pierce, MD Division of Global Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Jeff C. Huffman, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Medical Director, Inpatient Psychiatric Service, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Dan V. Iosifescu, M.D., M.Sc.
Associate Professor of Psychiatry, Harvard Medical School; Director of Translational Neuroscience, Depression Clinical and Research Program and Site Director, Bipolar Trials Network, Massachusetts General Hospital, Boston, Massachusetts

†Deceased.

Esther Jacobowitz Israel, M.D.
Assistant Professor of Pediatrics, Harvard Medical School; Associate Chief, Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital, Boston, Massachusetts

James L. Januzzi, Jr., M.D.
Associate Professor of Medicine, Harvard Medical School; Director, Cardiac Intensive Care Unit and Cardiology Division, Massachusetts General Hospital, Boston, Massachusetts

Michael S. Jellinek, M.D.
Professor of Psychiatry, Harvard Medical School; President, Newton Wellesley Hospital, Newton Lower Falls, Massachusetts; Chief, Child Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Nicholas Kontos, M.D.
Instructor in Psychiatry, Harvard Medical School; Director of Transplantation Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Karsten Kueppenbender, M.D.
Instructor in Psychiatry, Harvard Medical School; Assistant Psychiatrist, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Brian P. Kurtz, M.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Fellow in Child and Adolescent Psychiatry, Massachusetts General Hospital/McLean Hospital, Boston, Massachusetts

Isabel T. Lagomasino, M.D., M.S.H.S.
Assistant Professor of Psychiatry and Behavioral Sciences, University of Southern California, Keck School of Medicine; Director, Adult Psychiatry Residency Training Program, LAC + USC Medical Center, Los Angeles, California

Boris A. Lorberg, M.D.
Instructor in Psychiatry, Harvard Medical School; Clinical Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Bruce J. Masek, Ph.D.
Associate Professor of Psychology (Psychiatry), Harvard Medical School; Clinical Director, Child and Adolescent Outpatient Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Guy Maytal, M.D.
Instructor in Psychiatry, Harvard Medical School; Director, Urgent Care Psychiatry Service, Associate Director, Division of Outpatient Psychiatry,Palliative Care Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

†Edward Messner, M.D.
Associate Clinical Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

David Mischoulon, M.D., Ph.D.
Associate Professor of Psychiatry, Harvard Medical School; Associate Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Anna C. Muriel, M.D., M.P.H.
Instructor in Psychiatry, Harvard Medical School; Clinical Assistant in Psychiatry, Dana Farber Cancer Center, Boston, Massachusetts

George B. Murray, B.S., Ph.L., M.S., M.Sc., M.D., S.J.
Associate Professor of Psychiatry, Harvard Medical School; Senior Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Shamim H. Nejad, M.D.
Instructor in Psychiatry, Harvard Medical School; Director, Adult Burns and Trauma Surgery Psychiatry Consultation, Division of Psychiatry and Medicine, Massachusetts General Hospital, Boston, Massachusetts

Dana Diem Nguyen, Ph.D.
Research Specialist/Director of Operations, Potkin Research, University of California, Irvine, California

Ruta Nonacs, M.D., Ph.D.
Instructor in Psychiatry, Harvard Medical School; Assistant Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Dennis K. Norman, Ed.D.
Associate Professor of Psychology, Harvard Medical School; Chief of Psychology, Massachusetts General Hospital, Boston, Massachusetts

Sheila M. O'Keefe, Ed.D.
Instructor in Psychiatry, Harvard Medical School; Director of Psychology Training, Massachusetts General Hospital, Boston, Massachusetts

Michael W. Otto, Ph.D.
Professor of Psychology; Director, Center for Anxiety and Related Disorders, Boston University, Boston, Massachusetts

Brian A. Palmer, M.D., M.P.H.
Instructor in Psychiatry, Harvard Medical School; Staff Psychiatrist, McLean Hospital, Belmont, Massachusetts

George I. Papakostas, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Director, Treatment-Resistant Depression Studies, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Jennifer M. Park, M.D.
Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts; Walter Reed Army Medical Center, Washington, DC

Lawrence Park, M.A., M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Roy H. Perlis, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Director, Pharmacogenomics Research, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

†Deceased.

Margot Phillips, M.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Resident in Psychiatry at Massachusetts General Hospital/ McLean Adult Psychiatry Residency Training Program, Boston, Massachusetts

William F. Pirl, M.D., M.P.H.
Assistant Professor of Psychiatry, Harvard Medical School; Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Mark H. Pollack, M.D.
Professor of Psychiatry, Harvard Medical School; Director, Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital, Boston, Massachusetts

Laura M. Prager, M.D.
Assistant Professor of Psychiatry (Child Psychiatry), Harvard Medical School; Psychiatrist, Department of Child Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Jefferson B. Prince, M.D.
Instructor in Psychiatry, Harvard Medical School; Staff, Child Psychiatry, Massachusetts General Hospital, Boston, Massachusetts; Director of Child Psychiatry, North Shore Medical Center, Salem, Massachusetts

John Querques, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Associate Director, Psychosomatic Medicine-Consultation Psychiatry Fellowship Program, Massachusetts General Hospital, Boston, Massachusetts

Davin K. Quinn, M.D.
Medical Director, Psychiatric Consultation Service, University of New Mexico Hospital, Albuquerque, New Mexico

Terry Rabinowitz, M.D., D.D.S.
Professor of Psychiatry and of Family Medicine, University of Vermont College of Medicine; Medical Director, Division of Consultation Psychiatry and Psychosomatic Medicine and Medical Director, Telemedicine, Fletcher Allen Health Care, Burlington, Vermont

Paula K. Rauch, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Chief, Child Psychiatry Consultation Service to Pediatrics and Director, Marjorie E. Korff Parenting at a Challenging Time, Massachusetts General Hospital, Boston, Massachusetts

Scott L. Rauch, M.D.
Professor of Psychiatry, Harvard Medical School; Chair, Partners Psychiatry and Mental Health; President and Psychiatrist-in-Chief, McLean Hospital, Belmont, Massachusetts

John A. Renner, Jr., M.D.
Associate Professor of Psychiatry, Boston University School of Medicine; Consultant, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Joshua L. Roffman, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Jerrold F. Rosenbaum, M.D.
Stanley Cobb Professor of Psychiatry, Harvard Medical School; Chief of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Julie D. Ross, M.D., Ph.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Addictions Chief Resident, Massachusetts General Hospital/ McLean Hospital, Boston, Massachusetts

Kristin S. Russell, M.D.
Clinical Instructor in Psychiatry, Harvard Medical School; Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Kathy M. Sanders, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Director, Adult Psychiatric Resident Training, Massachusetts General Hospital/McLean Hospital, Boston, Massachusetts

Lisa Scharff, Ph.D.
Walden University School of Psychology, College of Social and Behavioral Sciences; Children's Hospital Boston, Departments of Anesthesiology and Psychiatry, Boston, Massachusetts

Steven C. Schlozman, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Co-Director, Medical Student Education in Psychiatry, Harvard Medical School; Associate Director, Child and Adolescent Psychiatry Residency, Massachusetts General Hospital/McLean Program in Child Psychiatry; Consultant, Pediatric Transplant Program, Massachusetts General Hospital; Staff Child Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Ronald Schouten, M.D., J.D.
Associate Professor of Psychiatry, Harvard Medical School; Director, Law and Psychiatry Service, Massachusetts General Hospital, Boston, Massachusetts

Linda C. Shafer, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Benjamin C. Silverman, M.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Fellow in Medical Ethics, Division of Medical Ethics, Harvard Medical School, Resident, Massachusetts General Hospital/ McLean Hospital Adult Psychiatry; Residency Program, Boston, Massachusetts

Patrick Smallwood, M.D.
Assistant Professor of Psychiatry, University of Massachusetts Medical School; Medical Director, Psychosomatic Medicine and Emergency Mental Health, University of Massachusetts Medical Center, Worcester, Massachusetts

Felicia A. Smith, M.D.
Assistant Professor of Psychiatry, Harvard Medical School; Director, Acute Psychiatry Service, Massachusetts General Hospital, Boston, Massachusetts

Jordan W. Smoller, M.D., Sc.D.
Associate Professor of Psychiatry, Harvard Medical School; Director, Psychiatric Genetics Program in Mood and Anxiety Disorders, and Assistant Vice Chair, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Robert M. Stern, M.D.
Director, Behavioral Health Services and Chair, Department of Psychiatry, Emerson Hospital, Concord, Massachusetts

Theodore A. Stern, M.D.
Endowed Professor of Psychiatry in the Field of Psychosomatic Medicine/Consultation, Harvard Medical School; Professor of Psychiatry, Harvard Medical School; Psychiatrist and Chief, Psychiatric Consultation Service, Massachusetts General Hospital, Boston, Massachusetts

Jonathan R. Stevens, M.D., M.P.H.
Instructor in Psychiatry, Harvard Medical School, Clinical Assistant in Psychiatry, Massachusetts General Hospital, Boston, Massachusetts; Child Psychiatrist, North Shore Medical Center, Salem, Massachusetts

Thomas D. Stewart, M.D.
Associate Clinical Professor of Psychiatry, Yale University School of Medicine; Consultant Psychiatrist, Yale New Haven Hospital, New Haven, Connecticut

Frederick J. Stoddard, Jr., M.D.
Associate Clinical Professor of Psychiatry, Harvard Medical School; Chief of Psychiatry, Shriners Burns Hospital; Senior Attending Psychiatrist, Massachusetts General Hospital Burn Service, Boston, Massachusetts

Joan M. Stoler, M.D.
Assistant Professor of Pediatrics, Harvard Medical School; Assistant Pediatrician, Medical Geneticist, Massachusetts General Hospital, Boston, Massachusetts

Paul Summergrad, M.D.
Dr. Francis S. Arkin Professor and Chairman, Department of Psychiatry; Professor of Medicine, Tufts University School of Medicine; Psychiatrist-in-Chief, Tufts Medical Center; Chairman, Tufts Medical Center Physicians Organization, Boston, Massachusetts

Owen S. Surman, M.D.
Associate Professor of Psychiatry, Harvard Medical School; Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Jennifer J. Thomas, Ph.D.
Clinical and Research Fellow, Harvard Medical School; Massachusetts General Hospital/McLean Hospital, Boston, Massachusetts

Adrienne O. van Nieuwenhuizen, B.A.
Research Coordinator, Depression Clinical and Research Program, Massachusetts General Hospital, Boston Massachusetts

Adele C. Viguera, M.D., M.P.H.
Assistant Professor of Psychiatry, Harvard Medical School; Associate Director, Perinatal and Reproductive Psychiatric Program, Massachusetts General Hospital, Boston, Massachusetts; Staff Psychiatrist; Cleveland Clinic Neurological Institute, Cleveland, Ohio

Betty Wang, M.D.
Instructor in Psychiatry, Harvard Medical School; Assistant Psychiatrist, Massachusetts General Hospital, Boston, Massachusetts

Marlynn Wei, M.D., J.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Adult Psychiatry, Resident at Massachusetts General Hospital/McLean Hospital, Boston, Massachusetts

Avery D. Weisman, M.D.
Professor Emeritus of Psychiatry, Harvard Medical School; Senior Psychiatrist (Retired), Massachusetts General Hospital, Boston, Massachusetts

Anthony P. Weiss, M.D., M.B.A.
Assistant Professor of Psychiatry, Harvard Medical School; Director of Quality Management, Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts

Charles A. Welch, M.D.
Instructor in Psychiatry, Harvard Medical School; Psychiatrist, Director, Somatic Therapies Service, Massachusetts General Hospital, Boston, Massachusetts

Ilse R. Wiechers, M.D., M.P.P.
Clinical Fellow in Psychiatry, Harvard Medical School; Chief Resident, Acute Psychiatry Service, Massachusetts General Hospital, Boston Massachusetts

Marketa M. Wills, M.D.
Clinical Fellow in Psychiatry, Harvard Medical School; Psychiatry Resident, Massachusetts General Hospital, Boston, Massachusetts

Curtis W. Wittmann, M.D.
Instructor in Psychiatry, Harvard Medical School; Attending Psychiatrist, Acute Psychiatry Service, Staff Psychiatrist, Bipolar Clinical Research Program, Massachusetts General Hospital, Boston, Massachusetts

Jonathan L. Worth, M.D.
Instructor in Psychiatry, Harvard Medical School; Urgent Care Psychiatry Clinic, Massachusetts General Hospital, Boston, Massachusetts

Daniel J. Zimmerman, M.D.
Clinical Instructor of Psychiatry, New York University School of Medicine; Inpatient Attending Psychiatrist, Bellevue Hospital Center, New York, New York

Preface

This sixth edition, revised and substantially expanded, was put together by a stalwart group of general hospital psychiatrists. It was designed to help busy practitioners care for patients on medical and surgical floors and in outpatient practices filled by co-morbid medical and psychiatric illness. The chapters, which cover specific illnesses and care settings, were crafted for readability. Moreover, clinical vignettes strategically placed throughout the book were meant to act as a nidus upon which clinical pearls would grow.

Consultation psychiatry, recently minted as a new subspecialty called *psychosomatic medicine*, involves the rapid recognition, evaluation, and treatment of psychiatric problems in the medical setting. Practitioners of psychosomatic medicine must also manage psychiatric reactions to medical illness, psychiatric complications of medical illness and its treatment, and psychiatric illness in those who suffer from medical or surgical illness. Because problems related to the affective, behavioral, and cognitive (the "ABCs") realms of dementia, depression, anxiety, substance abuse, disruptive personalities, and critical illness are faced on a daily basis, emphasis has been placed on successful strategies for their management by the consultant and by the physician of record.

Eight new chapters were added to this edition, and previously written chapters were revised and updated. Additions include discussions of the doctor–patient relationship, the psychiatric interview, sexual disorders and sexual dysfunction, emergency consultations, caring for children when a parent is ill, the rigors of psychiatric practice, quality assurance and quality improvement, and psychiatric research in the general hospital.

This book would not have been possible were it not for the steady hands of our acquisitions editor at Elsevier, Adrianne Brigido, and senior project manager, Cheryl Abbott. At the Massachusetts General Hospital, Judy Byford and Elena Muenzen helped shepherd us through thousands of emails, voice mails, FAXes, and photocopies associated with 54 chapters and scores of authors.

On behalf of the patients who suffer, we hope this edition improves the detection and treatment of psychiatric problems and brings much needed relief.

T.A.S.
G.L.F.
N.H.C.
M.S.J.
J.F.R.

1 Beginnings: Psychosomatic Medicine and Consultation Psychiatry in the General Hospital

Thomas P. Hackett, M.D.
Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.
Theodore A. Stern, M.D.
George B. Murray, B.S., Ph.L., M.S., M.Sc., M.D., S.J.
Gregory L. Fricchione, M.D.
Nicholas Kontos, M.D.

PSYCHOSOMATIC MEDICINE

A keen interest in the relationship between the psyche and the soma has been maintained in medicine since early times, and certain ancient physicians (such as Hippocrates) have been eloquent on the subject. A search for the precise origins of *psychosomatic medicine* is, however, a difficult undertaking unless one chooses to focus on the first use of the term itself. Johann Heinroth appears to have coined the term *psychosomatic* in reference to certain causes of insomnia in 1818.[1] The word *medicine* was added to *psychosomatic* first by the psychoanalyst Felix Deutsch in the early 1920s.[2] Deutsch later emigrated to the United States with his wife Helene, and both worked at Massachusetts General Hospital (MGH) for a time in the 1930s and 1940s.

Three streams of thought flowed into the area of psychosomatic medicine, providing fertile ground for the growth of general hospital and consultation psychiatry.[3,4] The psychophysiologic school, perhaps represented by the Harvard physiologist Walter B. Cannon, emphasized the effects of stress on the body.[5] The psychoanalytic school, best personified by the psychoanalyst Franz Alexander, focused on the effects that psychodynamic conflicts had on the body.[6] The organic synthesis point of view, ambitiously pursued by Helen Flanders Dunbar, tried with limited success to unify the physiologic and psychoanalytic approaches.[7]

HISTORY

The history of general hospital psychiatry in the United States in general,[8] and consultation–liaison (C-L) psychiatry in particular,[9] has been extensively reviewed elsewhere. For those interested in a more detailed account of both historic trends and conceptual issues of C-L psychiatry, the writings of Lipowski[10–15] are highly recommended.

In years gone by, controversy surrounded the use of the term *liaison* in C-L psychiatry. We believed that using the term *liaison* was confusing and unnecessary. It was confusing because no other service in the practice of medicine employed the term for its consultation activities. In addition, the activity it referred to—to teach nonpsychiatrists psychiatric and interpersonal skills—is done as a matter of course during the routine consultation. The term *liaison*, although still used, has to some extent fallen out of fashion.

In March 2003, the American Board of Medical Specialties unanimously approved the American Board of Psychiatry and Neurology's (ABPN's) issuance of subspecialty certification in psychosomatic medicine. The first certifying examinations were administered in 2005. As of 2009, the completion of an American Board of Medical Specialties–certified fellowship in psychosomatic medicine became mandatory for all who wish to sit for that examination. The achievement of subspecialty status for psychosomatic medicine is the product of nearly 75 years of clinical work by psychiatrists on medical–surgical units, an impressive accumulation of scholarly work contributing to the psychiatric care of general medical patients, and determined intellectual and organizational efforts by the Academy of Psychosomatic Medicine (APM). The latter's efforts included settling on the name *psychosomatic medicine* after *C-L psychiatry* met with resistance from the ABPN during the first application for subspecialty status in 1992.[16] *Psychosomatic medicine* was ultimately felt to best capture the field's heritage and work on mind–body relationships, though there remains controversy over the nebulous boundaries this name implies.[17]

When the history of consultation psychiatry is examined, 1975 seems to be the watershed year. Before 1975, scant attention was given to the work of psychiatrists in medicine. Consultation topics were seldom presented at the national meetings of the American Psychiatric Association. Even the American Psychosomatic Society, which has many

strong links to consultation work, rarely gave more than a nod of acknowledgment to presentations or panels discussing this aspect of psychiatry. Residency training programs on the whole were no better. In 1966, Mendel[18] surveyed training programs in the United States to determine the extent to which residents were exposed to a training experience in consultation psychiatry. He found that 75% of the 202 programs surveyed offered some training in consultation psychiatry, but most of it was informal and poorly organized. Ten years later, Schubert and McKegney[19] found only "a slight increase" in the amount of time devoted to C-L training in residency programs. Today, C-L training is mandated by the ABPN as part of general adult psychiatry training.

Several factors account for the growth of C-L psychiatry in the last quarter of the 20th century. One was the leadership of Dr. James Eaton, former director of the Psychiatric Education Branch of the National Institute of Mental Health (NIMH). Eaton provided the support and encouragement that enabled the creation of C-L programs throughout the United States. Another reason for this growth was the burgeoning interest in the primary care specialties, which required skills in psychiatric diagnosis and treatment. Finally, parallel yet related threats to the viability of the psychiatric profession from third-party payers and nonphysician providers were an incentive to (re-)medicalize the field. Although creation of the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (DSM-III), and increased pharmacotherapy are the two most obvious upshots of this trend,[20,21] an elevated profile for C-L psychiatry also emerged as uniquely tailored to the psychiatrist's skill set. For these reasons, and because of expanding knowledge in neuropsychiatry, consultation work has enjoyed a renaissance.

The origins of organized interest in the mental life of patients at the MGH dates back to 1873, when James Jackson Putnam, a young Harvard neurologist, returned from his grand tour of German departments of medicine to practice his specialty. He was awarded a small office under the arch of one of the famous twin flying staircases of the Bulfinch building. The office was the size of a cupboard and was designed to house electrical equipment. Putnam was given the title of "electrician." One of his duties was to ensure the proper function of various galvanic and faradic devices then used to treat nervous and muscular disorders. It is no coincidence that his office came to be called the "cloaca maxima" by Professor of Medicine George Shattuck. This designation stemmed from the fact that patients whose maladies defied diagnosis and treatment—in short, the "crocks"—were referred to young Putnam. With such a beginning, it is not difficult for today's consultation psychiatrist to relate to Putnam's experience and mission. Putnam eventually became a professor of neuropathology and practiced both neurology and psychiatry, treating medical and surgical patients who developed mental disorders. Putnam's distinguished career, interwoven with the acceptance of Freudian psychology in the United States, is chronicled elsewhere.[22]

In the late 1920s, Dr. Howard Means, chief of medicine, appointed Boston psychiatrist William Herman to study patients who developed mental disturbances in conjunction with endocrine disorders. Herman's studies are hardly remembered today, although he was honored by having a conference room at the MGH named after him.

In 1934, a department of psychiatry took shape when Stanley Cobb was given the Bullard Chair of Neuropathology and granted sufficient money by the Rockefeller Foundation to establish a ward for the study of psychosomatic conditions. Under Cobb's tutelage, the department expanded and became known for its eclecticism and for its interest in the mind–brain relationship. A number of European emigrants fled Nazi tyranny and were welcomed to the department by Cobb. Felix and Helene Deutsch, Edward and Grete Bibring, and Hans Sachs were early arrivals from the continent. Erich Lindemann came in the mid-1930s and worked with Cobb on a series of projects, the most notable being his study of grief, which came as a result of his work with victims of the 1942 Coconut Grove fire.

When Lindemann became chief of the Psychiatric Service in 1954, the Consultation Service had not yet been established. Customarily, the resident assigned to night call in the emergency department saw all medical and surgical patients in need of psychiatric evaluation. This was regarded as an onerous task, and such calls were often set aside until after supper in the hope that the disturbance might quiet in the intervening hours. Notes in the chart were terse and often impractical. Seldom was there any follow-up. As a result, animosity toward psychiatry grew. To remedy this, Lindemann officially established the Psychiatric Consultation Service under the leadership of Avery Weisman in 1956. Weisman's resident, Thomas Hackett, divided his time between doing consultations and learning outpatient psychotherapy. During the first year of the consultation service, 130 consultations were performed. In 1958, the number of consultations increased to 370, and an active research program was organized that later became one of the cornerstones of the overall operation.

By 1960, a rotation through the Consultation Service had become a mandatory part of the MGH residency in psychiatry. Second-year residents were each assigned two wards. Each resident spent 20 to 30 hours a week on the Consultation Service for 6 months. Between 1956 and 1960, the service attracted the interest of fellowship students, who contributed postgraduate work on psychosomatic topics. Medical students also began to choose the Consultation Service as part of their elective in psychiatry during this period. From our work with these fellows and medical students, collaborative research studies were initiated with other services. Examples of these early studies are the surgical treatment of intractable pain,[23,24] the compliance of duodenal ulcer patients with their medical regimen,[25] post-amputation depression in the elderly patient,[15] emotional maladaptation in the surgical patient,[26–30] and the psychological aspects of acute myocardial infarction.[31,32]

By 1970, Hackett, then chief of the Consultation Service, had one full-time (postgraduate year [PGY]-IV) chief resident and six half-time (PGY-III) residents to see consultations from the approximately 400 house beds. A private Psychiatric Consultation Service was begun, to systematize consultations for the 600 private beds of the hospital. A Somatic Therapies Service began and offered electroconvulsive therapy to treat refractory conditions. Three fellows and a full-time faculty member were added to the roster in 1976. Edwin (Ned) Cassem became chief of the

Consultation Service, and George Murray was appointed director of a new fellowship program in psychosomatic medicine and consultation psychiatry. In 1995, Theodore Stern was named chief of the Avery Weisman Psychiatric Consultation Service. Now both fellows and residents take consultations in rotation from throughout the hospital. Our Child Psychiatry Division, composed of residents, fellows, and attending physicians, provides full consultation to the 40 beds of the MGH Hospital for Children.

In July 2002, Gregory Fricchione was appointed director of the new Division of Psychiatry and Medicine, with a mission to integrate the various inpatient and outpatient medical–psychiatry services at the MGH and its affiliates while maintaining the diverse characteristics and strengths of each unit. The division includes the Avery D. Weisman Psychiatry Consultation Service, the MGH Cancer Center, the Psychosocial Oncology Disease Center, the Transplant Consultation Service, the Trauma and Burns Psychiatry Service, the Women's Consultation Service, the Cardiovascular Health Center Service, the Behavioral Medicine Service, and the Spaulding Rehabilitation Hospital's Behavioral and Mental Health Service. Psychiatrists from this division also attend in the human immunodeficiency virus (HIV) outpatient unit and the gastroenterology clinic.

PATIENT CARE, TEACHING, AND RESEARCH

The three functions provided by any consultation service are patient care, teaching, and research.

Patient Care

At the MGH, between 10% and 13% of all admitted patients are followed by a psychiatrist; roughly 3500 initial consultations are performed each year. The problems discovered reflect the gamut of conditions listed in the DSM-IV[33]; however, the most common reasons for consultation are related to depression, delirium, anxiety, substance abuse, character pathology, dementia, somatoform disorders or medically unexplained symptoms, and the evaluation of capacity.

Patients are seen in consultation only at the request of another physician, who must write a specific order for the consultation. When performing a consultation, the psychiatrist, like any other physician, is expected to provide diagnosis and treatment. This includes defining the reason for the consultation; reading the chart; gathering information from nurses and family members when indicated; interviewing the patient; performing the appropriate physical and neurologic examinations; writing a clear clinical impression and treatment plan; ordering or suggesting laboratory tests, procedures, and medications; speaking with the referring physician when indicated; and making follow-up visits until the patient's problems are resolved, the patient is discharged, or the patient dies.

Interviewing style, individual to begin with, is further challenged and refined in the consultation arena, where the psychiatrist is presented with a patient who typically did not ask to be seen and who is often put off by the very idea that a psychiatrist has been called. In addition, the hospital room setting and the threat of acute illness might cause the patient to be either more or less forthcoming than under usual circumstances. The stigma of mental illness and the fear of any illness are universal; they are part of every physician's territory, and each psychiatrist learns to deal with them in a unique way. Residents learn to coax cooperation from such patients by trial and error, by self-understanding, and by observing role models rather than by observing formulas. Essential, however, are interest in the patient's medical situation and an approach that is comparable to that used by a rigorous and caring physician in any specialty. Each consultation can thus be viewed as an opportunity to provide care, to de-stigmatize mental illness, and to de-stigmatize psychiatry by personally representing it, via manner, tone, and examination, as a proper medical specialty.

Teaching

Many consultation psychiatrists believe that teaching psychiatry to medical and surgical house officers cannot be done on a formal basis. When teaching is formalized in weekly lectures or discussion groups, attendance invariably lags. More than 30 years ago, Lindemann, in an attempt to educate medical house officers about the emotional problems of their patients, enlisted the help of several psychiatric luminaries from the Boston area. A series of biweekly lectures was announced, in which Edward and Grete Bibring, Felix and Helene Deutsch, Stanley Cobb, and Carl Binger, among others, shared their knowledge and skills. In the beginning, approximately a fifth of the medical house officers attended. Attendance steadily dwindled in subsequent sessions until finally the psychiatry residents had to be required to attend so as to infuse the lecturers with enough spirit to continue. This might be alleged to illustrate disinterest or intimidation on the part of the nonpsychiatric staff, but we think that such didactics are simply too far removed (geographically and philosophically) from their day-to-day work.

We believe that teaching, to be most effective and reliable, is best done at the bedside on a case-by-case basis. Each resident is paired with an attending physician for bedside supervision, and all new patients are interviewed by our C-L attending staff. Residents teach as well. Medical students, neurology residents, and other visiting trainees are supervised by PGY-III residents, the chief resident, the fellows, and our attending staff. Twice weekly, rounds are held with Stern, the chief resident, and the rest of the service. In 90 to 120 minutes, follow-ups on current cases are presented and discussed, and new cases are presented by the consulting resident.

Before each group of residents begin their 4-month half-time rotation (in July, November, and March), they receive 25 introductory 45-minute lectures on practical topics in consultation (e.g., how to write the note, how to perform the neurologic or neuropsychological examination, the nature of psychotherapy in consultation, ruling out organic causes of psychiatric symptoms, diagnosing delirium and dementia, using psychotropic medications [e.g., psychostimulants, intravenous haloperidol] in the medically ill, assessing decisional capacity, performing hypnosis, and managing functional somatic symptoms). In concert with the orientation lecture series, we provide residents with relevant articles and with an annotated bibliography.[34] The overall curriculum we provide is quite

similar to that recommended by the APM's Task Force on Residency Training in C-L psychiatry.[35]

Fellows attend the rounds of the Fellows Consultation Service, with Murray (director emeritus) and Fricchione (director) presiding three times per week; they see patients at the bedside with senior attending staff including Cassem several times each week. Fellows have an additional 4 hours per week of didactic sessions with Murray on advanced topics of consultation psychiatry, psychosomatic medicine, and neuropsychiatry; they also have individual supervision with Fricchione and the associate fellowship director (John Querques) each week. The Fellowship Program in Consultation Psychiatry, under the leadership of Murray, celebrated its 30th anniversary in 2006; it has trained 99 fellows through June 2009. Many have gone on to direct C-L programs across the United States.

Each resident makes two formal presentations (i.e., a 45-minute review of a topic chosen by the resident, which is elaborated on by a senior discussant for 45 minutes) during the 4-month rotation. These weekly psychosomatic conferences not only produce presentations of high quality but also lead to improved speaking skills, occasional publications, and the beginning of specialized interests and expertise for the resident.[36–45]

In the past, Stern joined medical house staff for work rounds three times a week in the medical intensive care unit, and he ran "autognosis" rounds on a weekly basis from 1979 into the early 2000s.[46] At these rounds, the feelings of the medical house officers toward patients were examined so that patients could be managed more effectively. Since their inception, only two house officers have refused to attend.

Research

Research activity by the Consultation Service, besides answering important questions, builds bridges between medical specialties. When physicians from other services are involved in research planning and when there is dual authorship of published accounts, friendships are firmly bonded, and differences fade. The general hospital population provides such a cornucopia of research material that a consultation service would be lax or unresponsive not to take advantage of it. Many examples are cited in the chapters that follow.[47–56]

Small research projects are the cornerstone of larger ones. So long as generativity is held as a value, research need not be funded through federal or state agencies. Projects can be assigned as such to medical students during their month on the service. They can also be suggested to fellows for more extensive development over the course of the year. What begins as a project with results and conclusions to be presented at psychiatric grand rounds can, over a year, develop into a full-fledged publication. This, in turn, might be the starting point for a larger investigation.

A filing system should be designed to keep potential research materials readily accessible. Systems of computer-based records in consultation services have been described. Strain and associates have devised one of them, and it is now in use in a number of C-L services throughout the United States.[54,55]

Once the direction of the consultation team has been pointed toward research and publication, the results usually fall into line. One of the distressing roadblocks en route to publication is the poor writing skill of many physicians. One or two resource people who can serve as editors and teachers can be of great help. For more than 3 decades, we have held a biweekly writing seminar, in which members submit manuscripts that are reviewed by the seminar group and two senior members of our department (Dr. Stern and the late Mrs. Eleanor Hackett). All efforts seem worthwhile once the printed page is in the author's hand. When a service begins to develop a shelf of publications authored by various members of the team, a pride of accomplishment exists, and this compounds the excitement of the research and stimulates renewed academic effort.

NEW DIRECTIONS

The approval of psychosomatic medicine as a psychiatric subspecialty brings with it changes in many domains of our service. Interestingly, some of these are revivals of older patterns of service provision to various medical domains. Perhaps inevitably, subspecialization invites subsubspecialization. In decades past, particular staff members carved out sectors of the hospital as areas of interest/work (e.g., burns, surgery, medical intensive care, rehabilitation, cardiology, oncology, obstetrics, and gynecology). After a while, the pendulum swung toward a more global, general consultation service. In more recent years, the pendulum has swung back, with more formalized reentry of staff into many of these areas, as well as into some others (e.g., infectious disease, gastroenterology).

Connected with this trend, fueled by a robust literature,[57,58] and codified in the Accreditation Council for Graduate Medical Education requirements for psychosomatic medicine fellowship training is the provision of "outpatient consultation" to primary care settings. Recognizing the importance of this latter approach, we have attempted innovative approaches (e.g., telepsychiatry and urgent care availability) to be of help to our primary care colleagues and to better serve their population of patients in need of psychiatric assistance. All of these endeavors expand potential training experiences and academic opportunities and introduce new logistical challenges to the administration of consultation psychiatry and psychosomatic medicine services.

SUMMARY

From early in medical history, curious physicians have investigated the mysteries of the mind–body relationship, developing a field of study called psychosomatic medicine. The energy of this intellectual enterprise has led to the growth of general hospital psychiatry, initially aided by Rockefeller Foundation funding in 1934, as well as the development of consultation psychiatry, supported through the funding of Eaton's NIMH program in the 1970s and 1980s. A subspecialty of psychiatry called psychosomatic medicine has recently been approved, which recognizes the maturation of the field and the growth that lies ahead.

At each step of the way, the MGH Psychiatric Consultation Service has played an important role. This book, which reviews the essentials of general hospital psychiatry, is a testimony to the caring, creativity, and diligence of those who have come before us.

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Approach to Consultation Psychiatry: Assessment Strategies

2

John Querques, M.D.
Theodore A. Stern, M.D.

My emphasis to the residents is: "Now that you've learned a lot about compassion and human dignity … you must learn to be competent," adding "or else." The goals for the trainee are specialty-competence, that is, some specific things about consultation: accountability, commitment, industry, discipline; these are the components that go into the make-up of a professional.

—Ned H. Cassem, M.D.[1]

This chapter provides a practical approach to the assessment of affective, behavioral, and cognitive problems of patients in the general hospital. We first survey the landscape of consultation psychiatry and then identify six broad domains of psychiatric problems commonly encountered in the medical setting. Next, we describe the differences in clinical approach, environment, interactive style, and use of language that distinguish psychiatry in the general hospital from practice in other venues. Then we offer a step-by-step guide to the conduct of a psychiatric consultation. The chapter concludes with a review of treatment principles critical to caring for the medically ill. Throughout this chapter, we emphasize the hallmarks of competence identified by Cassem[1] more than 2 decades ago: accountability, commitment, industry, and discipline.

CATEGORIES OF PSYCHIATRIC DIFFERENTIAL DIAGNOSIS IN THE GENERAL HOSPITAL

The borderland between psychiatry and medicine in which consultation psychiatrists ply their trade can be visualized as the area shared by two intersecting circles in a Venn diagram (Figure 2–1). As depicted in the figure and consistent with the fundamental tenet of psychosomatic medicine (i.e., that mind and body are indivisible), the likelihood that either a psychiatric or a medical condition will have no impact on the other is incredibly slim. Within the broad region of bidirectional influence (the area of overlap in the Venn diagram), the problems most commonly encountered on a consultation–liaison service can be grouped into six categories (modified from Lipowski[2]; see Figure 2–1). Examples of each classification follow.

Psychiatric Presentations of Medical Conditions

An elderly man underwent neurosurgery for clipping of an aneurysm of the anterior communicating artery. A few days after surgery, he became diaphoretic, confused, and agitated and was tachycardic and hypertensive. Because of a history of alcoholism, a diagnosis of alcohol withdrawal delirium was made. He remained confused despite aggressive benzodiazepine treatment. When he later became febrile, a lumbar puncture was done and the cerebrospinal fluid (CSF) analysis was consistent with herpes simplex virus (HSV) infection. His sensorium cleared after a course of acyclovir. *In this case, infection of the central nervous system (CNS) by HSV was heralded by delirium.*

Psychiatric Complications of Medical Conditions or Treatments

Newly diagnosed with human immunodeficiency virus (HIV) infection with a high viral load, a young man without a history of psychiatric illness began treatment with efavirenz, a nonnucleoside reverse transcriptase inhibitor. Within a few days, he experienced vivid nightmares, a known side effect of efavirenz. Over the next several weeks, the nightmares resolved. He continued antiretroviral treatment, but he became increasingly despondent with a full complement of neurovegetative symptoms of major depression. *A chronic, incurable viral illness—whose treatment caused a neuropsychiatric complication—precipitated a depressive episode.*

Psychological Reactions to Medical Conditions or Treatments

A woman with a history of preeclampsia during her first pregnancy was admitted with hypertension in the 38th week of her second pregnancy. Preeclampsia was diagnosed, and she delivered a healthy baby. As she prepared for discharge, and despite her obstetrician's reassurance, she fretted that a hypertensive catastrophe was going to befall her at home. *Pathologic anxiety resulted from an acute obstetric condition.*

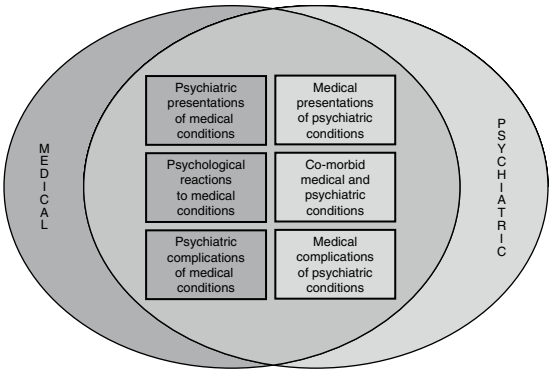

Figure 2–1. A representation of the overlap between medical and psychiatric care.

Medical Presentations of Psychiatric Conditions

A young female graduate student from another country, who for several years had habitually induced vomiting to relieve persistent abdominal pain, presented with generalized weakness and was found to have a serum potassium of 2.2 mEq/L. She had long since been diagnosed with bulimia nervosa, but the psychiatric consultant found no evidence for this disorder and instead diagnosed conversion disorder, construing her chronic abdominal pain as a converted symptom of psychological distress over leaving her family to study abroad. *Conversion disorder presented as persistent abdominal pain*.

Medical Complications of Psychiatric Conditions or Treatments

An obese man with schizophrenia treated with olanzapine (20 mg daily) gained 30 pounds in 6 months. Repeated measurements of fasting serum glucose were more than 126 mg/dL, consistent with a diagnosis of diabetes mellitus. *Treatment with an atypical antipsychotic was complicated by an endocrine condition*.

Co-Morbid Medical and Psychiatric Conditions

A middle-aged man with long-standing obsessive–compulsive disorder (OCD), effectively treated with high-dose fluoxetine, presented with cough, dyspnea, and fever. Chest radiography showed a left lower-lobe infiltrate, consistent with pneumonia. He defervesced after a few doses of intravenous (IV) antibiotics and was discharged to complete the antibiotic course at home. His OCD remained in remission. *Infectious and psychiatric conditions existed independently*.

THE ART OF PSYCHIATRIC CONSULTATION IN THE GENERAL HOSPITAL

Determining where on the vast border between psychiatry and medicine a patient's pathologic condition is located is the psychiatric consultant's fundamental task. As for any physician, his or her chief responsibility is diagnosis. The consultation–liaison psychiatrist is aided in this enterprise by appreciation of four key differences between general hospital psychiatry and practice in other venues: clinical approach, environment, style of interaction, and use of language.

Clinical Approach

A senior psychiatrist at the Massachusetts General Hospital (MGH) and director emeritus of its Psychosomatic Medicine–Consultation Psychiatry Fellowship Program, Dr. George Murray advises his students to think in three ways when consulting on patients: physiological, existential, and "dirty." Each element of this tripartite conceptualization is no more or less important than the other, and the most accurate formulation of a patient's problem will prove elusive without attention to all three.

First, psychiatrists are physicians and, as such, subscribe to the medical model: altered bodily structures and functions lead to disease; their correction through physical means leads to restoration of health. Although allegiance to this model may be impolitic in this era of biopsychosocial holism, the degree of morbidity in general hospitals is ever more acute and the technology brought to bear against it is increasingly more sophisticated.[3] Consultation psychiatrists who fail to keep pace with their medical and surgical colleagues jeopardize their usefulness to physicians and patients alike.

Alongside the physiologic frame of mind, consultation psychiatrists must think existentially; that is, they must nurture a healthy curiosity about the meaning of the illness to their patients at this particular moment in their lives and the circumstances in which their patients find themselves at particular moments in the course of an illness. What does it mean to a burn victim that he was brought by helicopter to a hospital in a neighboring state? What was he thinking during the airlift? Would he have thought differently if an ambulance had brought him to his local hospital? To be curious about such matters, the consulting psychiatrist must first *know* the details of the patient's situation, largely achieved by a careful reading of the chart. For example, ambulance (or helicopter) run sheets and emergency department notes often contain interesting and meaningful data about a patient's mental state in the aftermath of a tragic event. Armed with this information, the consultant can then *ask* the patient what the whole ordeal was like for him or her.

Consultation psychiatrists are wise to maintain a measured skepticism toward patients' and others' statements, motivations, and desires. In other words, they should consider the possibility that the patient (or another informant) is somehow distorting information to serve his or her own agenda. Providers of history can distort the truth in myriad ways, ranging from innocuous exaggeration of the truth to outright lies; their aims are equally legion: money, revenge, convenience, and cover-up of peccadilloes, infidelities, or crimes. For example, the beleaguered mother of a young woman with a borderline personality disorder embellished her daughter's suicidal comments in an effort to secure involuntary commitment for her daughter and respite for herself. By paying attention to his or her own countertransference—his or her personal reading of the limbic music[4]

emanating from the mother–daughter dyad—the psychiatric consultant called in to assess the patient's suicidality ably detected the mother's self-serving distortion and thus avoided unwitting collusion with it. This special case of distortion to remove a relative to a mental or other hospital has been termed the *Gaslight phenomenon*.[5–7] Although thinking "dirty" is merely a realization that people refract reality through the lens of their own personal experience, other health professionals—even some psychiatrists—bristle at even a consideration, let alone a suggestion, that patients and their families harbor unseemly ulterior motives. Consequently, this perspective does not make the consultation psychiatrist many friends; his thinking "dirty" may even earn him or her an unsavory reputation. However, neither an ever-widening social circle nor victory in popularity contests is the consultation–liaison psychiatrist's *raison d'être*—competent doctoring is.

Environment

The successful psychiatric consultant must be prepared to work in an atmosphere less formal, rigid, and predictable than one typically found in an office or a clinic; flexibility and adaptability are crucial. Patients are often seen in two-bedded rooms with nothing but a thin curtain providing only a semblance of privacy; roommates—as well as nurses, aides, dietary personnel, and other physicians—are frequent interlocutors. Cramped quarters are the rule, with IV poles, tray tables, and one or two chairs leaving little room for much else. When family members and other visitors are present, the physician may ask them to leave the room; alternatively, he or she may invite them to stay to "biopsy" the interpersonal dynamics among the family and friends, as was done in the case of the borderline patient described previously. The various alarms and warning signals of medical equipment (e.g., IV pumps, cardiac monitors, and ventilators) and assorted catheters and tubes traveling into and out of the patient's body add to the unique ambiance of the bedside experience that distinguishes it from the quiet comfort afforded by a private office. Perhaps off-putting at first, for the psychiatrist who, as Lewis Glickman in his book on consultation put it (as cited in Cassem[1]), loves medicine and is fascinated with medical illness, the exigencies of life and work in a modern hospital quickly become exciting and ultimately captivating.

Style of Interaction

The adaptability required by these environmental circumstances allows the psychiatric consultant to be more flexible in his or her relations with the patient. For example, psychiatric consultants should permit themselves to crouch at the bedside; lowering themselves to the recumbent patient's level can diminish apprehension and can minimize the inherent power differential between doctor and patient. Shaking hands or otherwise laying on of hands may achieve the same end. Performance of a physical examination provides an excellent opportunity to allay anxiety and dramatically distinguishes consultation work from office-based psychiatry, where any touching of a patient—let alone physical examination—is considered taboo. An offer to make the person more comfortable by adjusting the bed or getting the patient something to drink before beginning the interview goes a long way to building rapport. When the patient is unable to do even these simple things unaided, it is simply a kind, humane gesture. When the patient tends toward the cantankerous and irascible, concern for the patient's comfort may prevent the patient from expelling the consultant from the room. Finally, as a simple matter of respect, one should make every effort to leave the room as one found it (e.g., if towels and sheets are removed from a chair before sitting on it, they should be replaced upon getting up).

Use of Language

Allowance for flexibility also extends to psychiatrists' use of language; they can feel freer than they might in other practice settings to use humor, slang expressions, and perhaps even foul language. All of these varieties of verbal expression create a temporarily jarring juxtaposition between the stereotypical image of the austere, reserved physician and the present one; defenses may be briefly disabled just long enough to connect with the truth and allow connection with the patient. For example, in a technique taught by Murray, the psychiatrist raises a clenched fist in front of an angry but anger-phobic patient and asks him, "If you had one shot, where would you put it?" In this case, the sight and sound of a "healer" in boxer's pose inquiring about placement of a "shot" creates a curious, or even humorous, incongruity that disarms the patient's defenses and allows an otherwise intolerable emotion (anger) to emerge (if it is there in the first place).

A variant of this maneuver, substitution of a verbal expression of anger for the physical one, is also possible. For example, a 30-year-old man with leukemia refractory to bone-marrow transplantation was admitted with graft-versus-host disease. His mother and sister kept a near-constant vigil at his bedside. When he refused to eat and to talk to his family and the nurses, the psychiatrist was summoned. Quickly sizing up the situation, the consultant said to the young man, "It must be a pain to have your mother constantly hovering over you." The patient grinned slightly and answered in the affirmative. Use of a foul expression of the same sentiment would predictably have achieved a more robust response.

Lack of the formal arrangements of office-based psychiatric practice makes such techniques permissible in the general hospital, often to the delight of residents, who sometimes feel unnecessarily constrained in their interpersonal comportment and in whom even a little training unfortunately does much to limit their natural spontaneity.

THE PROCESS OF PSYCHIATRIC CONSULTATION IN THE GENERAL HOSPITAL

With this general overview of the art of consultation, we next outline the step-by-step approach to the actual performance of a psychiatric consultation. Table 2–1 summarizes the key points elaborated in the following text.

Speak Directly with the Referring Clinician

The consultative process begins with the receipt of the referral. With experience, the sensitive consultant begins to formulate preliminary hypotheses even at this early

TABLE 2–1 Procedural Approach to Psychiatric Consultation

Speak directly with the referring clinician.
Review the current and pertinent past records.
Review the patient's medications.
Gather collateral data.
Interview and examine the patient.
Formulate a diagnosis and management plan.
Write a note.
Speak directly with the referring clinician.
Provide periodic follow-up.

stage. For example, he or she recognizes a particular unit within the hospital or an individual physician and recollects previous consultations that originated from these sources. In addition, he or she may discern a difference in the way this consultation request was communicated compared with the form of previous requests. In a form of parallel process, this alteration in the usual routine—even if subtle and only in retrospect—often reflects something about the patient. Throughout the consultative process, these crude preliminary hypotheses thus formed are refined and ultimately either accepted or rejected. The continual revision of previous theories as additional data become available is a fundamental process in consultation–liaison psychiatry as it is in the whole of medicine.

The reason for the consultation stated in the request might differ from the real reason for the consultation. The team might accurately sense a problem with the patient but not capture it precisely. In some cases, they may be quite far afield, usually when the real reason for the consultation is difficulty in the management of a hateful patient.[8] It is up to the consultant to identify the core issue and ultimately address it in the consultation. Practically speaking, a special effort to contact the consultee is not usually required, because, in general, in the course of reading the chart or reviewing laboratory data, one encounters a member of the team and can inquire then about the consultation request.

Review the Current and Pertinent Past Records

A careful review of the current medical record is indispensable to a thorough and comprehensive evaluation of the patient. Perhaps no other element of the consultative process requires as much discipline as this one. The seasoned consultant is able to accomplish this task quite efficiently, knowing fruitful areas of the chart to mine. For example, nursing notes often contain behavioral data often lacking from other disciplines' notes; a well-written consultation provided by another service can provide a general orientation to a case, although the consultant must take care not to propagate error by failing to check primary data himself or herself. Other bountiful areas of the chart include notes written by medical students (who tend to be the most thorough of all), physical and occupational therapists (for functional data), and speech pathologists (for cognitive data). In reading the chart, the focus of the psychiatric consultant's attention varies according to the nature of the case and the reason for the consultation. In cases in which sensorium is altered, for example, careful note of changes in level of awareness, behavior, and cognition should be made, especially as they relate to changes in the medical condition and treatment.

Review the Patient's Medications

Regardless of the particulars of a case, detailed evaluation of medications, paying special attention to those recently initiated or discontinued, is always in order. For example, in the vignette presented previously, knowledge that the HIV-positive man had recently initiated treatment with efavirenz was key to accurately diagnosing the cause of his nightmares. Important medications the patient might have taken before admission, including those on which he may be physiologically dependent (e.g., benzodiazepines and narcotic analgesics), might inadvertently have been excluded from his current regimen. Patients who have been transferred among various units in the hospital may be at particular risk of such inadvertent omissions. In cases in which mental status changes resulting from withdrawal phenomena top the differential diagnosis, careful construction of a timeline of the patient's receipt of psychoactive agents is often the only way to identify the problem. In much the same way as infectious-disease specialists chart the administration of antibiotics in relation to culture results and dermatologists plot newly prescribed medications against appearance of rashes, the psychiatric consultant tabulates mental status changes, vital signs, and dosages of psychoactive medications to clarify the diagnostic picture. Such a procedure exemplifies the industry and discipline required of the competent consultant.

Gather Collateral Data

The gathering of collateral information from family, friends, and outpatient treaters is no less important in consultation work than in other psychiatric settings. For several reasons (e.g., altered mental status, denial, memory impairment, and malingering), patients' accounts of their history and current symptoms are often vague, spotty, and unreliable. Although data from other sources is therefore vital, the astute psychiatrist recognizes that their information, too, may be distorted by the same factors and by selfish interests, as already described. Consultation psychiatrists must guard against accepting any one party's version of events as gospel and must maintain an open mind in collecting a history informed from many angles.

Interview and Examine the Patient

Next follows the interview of the patient and performance of a mental status examination, in addition to relevant portions of the physical and neurologic examinations. We discussed earlier the differences between patient encounters in the general hospital and those in other venues.

A detailed assessment of cognitive function is not necessary in all patients. If there is no evidence that a patient has a cognitive problem, a simple statement to the effect that no gross cognitive problem is apparent is sufficient. However, even a slight hint that a cognitive disturbance is present should trigger performance of a more formal screen. We recommend the Folstein Mini-Mental State

Examination (MMSE)[9] for this purpose and supplement this test with others that specifically target frontal executive functions (e.g., clock drawing, Luria maneuvers, and cognitive estimations). Any abnormalities that turn up on these bedside tests should be comprehensively evaluated by formal neuropsychological testing. It is convenient if a psychologist—especially one trained specifically in neuropsychology—is affiliated with the consultation service. Conversely, if a patient is obviously inattentive, we would argue that performance of the MMSE (or similar tests) is not indicated, because one can predict a priori poor performance resulting from the subject's general inattention to the required tasks.

The consultant should at the very least review the physical examinations performed by other physicians. This does not, however, preclude doing his or her own examination of relevant systems, including the CNS, which, unless the patient is on the neurology service or is known to have a motor or a sensory problem, has likely been left unexamined. A number of physical findings can be discerned simply by observation: pupillary size (which is noteworthy with opioid withdrawal or intoxication); diaphoresis, either present (from fever or from alcohol or benzodiazepine withdrawal) or absent (associated with anticholinergic intoxication); and adventitious motor activity (e.g., tremors, tremulousness, or agitation). Vital signs are especially relevant in cases of substance withdrawal, delirium, and other causes of agitation. Primitive reflexes (e.g., snout, glabellar, and grasp), deep-tendon reflexes, extraocular movements, pupillary reaction to light, and muscle tone are among the key elements of the neurologic examination that the psychiatrist often checks.

Formulate a Diagnosis and Management Plan

Any physician's tasks are twofold: diagnosis and treatment. This dictum is no different for the psychiatrist, whether in the general hospital or elsewhere. To arrive at a diagnosis, laboratory testing comes after history and examination. By the time a psychiatric consultation is requested, most hospitalized patients have already undergone extensive laboratory testing, including comprehensive metabolic panels and complete blood cell counts; these should be reviewed. In constructing the initial parts of a management plan, the psychiatric consultant should attend to diagnostics and specifically consider each of the tests listed in Table 2–2, which we review presently. Therapeutic strategies are discussed in a later section.

Toxicology screens of both serum and urine are required any time a substance-use disorder is suspected and in cases of altered sensorium, intoxication, or withdrawal.

Well known by every student of psychiatry, syphilis, thyroid dysfunction, and deficiencies of vitamin B_{12} and folic acid are always included in an exhaustive differential diagnosis of virtually every neuropsychiatric disturbance. Although it is certainly possible that these conditions can *cause* any manner of psychiatric perturbation (e.g., dementia, depression, mania), more commonly these ailments coexist with other conditions, which together *contribute* to psychiatric disturbances. Although blood tests and treatments for these diseases are relatively easily accomplished, these tests should not be recommended reflexively in every case but only when a specific reason dictates (e.g., anemia for vitamin testing).

TABLE 2–2 Laboratory Tests in Psychiatric Consultation

- Toxicology
  - Serum
  - Urine
- Serology
  - RPR test
  - VDRL test
- TSH (thyrotropin)
- Vitamin B_{12} (cyanocobalamin)
- Folic acid (folate)
  - EEG
  - CSF analysis
- Neuroimaging
  - CT
  - MRI

CSF, Cerebrospinal fluid; *CT*, computed tomography; *EEG*, electroencephalography; *MRI*, magnetic resonance imaging; *RPR*, rapid plasma reagin; *TSH*, thyroid stimulating hormone; *VDRL*, Venereal Disease Research Laboratory.

For purposes other than evaluation of acute intracranial hemorrhage, cerebral magnetic resonance imaging (MRI) is preferred to computed tomography. MRI provides higher resolution and greater detail, particularly of subcortical structures of interest to the psychiatrist. A thorough consultation is incomplete without a reading of the actual radiology report of the study; merely reviewing the telegraphic summary in a house officer's progress note is insufficient, because important findings are often omitted. For example, an MRI scan that shows no abnormalities other than periventricular white matter changes is invariably recorded as "normal" or as showing "no acute change." Although periventricular white matter changes are not acute and their significance is arguable, they are certainly not normal and they should be documented in a careful psychiatric consultation note. They may be evidence of an insult that forms a substrate for depression or dementia and may be a predictive sign of sensitivity to usual dosages of psychotropic medications.

Electroencephalography (EEG) can be particularly helpful to document the presence of generalized slowing in patients thought by their primary physicians to have a functional problem. Such indisputable evidence of electric dysrhythmia often puts a sudden end to the primary team's skepticism. In cases of suspected complex partial seizures, depriving the patient of sleep the night before the EEG increases the likelihood that he or she will sleep during the test; against a background of slow activity in the sleeping state, any spikes or sharp waves indicating seizure activity will be more easily detected. Continuous EEG and video monitoring or ambulatory EEG monitoring may be necessary to catch aberrant electric activity. As with neuroimaging reports, the consultant psychiatrist must read the EEG report himself or herself; nonpsychiatrists commonly equate absence of "organized electrographic seizure activity" with normality, even though focal slowing may be evidence of seizure activity.

CSF analysis is often overlooked by psychiatrists and other physicians. However, it should be considered in cases

of altered mental status with fever, leukocytosis, or meningismus and when causes of beclouded consciousness are not obvious. In some cases (e.g., in the vignette of the man with HSV presented previously), some conditions initially considered causative are not, and the true culprit is identified only after a lumbar puncture is performed.

Any suspicion of a somatoform disorder (especially conversion disorder) should trigger referral for psychological testing with the Minnesota Multiphasic Personality Inventory (MMPI) or the shorter Personality Assessment Inventory. For example, MMPI results of the young female graduate student described previously may demonstrate the conversion (or psychosomatic) V pattern of marked elevations on the hypochondriasis and hysteria scales and a normal or slightly elevated result on the depression scale. These pencil-and-paper tests can also be useful in assessments of psychological contributions to pain. Projective testing (e.g., Rorschach inkblots) is more common in outpatient venues.

Write a Note

The psychiatric consultation note should be a model of clear, concise writing with careful attention to specific, practical diagnostic and therapeutic recommendations. Several reviews of this topic are available.[10,11] If the stated reason for the consultation differs from the consultee's more fundamental concern, both should be addressed in the note. If the referring physician adopts the consultant's recommendations, he or she should be able to transcribe them directly onto the order sheet or into computerized order-entry systems. "Note wars," criticism of the consultee, accusations of shoddy work, pejorative labels, and jargon should all be avoided. If the consultee chooses a diagnostic or therapeutic course equally appropriate to the consultant's suggested choice, an indication of agreement is more prudent than rigid insistence on the psychiatrist's preference. The consultant should avoid prognostication (e.g., "This patient will probably have decision-making capacity after his infection has resolved" or "This patient will likely need psychiatric hospitalization after he recovers from tricyclic antidepressant toxicity"). Such forecasts do not evince confidence in the consultant's skill if they prove inaccurate, may be invoked by the consultee even when they no longer apply, and are unnecessary if routine follow-up is provided (see later).

Speak Directly with the Referring Clinician

The consultative process is not complete without contact, either by phone or in person, with the referring physician or other member of the patient's team, especially if the diagnosis or recommended intervention warrants immediate attention.

Provide Periodic Follow-Up

The committed consultant sees the patient as often as is necessary to treat him or her competently, and the consultant holds himself or herself accountable for tracking the patient's clinical progress, following up on laboratory tests, refining earlier diagnostic impressions, and modifying diagnostic and treatment recommendations. The consultation comes to an end only when the problem for which the consultant was called resolves, any other concerns identified by the consultant are fully addressed, or the patient is discharged or dies. Rarely do any of these outcomes occur after a single visit, making repeated visits the rule and availability, even at inopportune times, crucial. However, the consultant is not obligated to continue consulting on a case when his or her recommendations are clearly being ignored.[12] In these cases, it is appropriate to sign off. Although clinical nurse specialists, nurse practitioners, physician assistants, and case managers may be available to locate psychiatric beds and secure insurance coverage for inpatient psychiatric stays for patients who require them, the psychiatric consultant should be ready and able to perform these duties.

PRINCIPLES OF PSYCHIATRIC TREATMENT IN THE GENERAL HOSPITAL

As in other practice settings, in the general hospital, psychiatric treatment proceeds along three fronts: biological, psychological, and social.

Biological Management

When prescribing psychopharmaceuticals for medically ill patients taking other medications, the consultant must be aware of pharmacokinetic profiles, drug–drug interactions, and adverse effects. These topics are considered in depth in Chapter 34.

Pharmacokinetic Profiles

Pharmacokinetics refers to a drug's absorption, distribution, metabolism, and excretion. Because an acutely medically ill patient might not be able to take medications orally, absorption is a primary concern in the general hospital setting. Often in such situations (e.g., in an intubated patient), a nasogastric tube is in place and medications can be crushed and administered through the nasogastric tube. However, if one is not in place, the psychiatric consultant is obliged to consider medications that can be given intramuscularly, intravenously, or in suppository form. In addition, orally disintegrating formulations may be available (e.g., mirtazapine, olanzapine, risperidone).

Many psychotropic medications are metabolized in the liver and excreted through the kidneys. Thus impaired hepatic and renal function can lead to increased concentrations of parent compounds and pharmacologically active metabolites. This problem is readily overcome by using lower initial doses and by performing slower titration. However, concern for metabolic alterations in medically ill patients should not justify use of homeopathic doses for indeterminate durations, because most patients ultimately tolerate and require standard regimens.

Drug–Drug Interactions

Many psychopharmaceuticals are metabolized by the cytochrome P450 isoenzyme system; many also inhibit various isoforms in this extensive family of hepatic enzymes, and the metabolism of many is, in turn, inhibited by other classes of medication, thus creating fertile ground for drug–drug interactions in patients taking several medications. This

topic is reviewed extensively in Chapter 34. Psychiatric consultants should also be aware that cigarette smoking induces the metabolism of many drugs. When patients are hospitalized and thus stop or curtail smoking, serum concentrations of these drugs (e.g., clozapine) increase, and propensity for adverse effects thus also increases.

Adverse Effects

Depending on the practice venue, the profile of adverse effects of concern to the psychiatrist varies. For example, the likelihood that tricyclic antidepressants will cause dry mouth and sedation may be of more concern in the outpatient setting than in the general hospital, where concern about the cardiac-conduction and gut-slowing effects will likely be of greater importance in patients recovering from myocardial infarction or bowel surgery. Traditional neuroleptics—often relegated to the second line in otherwise healthy patients with psychosis—may be preferable to the atypical agents in general medical settings, where patients with obesity, diabetes mellitus, and dyslipidemia may be seen for the complications of these conditions (e.g., myocardial infarction, stroke, and diabetic ketoacidosis).

TABLE 2–3 Personality Assessment and Management in the General Hospital

PERSONALITY TYPE	MAJOR TRAITS	REACTION TO ILLNESS	RECOMMENDED STRATEGIES
Dependent	Craves special attention Expects services on demand Requires constant reassurance	Perceived abandonment generates feeling of helplessness Increased anxiety prompts more demands	Express desire to provide comprehensive care Make minor concessions if possible
Obsessive	Values detail and order Becomes anxious with uncertain outcomes Well defended against fear and pain	Illness represents threat to self-control Need for certainty and control prevents questioning of staff, thus increasing anxiety	Provide ample information, using and defining medical terms Ally with patient's desire for mastery Allow patient to participate in medical decisions
Histrionic	Prematurely trusts others Uses repression, denial, and avoidance Dramatizes feelings	Illness represents threat to masculinity or femininity	Recognize patient's grace under pressure Omit details in reassuring patient
Masochistic	Plays the martyr role Seems to enjoy suffering Feels unappreciated	Illness represents deserved punishment Illness is welcomed as form of suffering Lack of recognition of martyr status risks noncompliance	Appreciate patient's suffering Recommend treatment as an additional burden that will aid others
Paranoid	Is suspicious, wary, and guarded Readily feels slighted Bickers when feeling persecuted	Illness represents an external assault Medical interventions generate suspicions and fear of harm	Inform patient completely about tests and treatments Acknowledge difficulty of illness
Narcissistic	Requests and receives help with difficulty Strives to appear smart, strong, and superior Fears dependence	Illness challenges self-esteem and superior stance Efforts to appear effectual and strong are redoubled	Recognize patient's strengths and knowledge Allow patient to participate in medical decisions Expect gaps in history, because more illness connotes weakness
Schizoid	Is aloof, uninvolved, and detached Prefers solitary occupations	Illness requires contact with caregivers Rejection risk spurs greater withdrawal	Recognize preference for isolation Minimize intrusions Assure patient of interest and concern

Adapted from Shuster JL, Stern TA: Intensive care units. In Wise MG, Rundell JR, editors: *The American Psychiatric Publishing textbook of consultation–liaison psychiatry: psychiatry in the medically ill*, ed 2, Washington, 2002, American Psychiatric Publishing, pp 753–770; Kahana RJ, Bibring GL: Personality types in medical management. In Zinberg NE, editor: *Psychiatry and medical practice in a general hospital*, New York, 1965, International Universities Press, pp 108–123; and Wool C, Geringer ES, Stern TA: The management of behavioral problems in the ICU. In Rippe JM, Irwin RS, Alpert JS et al, editors: *Intensive care medicine*, ed 2, Boston, 1991, Little, Brown, pp 1906–1916.

Psychological Management

Psychological management of the hospitalized medically ill patient begins—as does all competent treatment—with diagnosis, in this case, personality diagnosis. That is, the psychiatric consultant first appraises the patient's psychological strengths and vulnerabilities. Armed with this psychological balance sheet, the psychiatrist then uses this information therapeutically in how he or she phrases questions and comments to the patient and describes the patient to the medical and nursing staff. Several schemas have been developed to aid in such a personality assessment.[8,13,14] Groves's formulation is reviewed in Chapter 38; Table 2–3 summarizes Kahana and Bibring's approach.

The consultant must realize that the patient may find the psychiatrist the only outlet available to vent his or her feelings about treatment in the hospital. This is an appropriate function of the consultant—and, in fact, may be the tacit reason for the consultation. Relieved of his or her feelings, often hostile and at odds with the team's treatment efforts, the patient is thus better able to work with the team.

Social Management

Psychiatric consultants may be called on to help make decisions about end-of-life care (e.g., do-not-resuscitate and do-not-intubate orders), disposition to an appropriate living situation (e.g., home with services, assisted-living residence, skilled nursing facility, or nursing home), short-term disability, probate guardianship for a patient deemed clinically unable to make medical decisions for himself or herself, and involuntary psychiatric commitment. For patients who are agitated and thereby place themselves and others in harm's way, the consultant may recommend the use of various restraints (e.g., Posey vests, mitts [to prevent removing IV and other catheters], soft wrist restraints, and leather wrist and ankle restraints) and constant observation.

SUMMARY

Regardless of the practice setting, the basics of competent psychiatric care remain the diagnosis of affective, behavioral, and cognitive disturbances and their treatment by pharmacologic, psychological, and social interventions. The psychiatrist in the general hospital applies these fundamentals while remaining *accessible* to the consultee and to the patient, *adaptable* to the exigencies of the hospital environment, and *flexible* in clinical approach and interpersonal style. The consultation psychiatrist adheres to the tenets of competent doctoring: accountability, commitment, industry, and discipline.

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The Doctor–Patient Relationship

3

Christopher Gordon, M.D.
Margot Phillips, M.D.
Eugene V. Beresin, M.A., M.D.

The doctor–patient relationship—despite all the pressures of managed care, bureaucratic intrusions, and other systemic complications—remains one of the most profound partnerships in the human experience; in it, one person reveals to another his or her innermost concerns, in hope of healing.[1,2] In this deeply intimate relationship, when we earn our patients' trust, we are privileged to learn about fears and worries that our patients may not have shared—or ever will share—with another living soul; patients literally put their lives and well-being in our hands. For our part, we hope to bring to this relationship technical mastery of our craft, wisdom, experience, and humility as well as our physicianly commitment to stand by and with our patient—that is, not to be driven away by any degree of pain, suffering, ugliness, or even death itself. We foreswear our own gratification, beyond our professional satisfaction and reward, to place our patients' interests above our own. We hope to co-create a healing relationship, in which our patients can come to understand with us the sources of suffering and the options for care and healing, and to partner with us in the construction of a path toward recovery.

In clinical medicine the relationship between doctor and patient is not merely a vehicle through which to deliver care. Rather, it is one of the most important aspects of care itself. Excellent clinical outcomes—in which patients report high degrees of satisfaction, work effectively with their physicians, adhere to treatment regimens, experience improvements in the conditions of concern to them, and proactively manage their lives to promote health and wellness—are far more likely to arise from relationships with doctors that are collaborative and in which patients feel heard, understood, respected, and included in treatment planning.[3–6] On the other hand, poor outcomes—including noncompliance with treatment plans, complaints to oversight boards, and malpractice actions—tend to arise when patients feel unheard, disrespected, or otherwise out of partnership with their doctors.[7–9] Collaborative care not only leads to better outcomes but also is more efficient than noncollaborative care in achieving good outcomes.[10,11] The relationship matters.

An effective doctor–patient relationship may be more critical to successful outcomes in psychiatry (because of the blurred boundaries between the conditions from which patients suffer and the sense of personhood of the patients themselves) than it is in other medical specialties. In psychiatry, more than in most branches of medicine, there is a sense that when the patient is ill, there is something wrong with the person as a whole, rather than that the person has or suffers from a discrete condition. Our language aggravates this sense of personal defectiveness or deficiency in psychiatric illness. We tend to speak of "being depressed" or "being bipolar" as if these were qualities of the whole person rather than a condition to be dealt with. Even more hurtfully, we sometimes speak of people as "borderlines" or "schizophrenics" as if these labels summed up the person as a whole. This language, together with the persistent stigma attached to mental illness in our culture, amplifies the shame and humiliation that patients may experience in any doctor–patient interaction[12] and makes it even more imperative that the physician work to create a safe relationship.

Moreover, if we seek to co-create a healing environment in which the patient feels understood (as a basis for constructing a path toward recovery), psychiatry more than any other branch of medicine requires us to attend thoughtfully to the whole person, even to parts of the person's life that may seem remote from the person's areas of primary concern. This is especially salient in the general hospital, where a patient's medical problem may cause clinicians to overlook critically important aspects of the person's current relationships and social environment, from long-standing psychological issues, and from the person's spiritual life and orientation. Much of the time, these psychological, social, or spiritual aspects shed a bright light on the nature of the person's distress (Figure 3–1). There must be time and space in the doctor–patient relationship to know the person from several perspectives[13]: in the context of the person's biological ailments and vulnerabilities; in the setting of the person's current social connections, supports, and stressors; in the context of the person's earlier psychological issues; and in the face of the person's spirituality.[14]

UNIQUE ASPECTS OF THE DOCTOR–PATIENT RELATIONSHIP IN THE GENERAL HOSPITAL

In the general hospital, the doctor–patient relationship has several unique features. To begin with, a medical problem is usually the cornerstone of doctor–patient encounters. This simple fact has several key consequences.

First, the relationship occurs in the context of a complex interplay of psychiatric and medical symptoms and illnesses (see Figure 2–1) that may each stem from a variety of etiologies; the doctor–patient relationship must assess and attempt to address each of these domains.

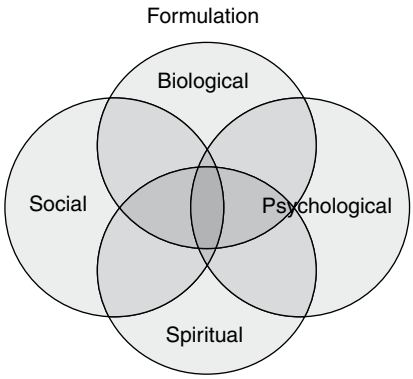

Figure 3–1. Graphic representation of frameworks that facilitate an understanding of the patient.

Second, the dynamics of power and trust in the doctor–patient relationship may be different than in outpatient settings. In the hospital patients usually have not asked for a meeting with a psychiatrist, nor do they understand why they should have done so. For instance, a psychiatrist may be called to evaluate a patient who is refusing treatment or who has developed hallucinations after a cholecystectomy. The context of care affects the patient's willingness and ability to engage in a relationship with a psychiatric physician. Doctors must be mindful of patient autonomy—which is typically strained by illness—and strive to maintain a patient-centered approach.

Third, the presence of a primary medical or surgical team changes a dyadic relationship into a complex doctor–patient–doctor triad. Both sets of physicians and the patient can feel pulled in different directions when there is disagreement about treatment. Physicians and patients alike tend to categorize illness and treatments as "medical" and "psychiatric." [15] Successful doctor–patient relationships collaborate in the service of patient care (Figure 3–2).

Fourth, the hospital environment challenges privacy, space, and time and hinders the clinical encounter. For example, assessing whether a patient who is losing weight after a stroke is depressed may be especially difficult because of barriers to communication. The hospital roommate may have visitors who interrupt or inhibit the patient from expressing himself or herself, or the patient may have intrinsic barriers to communication (e.g., an aphasia or intubation). Clinicians who practice in the general hospital should be aware of the unique aspects of providing care in this setting and tailor their clinical approach accordingly. Chapter 2 reviews some differences in approach, language, and style that may be applicable to care in the general hospital. Ultimately, regardless of setting, the doctor–patient relationship is at the core of the clinical encounter. The following sections will explore provision of patient-centered care, conduct of the clinical interview, and creation of a clinical formulation and treatment plan; all of them are facilitated by a therapeutic doctor–patient relationship.

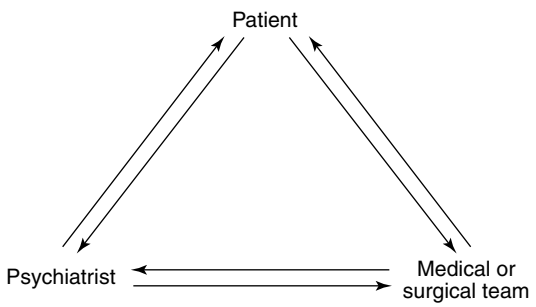

Figure 3–2. Patient–doctor relationships in the general hospital.

THE OPTIMAL HEALING ENVIRONMENT: PATIENT-CENTERED CARE

Although cultural factors limit the validity of this generalization, patients generally prefer care that centers on their own concerns; addresses their perspective on these concerns; uses language that is straightforward, is inclusive, and promotes collaboration; and respects the patient as a fully empowered partner in decision-making.[16–18] This model of care may be well denoted by the term *patient-centered care*[10,19,20] or, even better, *relationship-centered care*. In *Crossing the Quality Chasm*, the Institute of Medicine identified person-centered practices as key to achieving high-quality care that focuses on the unique perspective, needs, values, and preferences of the individual patient.[21] Person-centered care involves a collaborative relationship in which two experts—the practitioner and the patient—attempt to blend the practitioner's knowledge and experience with the patient's unique perspective, needs, and assessment of outcome.[18,22,23]

In relationship-centered practice, more than patient-centered practice, the physician does not cede decision-making authority or responsibility to the patient and family but rather enters into a dialogue about what the physician thinks is best. Most patients and families seek a valued doctor's answer to the question (stated or not), "What would you do if this were your family member?" This transparent and candid collaboration conveys respect and concern. Enhanced autonomy involves a commitment to know the patient deeply, to respect the patient's wishes, to share information openly and honestly (as the patient desires), to involve others at the patient's direction, and to treat the patient as a partner (to the greatest extent possible).

In patient-centered care, there is active management of communication to avoid inadvertently hurting, shaming, or humiliating the patient through careless use of language or other slights. When such hurt or other error occurs, the practitioner apologizes clearly and in a heartfelt way to restore the relationship.[24]

The role of the physician in patient-centered care is one of an expert who seeks to help a patient co-manage his or her health to whatever extent is most comfortable for that particular person. The role is not to cede all important decisions to the patient.[21,25]

The patient-centered physician attempts to accomplish six goals (Table 3–1).[26] First, the physician endeavors to create conditions of welcome, respect, and safety so that the patient can reveal his or her concerns and perspective. Second, the physician endeavors to understand the patient as a whole person, listening to both the "lyrics" and the "music" of what is communicated. Third, the physician confirms and demonstrates his or her understanding

TABLE 3–1 Six Goals of Patient-Centered Care[26]

- Create conditions of safety, respect, and welcome.
- Seek to understand the patient's perspective.
- Confirm an understanding of the problem(s) via direct communication.
- Synthesize information into diagnoses and problem lists.
- Formulate and share thoughts about the illness.
- Negotiate a plan of action with the patient.

through direct, nonjargonistic language to the patient. Fourth, if the physician successfully establishes common ground on the nature of the problem as the patient perceives it, an attempt is made to synthesize these problems into workable diagnoses and problem lists. Fifth, through the use of technical mastery and experience, a path is envisioned toward healing, and it is shared with the patient. Finally, together, the physician and patient can then negotiate the path that makes the most sense for this particular patient.

Through all of this work, the physician models and cultivates a relationship that values candor, collaboration, and authenticity; it should be able to withstand and even welcome conflict, as a healthy part of human relationships.[25] In so doing, the physician–patient partnership forges a relationship that can withstand the vicissitudes of the patient's illness, its treatment, and conflict in the relationship itself. In this way, the health of the physician–patient relationship takes its place as an important element on every problem list, to be actively monitored and nurtured as time passes.

Physician Practice in Patient-Centered Care

Physicians' qualities have an impact on the doctor–patient relationship. These qualities support and enhance—but are not a substitute for—technical competence and cognitive mastery. Perhaps most important is a quality of mindfulness,[27] as described by Messner,[28] acquired through a process of constant autognosis, or self-awareness. Mindfulness appreciates that a person's emotional life (i.e., of both the physician and the patient) has meaning and importance and deserves our respect and attention. Mindfulness involves acceptance of feelings in both parties without judgment and with the knowledge that feelings are separate from acts. It also enhances an awareness of our ideals, values, biases, strengths, and limitations—again, in both the patient and doctor.

Mindfulness, which springs from Buddhist roots,[29] has offered wisdom to the practice of psychotherapy (e.g., helping patients tolerate unbearable emotions without action and helping clinicians tolerate the sometimes hideous histories their patients share with them).[30] It helps physicians find a calm place from which to build patient relationships.[31] Mindfulness also counsels us to be compassionate, without a compulsion to act on feelings. This quality is an invaluable asset to consultation psychiatrists in the general hospital, particularly with difficult patients who evoke strong emotions in medical and surgical teams. Thus the physician can be informed by the wealth of his or her inner emotional life, without being driven to act on these emotions; this can serve as a model for the relationship with the patient.

Empathy (the ability to imagine a patient's perspective, express genuine care and compassion, and communicate understanding back to the patient) is another important quality for physicians.[32] Stated differently, empathy involves "identifying a patient's emotional state accurately, naming it, and responding to it appropriately."[33] Studies have shown that physician empathy promotes more complete history-taking, enhances patient satisfaction, and improves adherence to treatment.[32,34] Conversely, simple reassurance without empathic exploration of the patient's concerns has been linked to increased visits and cost.[35] Empathy may even decrease medical–legal risk;[36] one study by Ambady and colleagues suggested that surgeons' tone of voice corresponded to malpractice rates.[37]

Communication of empathy can be achieved by both verbal and nonverbal means. Listening, establishing eye contact, expressing emotion (e.g., through facial expressions and body language, such as leaning forward, and modulating the tone of voice) are several components of empathy. Other personal qualities in the physician that promote healthy and vibrant relationships with patients include humility, genuineness, optimism, good humor, candor, a belief in the value of living a full life, and transparency in communication.[38]

Important communication skills include the ability to elicit the patient's perspective, help the patient feel understood, explain conditions and options using clear and nontechnical language, generate input and consensus about paths forward in care, acknowledge difficulty in the relationship without aggravating it, welcome input and even conflict, and work through difficulty.[39–41]

One of the most important ingredients of successful doctor–patient relationships (and one that is in terribly short supply) is time.[42] There is simply no substitute for or quick alternative to sitting with a person and taking the time to get to know that person in depth, in a private setting free from intrusions and interruptions. In the general hospital, where there are frequent interruptions, this scenario may seem impossible. However, most physicians know that patients want our full and undivided attention.

COLLABORATION AROUND HISTORY-TAKING

One major goal of an initial interview is to generate a database that will support a comprehensive differential diagnosis. However, there are other overarching goals, including demystifying and explaining the process of collaboration, finding out what is troubling and challenging the patient, co-creating a treatment path to address these problems, understanding the person as a whole, encouraging the patient's participation, welcoming feedback, and modeling a mindful appreciation of the complexity of human beings (including our inner emotional life).[43,44] At the end of the history-taking—or to use more collaborative language, after building a history with the patient[45]—a conversation should be feasible about paths toward healing and the patient's and doctor's mutual roles in that process (in which the patient feels heard, understood, confident in the outcome, and committed to the partnership).

In the general hospital, the psychiatric interview may stem from a request from the medical or surgical team.

In this case, it may be tempting to view the interview as serving the primary medical or surgical team. However, the fundamental goals and principles of the interview remain the same. Chapter 4 provides an approach to the key components of the content of a psychiatric interview. Chapter 2 discusses the approach to performing a psychiatric consultation in the general hospital.

Effective Clinical Interviewing

Effective skills and traits for clinical interviewing include friendliness, warmth, a capacity to help patients feel at ease in telling their stories, and an ability to engage the person in a mutual exploration of what is troubling him or her. Demystification of the clinical encounter, by explaining what we are doing before we do it and by making our thinking as transparent and collaborative as possible, promotes good interviews.[46] Similarly, pausing often to ask the patient if we understand clearly or seeking the patient's input and questions promotes bidirectional conversations (rather than one-sided interrogation) and can yield deeper information.[47]

One useful technique involves offering to tell the patient what we already know about him or her. For example, "I wonder if it would be helpful if I told you what Dr. Smith mentioned to me when she called to refer you to me? That way, if I have any information wrong, you could straighten it out at the outset." In the emergency department, in which we usually have a chart full of information, or when doing consultations on medical–surgical patients, this technique allows us to "show our cards" before we ask the patient to reveal information about himself or herself. Moreover, by inviting correction, we demonstrate at the outset that we value the person's input. Last, this technique allows us to put the person's story in neighborly, nonpathological language, setting the stage for the interview to follow. For example, if the chart reveals that the person has been drinking excessively and may be depressed, we can say, "It looks like you have been having a hard time recently," leaving to the patient the opportunity to fill in details.[48]

Having opened the interview, the doctor remains quiet to make room for the person to tell his or her story, encouraging (with body language, open-ended questions, and other encouragement) the person to say more. The temptation to jump too early to closed-ended symptom checklists should be eschewed. One study of 73 recorded doctor–patient encounters revealed that doctors interrupted patients after an average of 18 seconds and did not allow them to complete their opening statement in 69% of cases.[49] We should venture to listen deeply, to both the words and the music.

After a reasonable amount of time, it is often helpful for the physician to summarize what he or she has heard and to establish whether he or she understands accurately what the patient is trying to say. Saying "Let me see if I understand what you are saying so far" is a good way of moving to this part of the interview. In reflecting back to the patient our summary of what we have heard, careful use of language is important. Whenever possible, use of inflammatory or otherwise inadvertently hurtful language should be avoided ("So it sounds like you were hallucinating and perhaps having other psychotic symptoms") in favor of neighborly, neutral language ("Sounds like things were difficult—did I understand you to say you were hearing things that troubled you?"). Whenever possible, it is preferable to use the exact words that the patient has used to describe his or her emotional state. For example, if the person says, "I have been feeling so tired, just so very, very tired—I feel like I have nothing left," and we say, "It sounds as if you have been exhausted," we may or may not convey to the person that we have understood them; however, if we say, "You have been just so terribly tired," it is more likely that the person will feel understood.

One measure of rapport comes from getting the "nod"—that is, simply noticing if in the early stages of the interview, the patient is nodding at us in agreement and otherwise giving signs of understanding and of feeling understood.[46] If the nod is absent, it is a signal that something is amiss—either we have missed something important, have inadvertently offended the person, have failed to explain our process, or have otherwise derailed the relationship. A clinical interview without the nod is an interview in peril. Often a simple apology if a person has been kept waiting or an acknowledgment of something in common ("Interesting—I grew up in Maryland, too!") can go a long, long way toward creating connection and rapport.

Having established a tone of collaboration, identified the problem, and gotten the nod, the next area of focus is the history of present illness. Letting the person tell his or her story is important when eliciting the history of present illness. For many people, it is a deeply healing experience merely to be listened to in an empathic and attuned way.[48] It is best to listen actively (by not interrupting and by not focusing solely on establishing the right diagnosis) and to make sure to "get it right" from the patient's point of view. When the physician hypothesizes that the patient's problem may be more likely to be in the psychological or interpersonal realm, it is especially important to give the patient a chance to share what is troubling him or her in an atmosphere of acceptance and empathy. For many people it is a rare and healing experience to be listened to attentively, particularly about a subject that may have been a source of private suffering for some time.

In taking the history of present illness, under the pressure of time, the physician may erroneously rely too heavily on symptom checklists or ask a series of closed-ended questions to rule in or rule out a particular diagnosis (e.g., major depression). Doing this increases the risk of prematurely closing off important information that the patient might otherwise impart about the social or psychological aspects of the situation.

Having sketched in the main parameters of the person's history of the current issue, it may be wise to inquire about the last time the patient felt well with respect to this problem: the earliest symptoms recollected; associated stresses, illnesses, and changes in medications; attempts to solve the problem and their effects; and how the person elected to get help for the problem at the present time. This may be a time to summarize, review, and request clarification.

As the interviewer moves to different sections of the history, he or she may want to consider explaining what he or she is doing and why: "I'd like now to ask some questions about your psychiatric history, if any, to see if anything like this has happened before." This guided interviewing tends

to demystify what the interviewer is doing and to elicit collaboration.[46,50] Chapter 4 discusses each component of the psychiatric interview in more detail.

The social and developmental history offers a rich opportunity for data-gathering in the social and psychological realms. Where the person grew up, what family life was like, what culture the person identifies with, how far the person advanced in school, what subjects the person preferred, and what hobbies and interests the person has are all fertile lines of pursuit. Marital and relationship history, whether the person has been in love, who the person admires most, and who has been most important in the person's life are even deeper probes into this aspect of the person's experience. A deep and rapid probe into a person's history can often be achieved by the simple question, "What was it like for you growing up in your family?"[51] Spiritual orientation and practice (e.g., whether the person ever had a spiritual practice and, if so, what happened to change it) fit well into this section of the history.[52]

The formal mental status examination continues the line of inquiry that was begun in the history of present illness (i.e., the symptom checklists to rule in or rule out diagnostic possibilities and to ask more about detailed signs and symptoms to establish pertinent positives and negatives in the differential diagnosis).

An extremely important area, and one all too frequently given short shrift in diagnostic evaluations, is the area of the person's strengths and capabilities. As physicians, we are trained in the vast nosology of disease and pathology, and we admire the most learned physician as one who can detect the most subtle or obscure malady; indeed, these are important physicianly strengths, to be sure. But there is regrettably no comparable nosology of strengths and capabilities. Yet, in the long road to recovery it is almost always the person's strengths on which the physician relies to make a partnership toward healing. It is vitally important that the physician note these strengths and let the person know that the physician sees and appreciates them.[45]

Sometimes strengths are obvious (e.g., high intelligence in a young person with a first-break psychosis or a committed and supportive family surrounding a person with recurrent depression). At other times, strengths are more subtle or even counterintuitive—for example, seeing that a woman who cuts herself repeatedly to distract herself from the agony of remembering past abuse has found a way to live with the unbearable; to some extent this is true, and this is a strength. Notable, too, may be her strength to survive, her faith to carry on, and other aspects of her life (e.g., a history of playing a musical instrument, a loving concern for children, a righteous rage that galvanizes her to make justice in the world). Whatever the person's strengths, we must note them, acknowledge them, and remember them. An inability to find strengths and capacities to admire in a patient (alongside other attributes that may be a great deal less admirable) is almost always a sign of countertransference malice and bears careful thought and analysis.

Finally, a clinical diagnostic interview should always include an opportunity for the patient to offer areas for discussion: "Are there areas of your life that we have not discussed that you think would be good for me to know about?" or "Are there things we have mentioned that you'd like to say more about?" or "Is there anything I haven't asked you about that I should have?"

PLANNING THE PATH FORWARD: CREATING A CLINICAL FORMULATION

Having heard the patient's story, the physician next formulates an understanding of the person that can lead to a mutually developed treatment path. A formulation is not the same thing as a diagnosis. A diagnosis describes a condition that can be reasonably delineated and described to the person and that implies a relatively foreseeable clinical course; usually it implies options of courses of treatment. As important as a diagnosis is in clinical medicine, a diagnosis alone is insufficient for effective treatment planning and is an inadequate basis for work by the doctor–patient dyad.

In psychiatry one method for creating a formulation is to consider each patient from a bio-socio-psycho-spiritual perspective, thinking about each patient from each of four perspectives.[14] The first of these is biological: Could the person's suffering be due, entirely or in part, to a biological condition of some sort (either from an acquired condition [such as hypothyroidism] or a genetic "chemical imbalance" [such as some forms of depression and bipolar disorder])? The second model is social: Is there something going on in the person's life that is contributing to his or her suffering, such as an abusive relationship, a stressful job, a sick child, or financial trouble? The third model is psychological: Although this model is more subtle, most patients will acknowledge that practically everyone has baggage from the past, and sometimes this baggage contributes to a person's difficulties in the present. The fourth model is spiritual: Although this model is not relevant for all people, sometimes it is very important. For people who at one point had faith but lost it or for whom life feels empty and meaningless, conversation about the spiritual aspects of their suffering sometimes taps into important sources of difficulty and sometimes into resources for healing.[52]

These four models—biological "chemical imbalances," current social stressors, psychological baggage, and spiritual issues—taken together provide an excellent framework for understanding most people (see Figure 3–1). One of the beauties of this method is that these models are not particularly pathologizing or shame-inducing. On the contrary, they are normalizing and emphasize that all of us are subject to these same challenges. This opens the way to collaboration.

Whereas the biological, social, and spiritual models are fairly easy to conceptualize, the formulation of psychological issues can seem particularly daunting to physicians and to patients alike, given that every person is dizzyingly complex. It can seem almost impossible to formulate a psychological perspective of a person's life that is neither simplistic and jargon-ridden nor uselessly complex (and often jargon-ridden). A useful method for making sense of the psychological aspects of the person's life is to consider whether there are recurrent patterns of difficulty, particularly in important relationships as the person looks back on his or her life.[14] The most useful information when assessing this model is information about the most important relationships in this person's life (in plain, nontechnical terms—not only current important relationships, for which we need to

assess current social function, but also past important relationships). In this way, for example, it may become clear that the person experienced his relationship with his father as abusive and hurtful and has not had a relationship with any other person in authority since then that has felt truly helpful and supportive. This information in turn may shed light on the person's current work problems and illuminate some of the person's feelings of depression.

Underlying our inquiry regarding whether there may be significant recurrent patterns in the person's life that shed light on his or her current situation is the critical notion that these patterns almost always began as attempts to cope and represent creative adaptations or even strengths. Often, these patterns—even when they involve self-injury or other clearly self-destructive behaviors—began as creative solutions to apparently insoluble problems. For example, self-injury may have represented a way of mastering unbearable feelings and may have felt like a way of being in control while remaining alive under unbearable circumstances. It is important that the doctor appreciate that most of the time these self-defeating behaviors began as solutions and often continue to have adaptive value in the person's life. If we fail to appreciate the creative, adaptive side of the behavior, the person is likely to feel misunderstood, judged harshly, and possibly shamed.

Practically everyone finds the four models understandable and meaningful. Moreover, and importantly, these four models avoid language that overly pathologizes the person, and they use language that tends to universalize the patient's experience. This initial formulation can be a good platform for a more in-depth discussion of diagnostic possibilities. With this framework the differential diagnosis can be addressed from a biological perspective, and acute social stressors can be acknowledged. The diagnosis and treatment can be framed in a manner consistent with the person's spiritual orientation. Fleshing out the psychological aspects can be more challenging, but this framework creates a way of addressing psychological patterns in a person's life and his or her interest in addressing them and ability to do so.

TREATMENT PLANNING

Having a good formulation as a frame for a comprehensive differential diagnosis permits the doctor and the patient to look at treatment options (including different modalities or even alternative therapies or solutions not based in traditional medicine). It is possible from this vantage point to look together at the risks and benefits of various approaches, as well as the demands of different approaches (the time and money invested in psychotherapy, for example, or the side effects that are expectable in many medication trials). The sequence of treatments, the location, the cost, and other parameters of care can all be made explicit and weighed together.

This approach also is effective in dealing with situations in which the physician's formulation and that of the patient differ, so that consultation and possibly mediation can be explored.[14] For example, the physician's formulation and differential diagnosis for a person might be that the person's heavy drinking constitutes alcohol abuse or possibly dependence and that cessation from drinking and the active pursuit of sobriety is a necessary part of the solution to the patient's chronic severe anxiety and depression. The patient, on the other hand, may feel that if the doctor were offering more effective treatment for his anxiety and depression, he would then be able to stop drinking. An explicit formulation enables the patient and the doctor to see where and how they disagree and to explore alternatives. For example, in the case cited the physician could offer to meet with family members with the patient, so both could get family input into the preferred solution; alternatively, the physician could offer the patient a referral for expert psychopharmacological consultation to test the patient's hypothesis.

TABLE 3–2 Strategies to Build the Doctor–Patient Relationship

- Encourage the patient to tell his or her story.
- Explain the process of the clinical encounter at the outset.
- Use open-ended questions early in the interview.
- Elicit the patient's understanding of the problems.
- Summarize information and encourage the patient to correct any misinformation.
- Look for the "nod" as an indication of collaboration.
- Provide transitional statements when moving to new sections of the history.
- End the interview with an opportunity for the patient to add or correct information.
- Formulate according to the bio-psycho-social-spiritual model.
- Share your formulation with the patient and negotiate a plan for treatment.

In either case, however, the use of an explicit formulation in this way can identify problems and challenges early in the evaluation phase and can help the physician avoid getting involved in a treatment under conditions that make it likely to fail. Mutual expectations can be made clear (e.g., the patient must engage in a 12-step program, get a sponsor, and practice sobriety for the duration of the treatment together), and the disagreement can be used to forge a strong working relationship, or the physician and patient may agree not to work together.

The formulation and differential diagnosis are of course always in flux, as more information becomes available and the doctor and patient come to know each other more deeply. Part of the doctor's role is to welcome and nurture, to change, and to promote growth, allowing the relationship to grow as part of the process (Table 3–2).[14]

OBSTACLES AND DIFFICULTIES IN THE DOCTOR–PATIENT RELATIONSHIP

Lazare and colleagues[23] pioneered the patient's perspective as a customer of the health care system. Lazare[12] subsequently addressed the profound importance of acknowledging the potential for shame and humiliation in the doctor–patient encounter and most recently has written a treatise on the nature and power of true, heartfelt apology.[24] Throughout his work, Lazare has addressed the inevitable occurrence of conflict in the doctor–patient relationship (as in all important human relationships) and offered wise counsel for negotiating with the patient as a true partner to find creative solutions.[53]

Conflict and difficulty may arise from the very nature of the physician's training, language, or office environment. Physicians who use overly technical, arcane, or obtuse language distance themselves and make communication difficult. Physicians may lose sight of how intimidating, arcane, and forbidding medical practice—perhaps especially psychiatry—can appear to the uninitiated, unless proactive steps toward demystification occur. Similarly, overreliance on so-called objective measures, such as symptom checklists, questionnaires, tests, and other measurements, may speed diagnosis but alienate patients from effective collaboration. More insidious may be assumptions regarding the supposed incapacity of psychiatric patients to be full partners in their own care. Hurtful, dismissive language or a lack of appreciation for the likelihood that a patient has previously experienced hurtful care may damage the relationship.[15] Overly brief, symptom-focused interviews that fail to address the whole person, as well as his or her preferences, questions, and concerns, are inadequate foundations for an effective relationship.

Conflict may also arise from the nature of the problem to be addressed. In general, patients are interested in their illness—how they experience their symptoms, how their health can be restored, how to ameliorate their suffering—whereas physicians are often primarily concerned with making an accurate diagnosis of an underlying disease.[54] Moreover, physicians may erroneously believe that the patient's chief complaint is the one that the patient gives voice to first, whereas patients often approach their doctors warily, not leading with their main concern, which they may not voice at all unless conditions of safety and trust are established.[55] Any inadvertent shaming of the patient makes the emergence of the real concern all the less likely.[12]

Physicians may misunderstand a patient's readiness to change and assume that once a diagnosis or problem is identified, the patient is prepared to work to change it. In actuality, a patient may be unable or unwilling to acknowledge the problem that is obvious to the physician or, even if able to acknowledge it, may not be prepared to take serious action to change it. Clarity about where the patient is in the cycle of change[56,57] can clarify such misunderstanding and help the physician direct his or her efforts at helping the patient become more ready to change, rather than fruitlessly urging change to which the patient is not committed. Similarly, physicians may underestimate social, psychological, or spiritual aspects of a person's suffering that complicate the person's willingness or ability to partner with the physician toward change. A deeply depressed patient, for example, whose sense of shame and worthlessness is so profound that the person feels that he or she does not deserve to recover, may be uncooperative with a treatment regimen until these ideas are examined in an accepting and supportive relationship.

Conflict may arise, too, over the goals of the work. Increasingly, mental health advocates and patients promote recovery as a desired outcome of treatment, even for severe psychiatric illness. Working toward recovery in schizophrenia or bipolar disorder, which most psychiatrists regard as lifelong conditions that require ongoing management, may seem unrealistic or even dishonest.[58]

It may be useful for physicians to be aware that the term *recovery* is often used in the mental health community to signify a state analogous to recovery from alcoholism or other substance abuse.[59] In this context, one is never construed to be a recovered alcoholic but rather a recovering alcoholic—someone whose sobriety is solid; who understands his or her condition and vulnerabilities well; who takes good care of himself or herself; and who is ever alert to risks of relapse, to which the person is vulnerable for his or her entire life.

In a mental health context, *recovery* similarly connotes a process of reclaiming one's life, taking charge of one's options, and stepping out of the position of passivity and victimization that major mental illness often entails, particularly if it involves involuntary treatment, stigmatization, or downright oppression. From this perspective, recovery means moving beyond symptomatic control of the disease to having a full life of one's own design (including work, friends, sexual relationships, recreation, political engagement, spiritual involvement, and other aspects of a full and challenging life).

Other sources of conflict in the doctor–patient relationship may include conflict over methods of treatment (a psychiatrist, perhaps, who emphasizes medication to treat depression to the exclusion of other areas of the patient's life, such as a troubled and depressing marriage), over the conditions of treatment (e.g., the frequency of interactions or access to the physician after hours), or over the effectiveness of treatment (e.g., the psychiatrist believes that antipsychotic medications restore a patient's function, whereas the patient believes the same medications create a sense of being drugged and "not myself").[18]

In these examples, as in so many challenges on the journey of rendering care, an answer may lie not solely in the doctor's offered treatment, nor in the patient's resistance to change, but in the vitality, authenticity, and effectiveness of the doctor–patient relationship.

CONCLUSION

The doctor–patient relationship is a key driver of clinical outcomes—both in promoting desired results and in preventing adverse outcomes. An effective doctor–patient relationship involves both parties in co-creating a working relationship that is reliable, effective, and durable. The doctor–patient relationship in the general hospital has several unique features, including limited privacy, the interplay of medical and psychiatric illness, and the interplay of relationships among the psychiatrist, the patient, and the medical or surgical team. The relationship promotes good outcomes by creating an empowered, engaged, and active partnership with patients who feel heard and accurately understood by their physicians. Successful relationships require physicians to practice a welcoming stance, participatory decision-making, and mindfulness about both the patient's and the physician's inner lives. Especially in psychiatry, the physician must understand and relate to the patient as a whole person, which requires both accurate diagnosis and formulation, blending biological, social, psychological, and spiritual perspectives. Conflict is an inevitable aspect of all important relationships and, properly managed, can deepen and strengthen them. In the doctor–patient relationship, conflict can arise from many sources and can either derail the relationship or provide an opportunity to improve communication, alliance, and commitment.

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4 The Psychiatric Interview

Eugene V. Beresin, M.A., M.D.
Margot Phillips, M.D.
Christopher Gordon, M.D.

The purpose of the initial psychiatric interview is to build a relationship and a therapeutic alliance with an individual or a family, to collect, organize, and synthesize information about present and past thoughts, feelings, and behaviors. The relevant data derive from several sources: observing the patient's behavior with the examiner and with others present (including medical staff); attending to the emotional responses of the examiner; obtaining pertinent medical, psychiatric, social, cultural, and spiritual history (using collateral resources if possible); and performing a mental status examination. The initial evaluation should enable the practitioner to develop a clinical formulation that integrates biological, psychological, and social dimensions of a patient's life and establish provisional clinical hypotheses and questions—the differential diagnosis—that need to be tested empirically in future clinical work.

A collaborative review of the formulation and differential diagnosis can provide a platform for developing (with the patient) options and recommendations for treatment, taking into account the patient's amenability for therapeutic intervention.[1] Finally, the interview must generate a relationship both with the patient and with the primary medical or surgical team as the basis of future collaboration for treatment.

Few medical encounters are more intimate and potentially frightening and shameful than the psychiatric examination.[2] As such, it is critical that the examiner create a safe space for the kind of deeply personal self-revelation required.

Several methods of the psychiatric interview are examined in this chapter. These methods include the following: promoting a healthy and secure attachment between doctor and patient that promotes self-disclosure and reflection and lends itself to the creation of a coherent narrative of the patient's life; appreciating the context of the interview that influences the interviewer's clinical technique; establishing an alliance around the task at hand and fostering effective communication; collecting data necessary for creating a formulation of the patient's strengths and weaknesses, a differential diagnosis, and recommendations for treatment, if necessary; educating the patient about the nature of emotional, behavioral, and interpersonal problems and psychiatric illnesses (while preparing the patient for a psychiatric intervention, if indicated and agreed on, and setting up arrangements for follow-up); using special techniques with children, adolescents, and families; understanding difficulties and errors in the psychiatric interview; and documenting the clinical findings for the medical record and communicating with other clinicians involved in the patient's care.

LESSONS FROM ATTACHMENT THEORY, NARRATIVE MEDICINE, AND MINDFUL PRACTICE

"I'm the spirit's janitor. All I do is wipe the windows a little bit so you can see for yourself."
Godfrey Chips, Lakota Medicine Man[3]

Healthy interactions with "attachment figures" in early life (e.g., parents) promote robust biological, emotional, and social development in childhood and throughout the life cycle.[4] The foundations for attachment theory are based on research findings in cognitive neuroscience, genetics, and brain development, and they indicate an ongoing and lifelong dance between an individual's neural circuitry, genetic predisposition, brain plasticity, and environmental influences.[5] Secure attachments in childhood foster emotional resilience[6] and generate skills and habits of seeking out selected attachment figures for comfort, protection, advice, and strength. Relationships based on secure attachments lead to effective use of cognitive functions, emotional flexibility, enhancement of security, assignment of meaning to experiences, and effective self-regulation.[5] In emotional relationships of many sorts, including the student–teacher and doctor–patient relationships, there may be many features of attachment present (such as seeking proximity, or using an individual as a "safe haven" for soothing and as a secure base).[7]

What promotes secure attachment in early childhood, and how may we draw from this in understanding a therapeutic doctor–patient relationship and an effective psychiatric interview? The foundations for secure attachment for children (according to Siegel) include several attributes ascribed to parents[5] (Table 4–1).

We must always be mindful not to patronize our patients and to steer clear of the paternalistic power dynamics that could be implied in analogizing the doctor–patient relationship to one between parent and child; nonetheless, if we substitute "doctor" for "parent" and similarly substitute "patient" for "child," we can immediately see the relevance to clinical practice. We can see how important each of these elements is in fostering a doctor–patient relationship that is open, honest, mutual, collaborative, respectful, trustworthy, and secure. Appreciating the dynamics of secure attachment also deepens the meaning of "patient-centered" care. The medical literature clearly indicates that good outcomes

TABLE 4–1 Elements That Contribute to Secure Attachments

- Communication that is collaborative, resonant, mutual, and attuned to the cognitive and emotional state of the child.
- Dialogue that is reflective and responsive to the state of the child. This creates a sense that subjective experience can be shared, and allows for the child "being seen." It requires use of empathy, "mindsight," and an ability to "see," or be in touch with, the child's state of mind.
- Identification and repair of miscommunications and misunderstandings. When the parent corrects problems in communication, the child can make sense of painful disconnections. Repair of communication failures requires consistent, predictable, reflective, intentional, and mindful caregiving. The emphasis here is on mindfulness and reflection. Mindfulness in this instance is an example of a parent's ability for self-awareness, particularly of his or her emotional reactions to the child and the impact of his or her words and actions on the child.
- Emotional communication that involves sharing feelings that amplify the positive and mitigate the negative.
- Assistance in the child's development of coherent narratives that connect experiences in the past and present, creating an autobiographical sense of self-awareness (using language to weave together thoughts, feelings, sensations, and actions as a means of organizing and making sense of internal and external worlds).

and patient satisfaction involve physician relationship techniques that center on reflection, empathy, understanding, legitimization, and support.[8,9] Patients reveal more about themselves when they trust their doctors, and trust has been found to relate primarily to behavior during clinical interviews[9] rather than to any preconceived notion of competence of the doctor or behavior outside the office.

Particularly important in the psychiatric interview is the facilitation of a patient's narrative. The practice of narrative medicine involves an ability to acknowledge, absorb, interpret, and act on the stories and struggles of others.[10] Charon[10] describes the process of listening to patients' stories as a process of following the biological, familial, cultural, and existential thread of the situation. It encompasses recognizing the multiple meanings and contradictions in words and events; attending to the silences, pauses, gestures, and nonverbal cues; and entering the world of the patient, while simultaneously arousing the doctor's own memories, associations, creativity, and emotional responses—all of which are seen in some way by the patient.[10] Narratives, like all stories, are co-created by the teller and the listener. Storytelling is an age-old part of social discourse that involves sustained attention, memory, emotional responsiveness, nonverbal responses and cues, collaborative meaning-making, and attunement to the listener's expectations. It is a vehicle for explaining behavior. Stories and storytelling are pervasive in society as a means of conveying symbolic activity, history, communication, and teaching.[5] If a physician can assist the patient in telling his or her story effectively, reliable and valid data will be collected and the relationship solidified. Narratives are facilitated by authentic, compassionate, and genuine engagement.

A differential diagnosis detached from the patient's narrative is arid; even if it is accurate it may not lead to an effective and mutually designed treatment path. By contrast, an accurate and comprehensive differential diagnosis that is supported by an appreciation of the patient's narrative is experienced by both patient and physician as more three-dimensional, more real, and more likely to lead to a mutually created and achievable plan, with which the patient is much more likely to "comply."

Creating the optimal conditions for a secure attachment and the elaboration of a coherent narrative requires mindful practice. Just as the parent must be careful to differentiate his or her emotional state and needs from the child's and be aware of conflicts and communication failures, so too must the mindful practitioner. Epstein[11] noted that mindful practitioners attend in a nonjudgmental way to their own physical and mental states during the interview. Their critical self-reflection allows them to listen carefully to a patient's distress, to recognize their own errors, to make evidence-based decisions, and to stay attuned to their own values so that they may act with compassion, technical competence, and insight.[11]

Self-reflection is critical in psychiatric interviewing. Reflective practice entails observing ourselves (including our emotional reactions to patients, colleagues, and illness); our deficits in knowledge and skill; our personal styles of communicating; our responses to personal vulnerability and failure; our willingness or resistance to acknowledge error, to apologize, and to ask for forgiveness; and our reactions to stress. Self-awareness allows us to be aware of our own thinking, feelings, and action while we are in the process of practicing. By working in this manner, a clinician enhances his or her confidence, competence, sensitivity, openness, and lack of defensiveness—all of which assist in fostering secure attachments with patients, and help them share their innermost fears, concerns, and problems.

THE CONTEXT OF THE INTERVIEW: FACTORS INFLUENCING THE FORM AND CONTENT OF THE INTERVIEW

All interviews occur in a context. Awareness of the context may require modification of clinical interviewing techniques. There are four elements to consider: the setting, the situation, the subject, and the significance.[12]

The Setting

Patients are exquisitely sensitive to the environment in which they are evaluated. There is a vast difference between being seen in an emergency department (ED), on a medical floor, on an inpatient or partial hospital unit, in a psychiatric outpatient clinic, in a private doctor's office, in a school, or in a court clinic. In the ED or on a medical or surgical floor, space for private, undisturbed interviews is usually inadequate. Such settings are filled with action, drama, and hospital personnel who race around. ED visits may require long waits and contribute to impersonal approaches to patients and negative attitudes towards psychiatric patients. For a patient with borderline traits who is in crisis, this can only create extreme frustration and exacerbate chronic fears of deprivation, betrayal, abandonment,

aloneness, and regression.[13] For these and for higher functioning patients, the public nature of the environment and the frantic pace of the emergency service may make it difficult for the patient to present personal, private material calmly. It is always advisable to ask the patient directly how comfortable he or she feels in the examining room, and to try to ensure privacy and a quiet environment with minimal distractions.

The setting must be comfortable for the patient and the physician. If the patient is agitated, aggressive, or threatening, it is always important to calmly assert that the examination must require that everyone is safe and that we will only use words and not actions during the interview. Hostile patients should be interviewed in a setting in which the doctor is protected. In some instances, local security may need to be called to ensure safety.

The Situation

Many individuals seek psychiatric help because they are aware that they have a problem. Given the limitations placed on psychiatrists by some managed care panels, access to care may be severely limited. It is not unusual for a patient to present to an ED in crisis after having called multiple psychiatrists, only to find that their practices are all filled. The frustrating process of finding a psychiatrist sets the stage for some patients to either disparage the field and the health care system, or to idealize the psychiatrist who has made the time for the patient. In either case, much goes on before the first visit that may significantly affect the initial interview. To complicate matters, the evaluator needs to understand previous experience with psychiatrists and psychiatric treatment. Sometimes a patient had a negative experience with another psychiatrist—perhaps the result of a mismatch of personalities, a style that was ineffective, a treatment that did not work, or other problems. Many will wonder about a repeat performance. In all cases, in the history and relationship building, it is propitious to ask about previous treatments (e.g., what worked and what did not, and particularly how the patient felt about the psychiatrist). There should be reassurance that this information is held in confidence, though in a hospital setting the clinician should discuss that information may be shared with the medical or surgical team.

Other patients may come reluctantly or even with great resistance. Many arrive in the ED at the request or demand of a loved one, friend, colleague, or employer because of behaviors deemed troublesome. The patient may deny any problem or simply be too terrified to confront a condition that is bizarre, unexplainable, or "mental." Some conditions are ego-syntonic, such as anorexia nervosa. A patient with this eating disorder typically sees the psychiatrist as the enemy—as a doctor who wants to make her "get fat." For resistant patients, it is often very useful to address the issue at the outset. With an anorexic patient referred by her internist and brought in by family, one could begin by saying, "Hi, Ms. Jones. I know you really don't want to be here. I understand that your doctor and family are concerned about your weight. I assure you that my job is first and foremost to understand your point of view. Can you tell me why you think they wanted you to see me?" Another common situation with extreme resistance is the individual with alcohol abuse who is brought in by a spouse or friend (and clearly not ready to stop drinking). In this case you might say, "Good morning, Mr. Jones. I heard from your wife that she is really concerned about your drinking, and your safety, especially when driving. First, let me tell you that neither I nor anyone else can stop you from drinking. That is not my mission today. I do want to know what your drinking pattern is, but more than that, I want to get the picture of your entire life to understand your current situation." Extremely resistant patients may be brought involuntarily to an emergency service, often in restraints, by police or ambulance, because they are considered dangerous to themselves or others. It is typically terrifying, insulting, and humiliating to be physically restrained. Regardless of the reasons for admission, unknown to the psychiatrist, it is often wise to begin the interview as follows: "Hi, Ms. Carter, my name is Dr. Beresin. I am terribly sorry you are strapped down, but the police and your family were very upset when you locked yourself in the car and turned on the ignition. They found a suicide note on the kitchen table. Everyone was really concerned about your safety. I would like to discuss what is going on, and see what we can do together to figure things out."

In the general hospital, a physician is commonly asked to perform a psychiatric evaluation on a patient who is hospitalized on a medical or surgical service with symptoms arising during medical or surgical treatment. These patients may be delirious and have no idea that they are going to be seen by a psychiatrist. This was never part of their agreement when they came into the hospital for surgery, and no one may have explained the risk of delirium. Some may be resistant, others confused. Other delirious patients are quite cognizant of their altered mental status and are extremely frightened. They may wonder whether the condition is going to continue forever. For example, if we know a patient has undergone abdominal surgery for colon cancer, and has been agitated, sleepless, hallucinating, and delusional, a psychiatric consultant might begin, "Good morning, Mr. Harris. My name is Dr. Beresin. I heard about your surgery from Dr. Rand and understand you have been having some experiences that may seem kind of strange or frightening to you. Sometimes after surgery, people have a reaction to the procedure or the medications used that causes difficulties with sleep, agitation, and mental confusion. This is not unusual, and it is generally temporary. I would like to help you and your team figure out what is going on and what we can do about this." Other requests for psychiatric evaluation may require entirely different skills, such as when the medical team or emergency service seeks help for a family who lost a loved one.

In each of these situations, the psychiatrist needs to understand the nature of the situation and to take this into account when planning the evaluation. In the aforementioned examples, only the introduction was addressed. However, when we see the details (discussed next) about building a relationship and modifying communication styles and questions to meet the needs of each situation, other techniques might have to be employed to make a therapeutic alliance. It is always helpful to find out as much ancillary information as possible before the interview. This may be done by talking with the medical team and primary care physicians, by looking in an electronic medical record or patient chart, and by talking with family, friends, or professionals (such as police or emergency medical technicians).

The Subject

Naturally, the clinical interview needs to take into account features of the subject (including age, developmental level, gender, and cultural background, among others). Moreover, one needs to determine "who" the patient is. In families, there may be an identified patient (e.g., a conduct-disordered child or a child with chronic abdominal pain). However, the examiner must keep in mind that psychiatric and medical syndromes do not occur in a vacuum. Although the family has determined an "identified patient," the examiner should consider that, when evaluating the child, all members of the environment need to be part of the evaluation. A similar situation occurs when an adult child brings in an elderly demented parent for an evaluation. It is incumbent on the evaluator to consider the home environment and caretaking, in addition to simply evaluating the geriatric patient. In couples, one or both may identify the "other" as the "problem." An astute clinician remains neutral (i.e., does not "take sides") and allows each person's perspective to be clarified.

Children and adolescents require special consideration. Though they may, indeed, be the "identified patient," they are embedded in a home life that requires evaluation; the parent(s) or guardian(s) must help administer any prescribed treatment (e.g., psychotropic or behavioral). Furthermore, the developmental level of the child needs to be considered in the examination. Young children may not be able to articulate what they are experiencing. For example, an 8-year-old boy who has panic attacks may simply throw temper tantrums and display oppositional behavior when asked to go to a restaurant. Although he may be phobic about malls and restaurants, his parents simply see his behavior as defiance. When asked what he is experiencing, he may not be able to describe palpitations, shortness of breath, fears of impending doom, or tremulousness. However, if he is asked to draw a picture of himself at the restaurant, he may draw himself with a scared look on his face and with jagged lines all around his body. Then when specific questions are asked, he is able to acknowledge many classic symptoms of panic disorder. Chapter 42 will address the evaluation of children in greater detail.

Evaluation of adolescents raises additional issues. While some may come willingly, others are dragged in against their will. In this instance, it is very important to identify and to empathize with the teenager: "Hi, Tony. I can see this is the last place you want to be. But now that you've been hauled in here by your folks, we should make the best of it. Look, I have no clue what is going on, and don't even know if you are the problem! Why don't you tell me your story?" Teenagers may indeed feel like hostages. They may have *bona fide* psychiatric disorders or may be stuck in a terrible home situation. The most important thing the examiner must convey is that the teenager's perspective is important, and that this will be looked at, as well as the parent's point of view. It is also critical to let adolescents, as all patients, know about the rules and limits of confidentiality. Many children think that whatever they say will be directly transmitted to their parents. Surely this is their experience in school. However, there are clear guidelines about adolescent confidentiality, and these should be delineated at the beginning of the clinical encounter. Confidentiality is a core part of the evaluation, and it will be honored for the adolescent; it is essential that this be communicated to them so they may feel safe in divulging very sensitive and private information without fears of repercussion. Issues such as sexuality, sexually transmitted diseases, substance abuse, and mental health are protected by state and federal statutes. There are, however, exceptions; one major exception is that if the patient or another is in danger by virtue of an adolescent's behavior, confidentiality is waived.[14]

The Significance

Psychiatric disorders are commonly stigmatized and subsequently are often accompanied by profound shame, anxiety, denial, fear, and uncertainty. Patients generally have a poor understanding of psychiatric disorders, either from lack of information, myth, or misinformation from the media (e.g., TV, radio, and the Internet).[15] Many patients have preconceived notions of what to expect (bad or good), based on the experience of friends or family. Some patients, having talked with others or having searched online, may be certain or very worried that they suffer from a particular condition, and this may color the information presented to an examiner. A specific syndrome or symptom may have idiosyncratic significance to a patient, perhaps because a relative with a mood disorder was hospitalized for life, before the deinstitutionalization of people with mental disorders. Hence, he or she may be extremely wary of divulging any indication of severe symptoms lest lifelong hospitalization result. Obsessions or compulsions may be seen as clear evidence of losing one's mind, having a brain tumor, or becoming like Aunt Jessie with a chronic psychosis.[12] Some patients (based on cognitive limitations) may not understand their symptoms. These may be normal, such as the developmental stage in a school-age child, whereas others may be a function of mental retardation, Asperger syndrome, or cerebral lacunae secondary to multiple infarcts following embolic strokes.

Finally, there are significant cultural differences in the way mental health and mental illness are viewed. Culture may influence health-seeking and mental health–seeking behavior, the understanding of psychiatric symptoms, the course of psychiatric disorders, the efficacy of various treatments, or the kinds of treatments accepted.[16] Psychosis, for example, may be viewed as possession by spirits. Some cultural groups have much higher completion rates for suicide, and thus previous attempts in some individuals should be taken more seriously. Understanding the family structure may be critical to the negotiation of treatment; approval by a family elder could be crucial in the acceptance of professional help.

ESTABLISHING AN ALLIANCE AND FOSTERING EFFECTIVE COMMUNICATION

Studies of physician–patient communication have demonstrated that good outcomes flow from effective communication; developing a good patient-centered relationship

is characterized by friendliness, courtesy, empathy, and partnership building, and by the provision of information. Positive outcomes have included benefits to emotional health, symptom resolution, and physiological measures (e.g., blood pressure, blood glucose level, and pain control).[17–20]

In 1999 leaders and representatives of major medical schools and professional organizations convened at the Fetzer Institute in Kalamazoo, Michigan, to propose a model for doctor–patient communication that would lend itself to the creation of curricula for medical and graduate medical education, and for the development of standards for the profession. The goals of the Kalamazoo Consensus Statement[21] were to foster a sound doctor–patient relationship and to provide a model for the clinical interview. The key elements of this statement are summarized in Table 4–2, and are applicable to the psychiatric interview.

TABLE 4–2 Building a Relationship: The Fundamental Tasks of Communication

- Elicit the patient's story while guiding the interview by diagnostic reasoning.
- Maintain an awareness that feelings, ideas, and values of both the patient and the doctor influence the relationship.
- Develop a partnership with the patient and form an alliance in which the patient participates in decision-making.
- Work with patients' families and support networks.

Open the Discussion

- Allow the patient to express his or her opening statement without interruption.
- Encourage the patient to describe a full set of concerns.
- Maintain a personal connection during the interview.

Gather Information

- Use both open- and closed-ended questions.
- Provide structure, clarification, and a summary of the information collected.
- Listen actively, using verbal and nonverbal methods (e.g., eye contact).

Understand the Patient's Perspective

- Explore contextual issues (e.g., familial, cultural, spiritual, age, gender, and socioeconomic status).
- Elicit beliefs, concerns, and expectations about health and illness.
- Validate and respond appropriately to the patient's ideas, feelings, and values.

Share Information

- Avoid technical language and medical jargon.
- Determine if the patient understands your explanations.
- Encourage questions.

Reach Agreement on Problems and Plans

- Welcome participation in decision-making.
- Determine the patient's amenability to following a plan.
- Identify and enlist resources and supports.

Provide Closure

- Ask if the patient has questions or other concerns.
- Summarize and solidify the agreement with a plan of action.
- Review the follow-up plans.

BUILDING THE RELATIONSHIP AND THERAPEUTIC ALLIANCE

All psychiatric interviews must begin with a personal introduction and establish the purpose of the interview; this helps create an alliance around the initial examination. The interviewer should attempt to greet the person warmly and use words that demonstrate care, attention, and concern. Note-taking and use of computers should be minimized and, if used, should not interfere with ongoing eye contact. The interviewer should indicate that this interaction is collaborative, and that any misunderstandings on the part of patient or physician should be immediately clarified. In addition, the patient should be instructed to ask questions, interrupt, and provide corrections or additions at any time. The time frame for the interview should be announced. In general, the interviewer should acknowledge that some of the issues and questions raised will be highly personal, and that if there are issues that the patient has real trouble with, he or she should let the examiner know. Confidentiality should be assured at the outset of the interview. If the psychiatrist is meeting a hospitalized patient at the request of the primary medical or surgical team, this should be stated at the outset.

These initial guidelines set the tone, quality, and style of the clinical interview. An example of a beginning is, "Hi, Mr. Smith. My name is Dr. Beresin. It is nice to meet you. Your surgeon, Dr. Jones, asked me to meet with you because he is concerned that you haven't eaten or taken any of your medications since you've been in the hospital. I would like to discuss some of the issues or problems you are dealing with so that we can both understand them better, and figure out what kind of assistance may be available. I will need to ask you a number of questions about your life, both your past and present, and if I need some clarification about your descriptions I will ask for your help to be sure I 'get it.' If you think I have missed the boat, please chime in and correct my misunderstanding. Some of the topics may be highly personal, and I hope that you will let me know if things get a bit too much. We will have about an hour to go through this, and then we'll try to come up with a reasonable plan together. I do want you to know that everything we say is confidential. Do you have any questions about our job today?" This should be followed with an open-ended question about the reasons for the interview.

One of the most important aspects of building a therapeutic alliance is helping the patient feel safe. Demonstrating warmth and respect is essential. In addition, the psychiatrist should display genuine interest and curiosity in working with a new patient. Preconceived notions about the patient should be eschewed. If there are questions about the patient's cultural background or spiritual beliefs that may have an impact on the information provided, on the emotional response to symptoms, or on the acceptance of a treatment plan, the physician should note at the outset that if any of these areas are of central importance to the patient, he or she should feel free to speak about such beliefs or values. The patient should have the sense that both doctor and patient are exploring the history, life experience, and current symptoms together.

For many patients, the psychiatric interview is probably one of the most confusing examinations in medicine. The psychiatric interview is at once professional and profoundly intimate. We are asking patients to reveal parts of their life they may only have shared with extremely close friends, a spouse, clergy, or family, if anyone. And they are coming into a setting in which they are supposed to do this with a total stranger. Being a doctor may not be sufficient to allay the apprehension that surrounds this situation; being a trustworthy, caring human being may help a great deal. It is vital to make the interview highly personal and to use techniques that come naturally. Beyond affirming and validating the patient's story with extreme sensitivity, some clinicians may use humor and judicious self-revelation. These elements are characteristics of healers.[22]

An example should serve to demonstrate some of these principles. A 65-year-old deeply religious woman was seen to evaluate delirium following cardiac bypass surgery. She told the psychiatric examiner in her opening discussion that she wanted to switch from her primary care physician, whom she had seen for more than 30 years. As part of her postoperative delirium, she developed the delusion that he may have raped her during one of his visits with her. She felt that she could not possibly face him, her priest, or her family, and she was stricken with deep despair. Although the examiner may have recognized this as a biological consequence of her surgery and postoperative course, the patient's personal experience spoke differently. She would not immediately accept an early interpretation or explanation that her brain was not functioning correctly. In such a situation, the examiner must verbally acknowledge her perspective, seeing the problem through her eyes, and helping her see that he or she "gets it." For the patient, this was a horrible nightmare. The interviewer might have said, "Mrs. Jones, I understand how awful you must feel. Can you tell me how this could have happened, given your longstanding and trusting relationship with your doctor?" She answered that she did not know, but that she was really confused and upset. When the examiner established a trusting relationship, completed the examination, determined delirium was present, and explained the nature of this problem, they agreed on using haloperidol to improve sleep and "nerves." Additional clarifications could be made in a subsequent session after the delirium cleared.

As noted earlier, reliable mirroring of the patient's cognitive and emotional state and self-reflection of one's affective response to patients are part and parcel of establishing secure attachments. Actively practicing self-reflection and clarifying one's understanding helps to model behavior for the patient, as the doctor and patient co-create the narrative. Giving frequent summaries to "check in" on what the physician has heard may be very valuable, particularly early on in the interview, when the opening discussion or chief complaints are elicited. For example, consultation was requested after a 22-year-old woman who was hospitalized for emergency surgery refused to go to a rehabilitation facility. During the course of the psychiatric interview, the physician elicited a history of obsessive–compulsive symptoms during the past 2 years that led her to be housebound. The interviewer said, "So, Ms. Thompson, let's see if I get it. You have been stuck at home and cannot get out of the house because you have to walk up and down the stairs for a number of hours. If you did not 'get it right,' something terrible would happen to one of your family members. You also noted that you were found walking the stairs in public places, and that even your friends could not understood this behavior, and they made fun of you. You mentioned that you had to 'check' on the stove and other appliances being turned off, and could not leave your car, because you were afraid it would not turn off, or that the brake was not fully on, and again, something terrible would happen to someone. And you said to me that you were really upset because you knew this behavior was 'crazy.' How awful this must be for you! Did I get it right?" The examiner should be sure to see both verbally and nonverbally that this captured the patient's problem. If positive feedback did not occur, the examiner should attempt to see if there was a misinterpretation, or if the interviewer came across as judgmental or critical. One could "normalize" the situation and reassure the patient to further solidify the alliance by saying, "Ms. Thompson, your tendency to stay home, stuck, in the effort to avoid hurting anyone is totally natural given your perception and concern for others close to you. I do agree, it does not make sense, and appreciate that it feels bizarre and unusual. I can see why it would be upsetting to have to wait any longer to return home. I think we can better understand this behavior, and later I can suggest ways of coping and maybe even overcoming this situation through treatments that have been quite successful with others. However, I do need to get some additional information. Is that OK?" In this way, the clinician helps the patient feel understood—that anyone in that situation would feel the same way, and that there is hope. But more information is needed. This strategy demonstrates respect and understanding and provides support and comfort, while building the alliance.

DATA COLLECTION: BEHAVIORAL OBSERVATION, THE MEDICAL AND PSYCHIATRIC HISTORY, AND MENTAL STATUS EXAMINATION

Behavioral Observation

There is a lot to be learned about patients by observing them before, during, and after the psychiatric interview. It is useful to see how the patient interacts with support staff of the clinic and with family, friends, or others who accompany him or her to the appointment. In the interview one should take note of grooming, the style and state of repair of clothes, mannerisms, normal and abnormal movements, posture and gait, physical features (such as natural deformities, birth marks, cutting marks, scratches, tattoos, or piercings), skin quality (e.g., color, texture, and hue), language (including English proficiency, the style of words used, grammar, vocabulary, and syntax), and nonverbal cues (such as eye contact and facial expressions). All these factors contribute to a clinical formulation.

The Medical and Psychiatric History

Table 4–3 provides an overview of the key components of the psychiatric history.

Presenting Problems

The interviewer should begin with the presenting problem using open-ended questions. The patient should be encouraged to tell his or her story without interruptions. Many times the patient will turn to the doctor for elaboration, but it is best to let the patient know that he or she is the true expert and that only he or she has experienced this situation directly. It is best to use clarifying questions throughout the interview. For example, "I was really upset and worked up" may mean one thing to the patient and something else to an examiner. It could mean frustrated, anxious, agitated, violent, or depressed. Such a statement requires clarification. So, too, does a comment such as "I was really depressed." Depression to a psychiatrist may be very different for a patient. To some patients, depression means aggravated, angry, or sad. It might be a

TABLE 4–3 The Psychiatric History

Identifying Information
Name, address, phone number, and e-mail address
Insurance
Age, gender, marital status, occupation, children, ethnicity, and religion
For children and adolescents: primary custodians, school, and grade
Primary care physician
Psychiatrist, allied mental health providers
Referral source
Sources of information
Reliability

Chief Complaint/Presenting Problem(s)

History of Present Illness
Onset
Perceived precipitants
Signs and symptoms
Course and duration
Treatments: professional and personal
Effects on personal, social, and occupational or academic function
Co-morbid psychiatric or medical disorders
Psychosocial stressors: personal (psychological, medical), family, friends, work/school, legal, housing, and financial
Safety assessment: presence of suicidal or homicidal ideation, plan, intent, past attempts, access to weapons

Past Psychiatric History

Previous Episodes of the Problem(s)
Symptoms, course, duration, and treatment (inpatient or outpatient)
Suicide attempts or self-injurious behavior (dates, methods, consequences)

Psychiatric Disorders
Symptoms, course, duration, and treatment (inpatient or outpatient)

Past Medical History
Medical problems: past and current
Surgical problems: past and current
Accidents
Allergies
Immunizations
Current medications: prescribed and over-the-counter medications
Other treatments: acupuncture, chiropractic, homeopathic, yoga, and meditation
Tobacco: present and past use
Substance use: present and past use
Pregnancy history: births, miscarriages, and abortions
Sexual history: birth control, safe sex practices, and history of, and screening for, sexually transmitted diseases

Review of Systems

Family History
Family psychiatric history
Family medical history

Personal History: Developmental and Social History

Early Childhood
Developmental milestones
Family relationships
Family culture and languages

Middle Childhood
School performance
Learning or attention problems
Family relationships
Friends
Hobbies
Abuse

Adolescence
School performance (include learning and attention problems)
Friends and peer relationships
Family relationships
Psychosexual history
Dating and sexual history
Work history
Substance use
Problems with the law

Early Adulthood
Education
Friends and peer relationships
Hobbies and interests
Marital and other romantic partners
Occupational history
Military experiences
Problems with the law
Domestic violence (including emotional, physical, sexual abuse)

Midlife and Older Adulthood
Career development
Marital and other romantic partners
Changes in the family
Losses
Aging process: psychological and physical

Adapted from Beresin EV: *The psychiatric interview*. In Stern TA, editor: *The ten-minute guide to psychiatric diagnosis and treatment,* New York, 2005, Professional Publishing Group.

momentary agitated state or a chronic state. Asking more detailed questions not only clarifies the affective state of the patient, but also transmits the message that he or she knows best and that a real collaboration and dialogue is the only way we will figure out the problem. In addition, once the patient's words are clarified it is very useful to use the patient's own words throughout the interview to verify that you are listening.[23]

When taking the history, it is vital to remember that the patient's primary concerns may not be the same as the physician's. For example, although the examiner may be concerned about escalating mania due to high-dose steroids, the patient may be more concerned about her husband's unemployment and how this is making her agitated and sleepless. The psychiatrist may be called to consult on managing the steroid-induced mania, whereas the patient may be focused on how the psychiatrist may help her and her husband cope with family finances. In this case, her concerns should be validated. Additionally, the consultant should gently redirect her attention to her hospitalization and indicate that he is concerned about her inability to sleep and level of emotional intensity. If the patient feels the clinician and she are on the same page, this will facilitate the interview and enable the clinician to get a more detailed history and establish a diagnosis of mania. It is always useful to ask, "What are you most worried about?"

In discussing the presenting problems, it is best to avoid a set of checklist questions, but one should cover the bases to create a differential diagnosis based on the *Diagnostic and Statistical Manual*, *Fourth Edition*, *Text Revision* (DSM-IV-TR). It is best to focus largely on the chief complaint and presenting problems and to incorporate other parts of the history around this. The presenting problem is the reason for a referral and is probably most important to the patient, even though additional questions about current function and the past medical or past psychiatric history may be more critical to the examiner. A good clinician, having established a trusting relationship, can always redirect a patient to ascertain additional information (such as symptoms not mentioned by the patient, and the duration, frequency, and intensity of symptoms). Also, it is important to ask how the patient has coped with the problem and what is being done personally or professionally to help it. One should ask if there are other problems or stressors, medical problems, or family issues that exacerbate the current complaint. This is particularly relevant for patients who are hospitalized, because the period of hospitalization can have profound repercussions on a patient's emotional stability, family, finances, and future. After a period of open-ended questions about the current problem, the interviewer should ask questions about mood, anxiety, and other behavioral problems and how they affect the presenting problem.

A key part of the assessment of the presenting problem should be a determination of safety. Questions about suicide, homicide, domestic violence, and abuse must be included in the review of the current situation. Finally, one should ascertain how motivated the patient is for getting help and how the patient is faring in personal, family, social, and professional life. Without knowing more, since this is early in the interview, the examiner should avoid offering premature reassurance, but provide support and encouragement for therapeutic assistance that will be offered in the latter part of the interview.

Past Psychiatric History

After the initial phases of the interview, open-ended questions may shift to more focused questions. In the past psychiatric history, the interviewer should inquire about previous DSM-IV-TR Axis I and II diagnoses (including the symptoms of each, partial syndromes, how they were managed, and how they affected the patient's life). A full range of treatments, including outpatient, inpatient, and partial hospital care, should be considered. One should assess whether the patient has ever considered or attempted suicide. If so, ask what prompted the attempt, when it occurred, what means were used, and what the consequences were. In addition, one should also assess self-harm behaviors (such as cutting, burning, or intentional recklessness). It is most useful to ask what treatments, if any, were successful, and if so, in what ways. By the same token, the examiner should ask about treatment failures. This, of course, will contribute to the treatment recommendations provided at the close of the interview. This may be a good time in the interview to get a sense of how the patient copes under stress. What psychological, behavioral, and social means are employed in the service of maintaining equilibrium in the face of hardship? It is also wise to focus not just on coping skills, defenses, and adaptive techniques in the face of the psychiatric disorder, but also on psychosocial stressors in general (e.g., births, deaths, loss of jobs, problems in relationships, and problems with children). Discerning a patient's coping style may be highly informative and contribute to the psychiatric formulation. Does the patient rely on venting emotions, on shutting affect off and wielding cognitive controls, on using social supports, on displacing anger onto others, or on finding productive distractions (e.g., plunging into work)? Again, knowing something about a person's style of dealing with adversity uncovers defense mechanisms, reveals something about personality, and aids in the consideration of treatment options. For example, a person who avoids emotion, uses reason, and sets about to increase tasks in hard times may be an excellent candidate for a cognitive-behavioral approach to a problem. An individual who thrives through venting emotions, turning to others for support, and working to understand the historical origins of his or her problems may be a good candidate for psychodynamic psychotherapy, either individual or group.

Past Medical History

A number of psychiatric symptoms and behavioral problems are secondary to medical conditions, to the side effects of medications, and to drug–drug interactions (including those related to over-the-counter medications). The past medical history needs to be thorough and must include past and current medical and surgical conditions, past and current use of medications (including vitamins, herbs, and nontraditional remedies), use of substances (e.g., tobacco, alcohol, and other drugs [past and present]),

an immunization and travel history, pregnancies, menstrual history, a history of hospitalizations and day surgeries, accidents (including sequelae, if any), and sexual history (including use of contraception, abortions, history of sexually transmitted diseases, and testing for the latter). For hospitalized patients, assessment should include a thorough review of the patient's current hospital course, relevant laboratory test results and imaging studies, medication changes, and history from nurses, doctors, and social workers.

Review of Systems

By the time the examiner inquires about the past medical history and the review of systems, a checklist type of questioning is adopted in lieu of the previous format of interviewing. It is useful to elicit a complete review of systems following the medical history. A number of undiagnosed medical disorders may be picked up in the course of the psychiatric interview. For instance, night sweats, weight loss, and easy bruising in an elderly man with apathy may signify a malignancy that could be mistaken for depression. Many patients do not routinely see their primary care physician, and psychiatrists have a unique opportunity to consider medical conditions and their evaluation in the examination. Although not a formal part of the interview, laboratory testing is a core part of the psychiatric examination. Though this chapter refers to the interview, the review of systems may alert the clinician to order additional laboratory tests and consult the primary care physician about medical investigations.

Family History

The fact that many illnesses run in families requires an examiner to ask about the family history of medical, surgical, and psychiatric illnesses, along with their treatments.

Social and Developmental History

The developmental history is important for all psychiatric patients, but especially for children and adolescents, because prevention and early detection of problems may lead to interventions that can correct deviations in development. The developmental history for early and middle childhood and adolescence should include questions about developmental milestones (e.g., motor function, speech, growth, and social and moral achievements), family relationships in the past and present, school history (including grade levels reached and any history of attention or learning disabilities), friends, hobbies, jobs, interests, athletics, substance use, and any legal problems. Questions about adult development should focus on the nature and quality of intimate relationships, friendships, relationships with children (e.g., natural, adopted, products of assisted reproductive technology, and stepchildren), military history, work history, hobbies and interests, legal issues, and financial problems. Questions should always be asked about domestic violence (including a history of physical or sexual abuse in the past and present).

The social history should include questions about a patient's cultural background, including the nature of this heritage, how it affects family structure and function, belief systems, values, and spiritual practices. Culture can inform a patient's explanatory model of an illness for which he or she is hospitalized and may affect his or her interactions with medical staff. Questions should be asked about the safety of the community and the quality of the social supports in the neighborhood, the place of worship, or other loci in the community.

Assessing social factors (such as the availability of housing and primary supports) is of vital importance for hospitalized patients. For instance, knowing that a depressed patient is in danger of being evicted from her apartment while in the hospital is critical in performing an adequate safety assessment.

Use of Collateral Information

In addition to the patient interview, it is quite useful to obtain collateral information. Patients may have impaired insight into their behavior, so talking to other important people in the patient's life (such as a spouse or partner, siblings, children, parents, friends, and clergy) can yield important clinical information. For example, a patient who appears paranoid and mildly psychotic may deny such symptoms or not see them as problems. To understand the nature of the problem, its duration and intensity, and its impact on function, others may need to be contacted (with informed consent, of course). This applies to many other conditions, particularly substance abuse, in which the patient may deny the quantity used and the frequency of effects of substances on everyday life.

In the general hospital, several factors (e.g., delirium, confusion, dementia, pain, or sedation) can limit the patient's ability to give a full history. Collateral information is especially important in these cases. With the patient's permission, one should perform a thorough review of the medical chart. Medical personnel (including nurses, social workers, physical therapists, and primary care physicians) can provide data about the patient's symptoms and course. Moreover, they may know the patient over several years and have a useful perspective of the patient's attitudes toward illness and coping style.

Obtaining consent to contact others in a patient's life is useful not only for information gathering, but for the involvement of others in the treatment process, if needed. For children and adolescents, this is absolutely essential, as is obtaining information from teachers or other school personnel.

The Mental Status Examination

The mental status examination is part and parcel of any medical and psychiatric interview. Its traditional components are indicated in Table 4–4. Most of the data needed in this model can be ascertained by asking the patient about elements of the current problems. Specific questions may be needed for the evaluation of perception, thought, and cognition. Most of the information in the mental status examination is obtained by simply taking the psychiatric history and by observing the patient's behavior, affect, speech, mood, thought, and cognition.

Perceptual disorders include abnormalities in sensory stimuli. There may be misperceptions of sensory stimuli, known as *illusions*, for example, micropsia or macropsia (objects that appear smaller or larger, respectively, than they are). Phenomena such as this include distortions of external stimuli (affecting the size, shape, intensity, or

TABLE 4–4 The Mental Status Examination

General appearance and behavior: grooming, posture, movements, mannerisms, and eye contact
Speech: rate, flow, latency, coherence, logic, and prosody
Affect: range, intensity, lability
Mood: euthymic, elevated, depressed, irritable, anxious
Perception: illusions and hallucinations
Thought (coherence and lucidity): form and content (illusions, hallucinations, and delusions)
Safety: suicidal, homicidal, self-injurious ideas, impulses, and plans
Cognition:
- Level of consciousness
- Orientation
- Attention and concentration
- Memory (registration, recent and remote)
- Calculation
- Abstraction
- Judgment
- Insight

sound of stimuli). Distortions of stimuli that are internally created are hallucinations and may occur in one or more of the following modalities: auditory, visual, olfactory, gustatory, or kinesthetic.

Thought disorders may manifest with difficulties in the form or content of thought. Formal thought disorders involve the way ideas are connected. Abnormalities in form may involve the logic and coherence of thinking. Such disorders may herald neurological disorders, severe mood disorders (e.g., psychotic depression or mania), schizophreniform psychosis, delirium, or other disorders that impair reality testing. Examples of formal thought disorders are listed in Table 4–5.[24,25]

Disorders of the content of thought pertain to the specific ideas themselves. The examiner should always inquire about paranoid, suicidal, and homicidal thinking. Other indications of disorder of thought content include delusions, obsessions, and ideas of reference (Table 4–6).[25]

TABLE 4–5 Examples of Formal Thought Disorders

- **Circumstantiality:** a disorder of association with the inclusion of unnecessary details until one arrives at the goal of the thought
- **Tangentiality:** use of oblique, irrelevant, and digressive thoughts that do not convey the central idea to be communicated
- **Loose associations:** jumping from one unconnected topic to another
- **Clang associations:** an association of speech without logical connection dictated by the sound of the words rather than by their meaning; it frequently involves using rhyming or punning
- **Perseveration:** repeating the same response to stimuli (such as the same verbal response to different questions) with an inability to change the responses
- **Neologism:** made-up words; often a condensation of different words; unintelligible to the listener
- **Echolalia:** persistent repetition of words or phrases of another person
- **Thought-blocking:** an abrupt interruption in the flow of thought, in which one cannot recover what was just said

TABLE 4–6 Disorders of Thought Content

- **Delusions:** fixed, false, unshakable beliefs
- **Obsessions:** persistent thoughts that cannot be extruded by logic or reasoning
- **Idea of reference:** misinterpretation of incidents in the external world as having special and direct personal reference to the self

TABLE 4–7 Categories of the Mental Status Examination

- **Orientation:** for example, to time, place, person, and situation
- **Attention and concentration:** for example, remembering three objects immediately, in 1 and 3 minutes; spelling "world" backward; performing digit span; and serially subtracting 7 from 100
- **Memory:** registration, both recent and remote
  - Registration is typically a function of attention and concentration
  - Recent and remote memory are evaluated by recalling events in the short and long term
- **Calculations**
- **Abstraction:** assessed by the patient's ability to interpret proverbs or other complex ideas
- **Judgment:** evaluated by seeing if the patient demonstrates an awareness of personal issues or problems, and provides appropriate ways of solving them
- **Insight:** an assessment of self-reflection and an understanding of one's condition or the situation of others

The cognitive examination includes an assessment of higher processes of thinking. This part of the examination is critical for a clinical assessment of neurological function, and is useful for differentiating focal and global disorders, delirium, and dementia. The traditional model assesses a variety of dimensions (Table 4–7).[26]

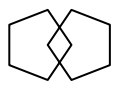
Alternatively, the Mini-Mental State Examination[27] may be administered (Table 4–8). This instrument is commonly used to assess dementia. One large study revealed a sensitivity of 87% and specificity of 82% of diagnosing dementia with a cutoff score of 24 out of 30 points. Use of this instrument cannot make the diagnosis of a mild dementia or focal neurological deficits. Its value may also be limited by the patient's educational level and primary language. Finally, the instrument is often invalid in the presence of delirium or other processes that impair attention and concentration.[28]

SHARING INFORMATION AND PREPARING THE PATIENT FOR TREATMENT

The conclusion of the psychiatric interview requires summarizing the symptoms and history and organizing them into a coherent narrative that can be reviewed and agreed on by the patient and the clinician. This involves recapitulating the most important findings and explaining the meaning of them to the patient. It is crucial to obtain an agreement on the clinical material and the way the story holds together for the patient. If the patient does not concur

TABLE 4–8 Mini-Mental State Examination

Orientation		
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (county) (town) (hospital) (floor)?
Registration		
3	( )	Name three objects: 1 second to say each. Then ask the patient all three after you have said them. Give 1 point for each correct answer. Then repeat them until the patient learns all three. Count trials and record.
Trials _____		
Attention and Calculation		
5	( )	Serial 7s: 1 point for each correct. Stop after five answers. Alternatively, spell "world" backward.
Recall		
3	( )	Ask for three objects repeated above. Give 1 point for each correct answer.
Language		
2	( )	Name a pencil and watch. (2 points)
1	( )	Repeat the following: "No ifs, ands, or buts." (1 point)
3	( )	Follow a three-stage command: "Take a piece of paper in your right hand, fold it in half, and put it on the floor." (3 points)
1	( )	Read and obey the following: "Close your eyes." (1 point)
1	( )	Write a sentence. It must contain a subject and a verb and be sensible. (1 point)
Visual–Motor Integrity		
1	( )	Copy design (two intersecting pentagons; all 10 angles must be present and 2 must intersect). (1 point)



Total score _____

Assess level of consciousness along a continuum:

Alert Drowsy Stupor Coma

Reproduced from Folstein MF, Folstein SE, McHugh PE: The Mini-Mental State Exam: a practical method for grading the cognitive state of patients for the clinician, *J Psychiatr Res* 12:189–198, 1975.

with the summary, the psychiatrist should return to the relevant portions of the interview in question and revisit the topics that are in disagreement.

This part of the interview should involve explaining one or more diagnoses to the patient (their biological, psychological, and environmental etiologies), as well as a formulation of the patient's strengths, weaknesses, and style of managing stress. The latter part of the summary is intended to help ensure that the patient feels understood. The next step is to delineate the kinds of approaches that the current standards of care would indicate are appropriate for treatment. If the diagnosis is uncertain, further evaluation should be recommended to elucidate the problem or co-morbid problems. This might require one or more of the following: further laboratory evaluation; medical, neurologic, or pediatric referral; psychological or neuropsychological testing; use of standardized rating scales; or consultation with a specialist (e.g., a psychopharmacologist or a sleep disorders or substance abuse specialist).

Education about treatment should include reviewing the pros and cons of various options. This is a good time to dispel myths about psychiatric treatments, either pharmacotherapy or psychotherapy. Both of these domains have significant stigma associated with them. For patients who are prone to shun pharmacotherapy (not wanting any "mind-altering" medications), it may be useful to "medicalize" the psychiatric disorder and note that common medical conditions involve attention to biopsychosocial treatment.[12] For example, few people would refuse medications for treatment of hypertension, even though it may be clear that the condition is exacerbated by stress and lifestyle. The same may be said for the treatment of asthma, migraines, diabetes, and peptic ulcers. In this light, the clinician can refer to psychiatric conditions as problems of "chemical imbalances"—a neutral term—or as problems with the brain, an organ people often forget when talking about "mental" conditions. A candid dialogue in this way, perhaps describing how depression or panic disorder involves abnormalities in brain function, may help. It should be noted that this kind of discussion should in no way be construed or interpreted as pressure—rather as an educational experience. Letting the patient know that treatment decisions are collaborative and patient-centered is absolutely essential in a discussion of this order.

A similar educational conversation should relate to the use of psychotherapies. Some patients disparage psychotherapies as "mumbo jumbo," lacking scientific evidence. In this instance, discussion can center around the fact that scientific research indicates that experience and the environment can affect biological function. An example of this involves talking about how early trauma affects child development, or how coming through an experience in war can produce posttraumatic stress disorder, a significant dysfunction of the brain. Many parents will immediately appreciate how the experiences in childhood affect a child's mood, anxiety, and behavior, though they will also point out that children are born with certain personalities and traits. This observation is wonderful because it opens a door for a discussion of the complex and ongoing interaction among brain, environment, and behavior.

THE EVALUATION OF CHILDREN AND ADOLESCENTS

Psychiatric disorders in children and adolescents will be discussed elsewhere in this book. In general, children and adolescents pose certain unique issues for the psychiatric interviewer. First, a complete developmental history is required. For younger children, most of the history is taken from the parents. Rarely are young children seen initially apart from parents. Observation of the child is critical. The examiner should notice how the child relates to the parents or caregivers. Conversely, it is important to note whether the adult's management of the child is appropriate. Does the child seem age appropriate in terms of motor function and growth? Are there any observable neurological impairments? The evaluator should determine whether speech, language, cognition, and social function are age appropriate. If possible, the examiner should provide toys for the evaluation in the emergency department or hospital ward. Collateral information from the pediatrician and schoolteachers is critical to verify or amplify parental and child-reported data.

Adolescents produce their own set of issues and problems for the interviewer.[29] A teenager may or may not be accompanied by a parent. However, given the developmental processes that surround the quests for identity and separation, the interviewer must treat the teen with the same kind of respect and collaboration as with an adult. The issue and importance of ensuring confidentiality have been mentioned previously. The adolescent also needs to hear at the outset that the interviewer would need to obtain permission to speak with parents or guardians, and that any information received from them would be faithfully transmitted to the patient.

Although all the principles of attempting to establish a secure attachment noted previously apply to the adolescent, the interview of the adolescent is quite different from that of an adult. Developmentally, teenagers are capable of abstract thinking and are becoming increasingly autonomous. At the same time, they are struggling with grandiosity that alternates with extreme vulnerability and self-consciousness and managing body image, sexuality and aggression, mood lability, and occasional regression to dependency—all of which makes an interview and relationship difficult. The interviewer must constantly consider what counts as normal adolescent behavior and what risk-taking behaviors, mood swings, and impulsivity are pathological. This is not easy, and typically teenagers need a few initial meetings for the clinician to feel capable of co-creating a narrative—albeit a narrative in progress. The stance of the clinician in working with adolescents requires moving in a facile fashion between an often-needed professional authority figure and a big brother or sister, camp counselor, and friend. The examiner must be able to know something about the particular adolescent's culture, to use humor and exaggeration, to be flexible, and to be empathic in the interview, yet not attempt to be "one of them." It is essential to validate strengths and weaknesses and to inspire self-reflection and some philosophical thinking—all attendant with the new cognitive developments since earlier childhood.

DIFFICULTIES AND ERRORS IN THE PSYCHIATRIC INTERVIEW

Dealing with Sensitive Subjects

A number of subjects are particularly shameful for patients. Such topics include sexual problems, substance abuse and other addictions, financial matters, impulsive behavior, bizarre experiences (such as obsessions and compulsions), domestic violence, histories of abuse, and symptoms of psychosis. Some patients will either deny or avoid discussing these topics. In this situation, nonthreatening, gentle encouragement and acknowledgment of how difficult these matters are may help. If the issue is not potentially dangerous or life-threatening to the patient or to others, the clinician may omit some questions known to be important in the diagnosis or formulation. If it is not essential to obtain this information in the initial interview, it may be best for the alliance to let it go, knowing the examiner or another clinician may return to it as the therapeutic relationship grows.

In other situations that are dangerous (such as occurs with suicidal, homicidal, manic, or psychotic patients), in which pertinent symptoms must be ascertained, questioning is crucial no matter how distressed the patient may become. In some instances when danger seems highly likely, transfer to a psychiatric hospital may be necessary for observation and further exploration of a serious disorder. Similarly, an agitated patient who needs to be assessed for safety may need sedation, restraints, or eventual transfer to a psychiatric hospital to complete a comprehensive evaluation, particularly if the cause of agitation is not known and the patient is not collaborating with the evaluative process.

Disagreements about Assessment and Treatment

There are times when a patient disagrees with a clinician's formulation, diagnosis, and treatment recommendations. Or the disagreement may be between the patient and the medical staff, with the psychiatrist in the challenging position of the intermediary. In either case, it is wise to listen to the patient and hear where there is conflict. This can serve to reestablish the alliance. It also may diffuse the

TABLE 4–9 Common Errors in the Psychiatric Interview

- Premature closure and false assumptions about symptoms
- False reassurance about the patient's condition or prognosis
- Defensiveness around psychiatric diagnoses and treatment, with arrogant responses to myths and complaints about psychiatry
- Omission of significant parts of the interview, due to theoretical bias of the interview (e.g., mind–body splitting)
- Recommendations for treatment when diagnostic formulation is incomplete
- Inadequate explanation of psychiatric disorders and their treatment, particularly not giving the patient multiple options for treatment
- Minimization or denial of the severity of symptoms, due to overidentification with the patient; countertransference phenomenon (e.g., as occurs with treatment of a "very important person" [VIP] in a manner inconsistent with ordinary best practice, with a resultant failure to protect the patient or others)
- Failure to establish a genuine, empathic rapport (e.g., by using brusque language, tone, or body posture)
- Use of an angry or dismissive style in response to a patient who is guarded or hostile
- Inadvertently shaming or embarrassing a patient, and not offering an apology

patient's need to defend himself or herself against what he or she may perceive as doctors "ganging up" on him or her. Then, the evaluator should systematically review what was said and how he or she interpreted the clinical findings. The patient should be encouraged to correct misrepresentations. Sometimes clarification will help the clinician and patient come to an agreement. At other times, the patient may deny or minimize a problem. In this case additional interviews may be necessary. It is sometimes useful to involve a close relative or friend, if the patient allows this. If the patient is a danger to self or others, however, protective measures will be needed, short of any agreement. If there is no imminent danger, explaining one's clinical opinion and respecting the right of the patient to choose treatment must be observed. It may also be necessary to work with the medical team to reach a compromise that takes into consideration the patient's goals and wishes when they differ from that of the medical team.

Errors in Psychiatric Interviewing

Common mistakes made in the psychiatric interview are provided in Table 4–9.

CONCLUSION

The purpose of the psychiatric interview is to establish a therapeutic relationship with the patient to collect, organize, and synthesize data that can become the basis for a formulation, differential diagnosis, and treatment plan. A fundamental part of establishing this relationship is fostering a secure attachment between doctor and patient, in order to facilitate mutual and open communication, to correct misunderstandings, and to help the patient create a cohesive narrative of his or her past and present situation. Interviews in the general hospital require modification in techniques in order to take into account four elements of the context: the setting, the situation, the subject, and the significance. Data collection should include behavioral observation, medical and psychiatric history, and a mental status examination.

The clinician should conclude the interview by summarizing the findings and the formulation, seeking agreement with the patient, and negotiating appropriate follow-up arrangements. All clinicians should be aware of difficulties in the psychiatric interview (such as shameful topics and disagreements about assessment or treatment). Common errors in an interview include premature closure and false assumptions about symptoms, false reassurance about a patient's condition, defensiveness around psychiatric diagnosis and treatment, maintenance of a theoretical bias about mental health and illness, inadequate explanations about psychiatric disorders and their treatment, minimization of the severity of symptoms, and inadvertent shaming of a patient without offering an apology.

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Functional Neuroanatomy and the Neurologic Examination

5

Anthony P. Weiss, M.D., M.B.A.
Stephan Heckers, M.D.

The brain is a complex and mysterious organ. Sealed away in its cranial vault, it is immune from the poking, prodding, visualizing, and auscultating that are central to the examination of other organs. The assessment of the brain and its peripheral extensions requires an indirect approach, one that evaluates the integrity of its functional capacity. Because there are many faculties associated with the brain, this functional assessment is lengthy and complex. One component of this evaluation is the neurologic examination, which can intimidate medical students and seasoned physicians alike. As a result, the neurologic examination is all too often omitted by the busy clinician, with the entire examination summarized as "grossly intact."

For the psychiatric consultant, the neurologic examination is an important component of every patient evaluation for several reasons. First, psychiatric symptoms (affective, behavioral, or cognitive) may result directly from underlying neurologic damage (e.g., stroke causing mood lability). It is the associated sensory and motor findings on examination that will uncover the root cause of these symptoms. Second, psychiatric symptoms are commonly seen in the context of neurologic disorders (e.g., depression in Parkinson's disease). In some cases, the psychiatric symptoms predate or predominate over the other features of the illness; a thorough examination by the psychiatrist may therefore lead to early recognition and treatment. Third, knowledge of the neurologic examination is crucial for distinguishing real neurologic deficits from simulated deficits associated with conversion disorders or malingering. The consultation psychiatrist is often called on to clarify this diagnostic dilemma. Finally, the psychiatrist must be aware of the numerous ways in which psychotropic medications can affect the sensory and motor systems of the brain (e.g., by causing dystonias and other movement disorders) and must be capable of assessing the severity of these adverse effects.

In this chapter, we hope to provide the consulting psychiatrist with both a theoretical and a pragmatic framework for the neurologic examination. First, we introduce a systematic overview of functional neuroanatomy, examining at a basic level the actual role of the nervous system in the human, and providing a simplified approach to the otherwise unimaginable complexity of billions of interconnected neurons. Then, we provide an outline for the neurologic examination itself, discussing the rationale for each component and providing a few clinically relevant pointers. By enumerating the main components of the standard examination and by attempting to relate them to the anatomic constructs developed herein, we hope to provide an organization to help in both the understanding and the recollection of each aspect of the examination.

FUNCTIONAL NEUROANATOMY

Why do we have a nervous system? What is the reason for its complexity in humans? By addressing these questions we gain a greater understanding not only of the nervous system as a whole but also of its component parts.

At its most basic level, the nervous system allows us to interact with the external world, serving as a bridge between the environment and our internal mental and physical worlds. Put another way, the nervous system allows us to respond in some fashion to environmental stimuli. In simpler organisms, there is little or no gap between stimulus and response, allowing little or no variability of response to a specific stimulus. In humans, however, there is a large evaluation step, which allows a carefully chosen response to a stimulus, one that may be influenced by the situational context.

Using an information-processing model, we can map these concepts in three distinct steps: *input* of sensory information through perceptual modules, the internal integration and *evaluation* of this information, and the production of a *response*. These steps are carried out by four main anatomic systems in the brain: the *thalamus*, the *cortex*, the *medial temporal lobe*, and the *basal ganglia* (Figure 5–1).

Sensory organs provide information about physical attributes of incoming information. Details of physical attributes (e.g., temperature, sound frequency, color) are conveyed through multiple segregated channels in each perceptual module. Information then passes through the thalamus, which serves as the gateway to cortical processing for all sensory data. Specifically, it is the relay nuclei (ventral posterior lateral, medial geniculate, and lateral geniculate) that convey sensory information from the sensory organs to the appropriate area of primary sensory cortex (i.e., S1, A1, or V1) (Figure 5–2).

The first step in the integration and evaluation of incoming stimuli occurs in unimodal association areas of the cortex, where physical attributes of one sensory domain are linked together. A second level of integration is reached in multimodal association areas, including regions in the parietal lobe and prefrontal cortex, which link together the physical attributes from different sensory domains. A third

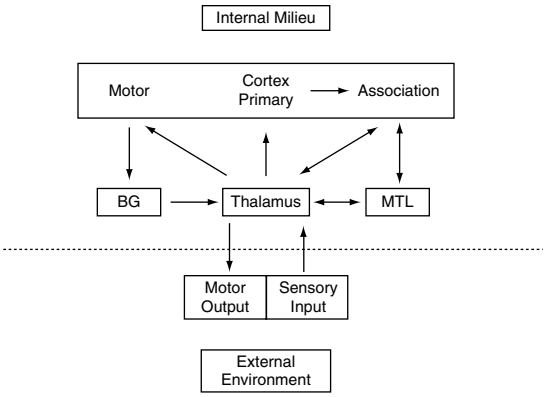

Figure 5–1. Basic circuitry of information processing. BG, basal ganglia; MTL, medial temporal lobe.

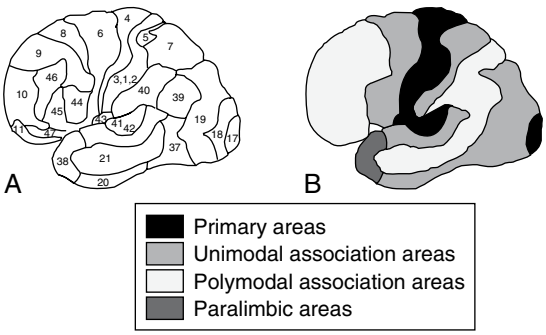

Figure 5–2. Functional role of areas in the human cerebral cortex. **A,** Map of cytoarchitectonic areas according to Brodmann. The parcellation of the cortical mantle into distinct areas is based on the microscopic analysis of neurons in the six layers of the cortex. **B,** Map of functional areas according to Mesulam. The primary sensory areas (visual = area 17; auditory = areas 41, 42; somatosensory = areas 3, 1, 2) and the primary motor area 4 are indicated in *black*. The association areas, dedicated to one stream of information processing (visual = areas 18, 19, 20, 37; auditory = area 22; somatosensory = areas 5, 7, 40; motor = areas 6, 44), are indicated in *dark gray*. The polymodal association areas, where all sensory modalities converge, are indicated in *light gray*. The temporal pole is part of the paralimbic areas, which occupy large regions on the medial surface of the brain (i.e., cingulate cortex and parahippocampal cortex). **A** from Brodmann K: *Vergleichende lokalisationslehre der grosshirnrinde in ihren prinzipien dargestellt auf grund des zellenbaues,* Leipzig, Germany, 1909, JA Barth; **B** from Mesulam M-M: *Principles of behavioral neurology,* Philadelphia, 1985, FA Davis.

level of integration is provided by input from limbic and paralimbic regions of the brain, including the cingulate cortex and regions of the medial temporal lobe (hippocampus and amygdala). It is at this third level of integration that the brain creates a representation of experience that has the spatiotemporal resolution and full complexity of the outside world, imbued with emotion and viewed in the context of prior experience. Evaluation and interpretation involve the comparison of new information with previously stored information and current expectations or desires. This allows the brain to classify information as new or old, or as threatening or nonthreatening.

Based on the result of evaluation and interpretation, the brain then creates a response, most often through motor action. The regions involved in generating this response include the motor cortex, the motor nuclei of the thalamus, the basal ganglia, and the cerebellum. The basal ganglia, which include the striatum (made up of the caudate and the putamen) and the globus pallidus, are charged with integrating and coordinating this motor output. The striatum receives input from the motor cortex, and it projects to the globus pallidus. The globus pallidus in turn relays the neostriatal input to the thalamus. The thalamus then projects back to the cortical areas that gave rise to the corticostriatal projections, thereby closing the cortico-striato-pallido-thalamo-cortical loop. This loop is thought to be the means by which motor control is enacted; damage to regions in this loop leads to disorders such as Parkinson's disease and Huntington's disease.

THE NEUROLOGIC EXAMINATION

The neurologic examination is a set of steps designed to probe the input, integration/evaluation, and output domains of information processing. We provide here an overview of the examination, using this framework. Our aim is to demystify the examination by presenting the rationale for its component parts. The examination presented here is not all-encompassing; see standard texts of neurology for complete details.

Input

Sensory information enters the central nervous system (CNS) by two routes: spinal nerves and cranial nerves. The former handle tactile information presented to the body, and the latter handle tactile information presented to the face and each of the remaining special senses (vision, hearing, smell, and taste).

Peripheral Sensory Examination

Peripheral sensation allows tactile exploration of our environment. Even the most thorough examiner could not test every square inch of the body for intact sensation, nor would this be necessary. Knowledge of the full sensory examination is important for the patient with a focal sensory complaint (see other texts for detailed information on peripheral nerve examination[1–9]). The main sensory modalities include the following:

Pain: Tested by pinprick (using disposable sterile pins)

Temperature: Tested by touching the skin with a cold metal object (e.g., a tuning fork)

Light touch: Tested by simply brushing the patient's skin with your hand or a moving wisp of cotton

Vibration sense: Tested by applying a "buzzing" tuning fork to the distal lower extremities

Proprioception: Best tested by Romberg's maneuver (which can be assessed during gait observation). Ask the patient to stand with the feet as close together as possible while still maintaining stability. Then ask the patient to close the eyes (ensure the patient that you will not let him or her fall). The patient with poor proprioception will begin to sway and lose balance after closing the eyes.

Sensory Cranial Nerves (I, II, V, VII, VIII)

Five cranial nerves serve an input function and are known as sensory cranial nerves, to distinguish them from those that play a motor/output or dual sensorimotor role (Table 5–1).

Olfactory Nerve (Cranial Nerve I)

Testing of the first cranial nerve is almost uniformly neglected, and the entire cranial nerve examination is often described as "II-XII within normal limits." This notation indicates little regard for the first cranial nerve, and it communicates little about the individual features of the examination.

The first cranial nerve runs along the orbital surface of the frontal lobe, an area that is otherwise clinically silent. Lesions in this area (e.g., a frontal lobe meningioma) may produce unilateral anosmia, occasionally as a sole symptom. Routine testing of smell is therefore quite important. A small vial of coffee provides a simple and convenient method for testing smell. The nostrils should be tested separately.

Optic Nerve (Cranial Nerve II)

The optic nerve and its posterior radiations run the entire length of the brain and produce different patterns of symptoms and signs depending on where they are compromised. A thorough visual examination can therefore be quite informative. It involves five components:

Funduscopic examination: The optic nerve is the only nerve that can be visualized directly. The physician should take advantage of this in assessing its integrity. A good funduscopic examination also reveals much about the systemic vascular system, and it is a critical guide to the presence of increased intracranial pressure.

Visual acuity: Testing of visual acuity (i.e., the actual strength of vision) is frequently ignored in the adult patient. This is unfortunate because poor vision can profoundly impair a patient's ability to function and is often reversible with corrective lenses or surgery. Acuity should be assessed in each eye while the patient is wearing current corrective lenses.

Pupillary measurement: Pupillary size represents the delicate balance between sympathetic and parasympathetic input to the ciliary muscles of the eye. The presence of abnormally large or small pupils reflects an imbalance and may be an important sign of disease or toxicity. Similarly, an inequality in pupillary size (anisocoria) can be an important hallmark of a severe intracranial pathologic condition. Each pupil should be measured in millimeters, with measurements clearly documented for future reference.

Pupillary reaction: The direct and consensual pupillary reaction to light, and the near reaction (accommodation), should be tested routinely. This assesses any damage in the afferent and efferent pathways that compose the pupillary response. A penlight and close observation are all that are necessary.

Confrontational visual fields: As noted previously, the visual system runs from the retina to the occipital cortex, involving a substantial area of the CNS. Lesions anywhere along this pathway lead to visual field cuts. Importantly, the patient is almost never aware of this abnormality of vision; careful testing is therefore required to elucidate it. Sit directly in front of the patient, and have him or her look into your eyes. The eyes should be tested separately by bringing an object

TABLE 5–1 The Cranial Nerves

NUMBER	NAME	SENSORY (INPUT), MOTOR (OUTPUT), OR BOTH?	FUNCTION
I	Olfactory	Sensory	Olfaction
II	Optic	Sensory	Vision
III	Oculomotor	Motor	Innervation of extraocular musculature
IV	Trochlear	Motor	Innervation of extraocular musculature
V	Trigeminal	Both	Facial sensation + innervation of muscles of mastication
VI	Abducens	Motor	Innervation of extraocular musculature
VII	Facial	Motor	Taste + innervation of muscles of facial expression
VIII	Vestibulocochlear	Sensory	Hearing + balance
IX	Glossopharyngeal	Both	Taste + innervation of stylopharyngeus muscle
X	Vagus	Both	Parasympathetic innervation + innervation to muscles of larynx and pharynx
XI	Spinal accessory	Motor	Innervation of the sternocleidomastoid and trapezius muscles
XII	Hypoglossal	Motor	Innervation of tongue

(e.g., a pin or a wiggling finger) into each visual quadrant. For the patient who is unable to cooperate in this fashion, simply having him or her count fingers displayed in each quadrant is another option.

Trigeminal Nerve (Cranial Nerve V)

The sensory component of the trigeminal nerve provides tactile sense to the face. As with sensory testing in general (see earlier), testing sensory integrity of the face can be a frustrating exercise if the examiner insists on precision. Unless the patient has a specific sensory complaint (e.g., a numb chin or facial pain), thorough testing of all sensory modalities is probably unnecessary. Testing light touch (by stroking the face with your fingers) or temperature sensitivity (using a cold metal tuning fork) is usually adequate. Asking the patient to quantify the degree of difference (e.g., "If this side is a dollar, how much is this side?") is generally not fruitful. Simply asking, "Does this feel normal on both sides?" saves time and will generally detect any abnormalities worth further investigation.

The trigeminal nerve also provides the input for the corneal reflex, the direct and the consensual blink seen in response to corneal irritation. Although testing for the corneal reflex can be helpful in localization of brainstem dysfunction (usually in the comatose patient), it is unfortunately both nonspecific and insensitive. It is therefore not done routinely.

Facial Nerve (Cranial Nerve VII)

The sensory component of the facial nerve (chorda tympani) transmits taste from the anterior two thirds of the tongue, running from the taste buds to the nucleus of the tractus solitarius in the medulla. Testing this aspect of the facial nerve involves the application of a sweet, sour, or salty solution (via a cotton-tipped swab) to the outstretched tongue. The yield of this component of the examination in the patient without specific gustatory complaints is minimal.

Acoustic Nerve (Cranial Nerve VIII)

In addition to its role in the maintenance of equilibrium (via the vestibular branch), the eighth cranial nerve is the primary input channel for auditory information. The acoustic nerve carries information from the hair cells in the organ of Corti, traveling through the internal auditory meatus to the pontomedullary junction of the brainstem. For the consulting psychiatrist, the examination of auditory function can be kept to a cursory check, but it should be included, particularly in geriatric patients. Rubbing fingers together near the ear may bring out high-pitched hearing deficits, a finding typically associated with presbycusis.

Integration and Evaluation

Even the simplest unicellular organisms have means by which they can sense and react to the environment. These responses are automatic and limited; the same stimulus results in the same response regardless of context. A number of these automatic or reflexive responses can be tested in the human, and some of them were discussed as part of the sensory evaluation (e.g., the pupillary light reflex and the corneal reflex). Three additional sets of reflexes are commonly probed in a standard neurologic examination:

Proprioceptive reflexes: Proprioceptive reflexes, also known as deep tendon reflexes (DTRs), are based on the simple reflex arcs that are activated by stretching (or tapping). Because they are influenced by the descending corticospinal tracts, DTRs can provide important information on the integrity of this pathway at several levels. The reader is probably familiar with the methods used to elicit the five major DTRs: biceps, triceps, brachioradialis, quadriceps (knee), and Achilles (ankle). The grading of each reflex is on a four-point scale, with a score of 2 (2+) designated as normal.

Nociceptive reflexes: Nociceptive reflexes are based on reflex arcs located in the skin (rather than muscle tendons) and are therefore elicited by scratching or stroking. These include the abdominal reflexes, cremasteric reflex, and anal wink, none of which is extensively used clinically. The major nociceptive reflex of clinical value is the plantar reflex. Stroking the sole of the foot should elicit plantar flexion of the toes. Babinski's sign, marked by an extensor response (i.e., dorsiflexion) of the toes, often with fanning of the toes and flexion of the ankle, is seen in pyramidal tract disease. It has become one of the most famous eponymic signs in medicine.

Primitive reflexes (release reflexes): Primitive reflexes are present at birth but disappear in early infancy. Their reappearance later in life is abnormal and often reflects frontal lobe disease. They include the grasp reflex (stroking the patient's palm leads to an automatic clutching of your finger between his thumb and index finger), the glabellar reflex (cessation of the natural blink response in response to repetitive tapping on the forehead), and the snout reflex (gentle tapping over the patient's upper lip causes a puckering of the lips). Note that this may also elicit a suck response, or a turning of the head toward the stroking stimulus (root reflex).

The Mental Status Examination

The brains of higher mammals, particularly the human, have the added capacity to integrate sensory information across domains, to evaluate this information, and to react in a manner consistent with past experience, current context, or future expectations. The ability to use these higher-level faculties is often considered part of the mental status examination. For routine purposes, the following four components compose an adequate examination. It is important that these components, unlike other features of the neurologic examination, be done in order, because basic functions must be intact to perform more complex tasks.

Level of consciousness: Consciousness lies on a continuum from full alertness to coma. Although the two extremes are generally obvious, the middle ground of attentional deficit can be subtle. Because inattention is a hallmark of delirium (an acute confusional state), a common and emergent medical condition, attention should be tested in all patients. Sustained attention is also a critical component for all other cognitive functions. Some common tests of attention include "serial 7s" (ask the patient to subtract 7 from 100 and to then continue to serially subtract 7 from the remainder) and digit span (have the patient repeat a randomly presented list of digits [a normal capacity is between five and seven digits], or have the patient spell a five-letter word [e.g., *world*] backward).

Language: Language is the means by which we present our thoughts to each other. Like other cognitive functions, language can be extraordinarily complex, with entire texts of aphasiology dedicated to its study. In general, the following three simple questions allow the examiner to draw valid conclusions about language in the individual patient (Figure 5–3):

- Is the language *fluent* or *nonfluent?* Independent of the actual words, does the speech sound like a language? Loss of the normal inflection and spacing of normal speech leads to nonfluent language production.
- Is *comprehension* normal or abnormal? Does the patient seem to understand what you are saying? A request to complete a one-step to three-step command (although complex commands may test more than just receptive language function) best assesses this. Asking simple yes-or-no questions (e.g., Were you born in Mexico? or Are we in the kitchen?) is another common method.
- Is *repetition* normal or abnormal? Have the patient repeat a phrase such as "no ifs, ands, or buts." This particular phrase is quite sensitive, given the difficulty of repeating conjunctions.

Memory: Memory function is generally divided into the following three components:

- *Immediate recall* is the ability to hold information long enough to use it (e.g., remembering a phone number given by the operator long enough to dial it). Immediate recall is heavily dependent on attention and is tested by both digit span and phrase repetition. Asking the patient to repeat three named items (e.g., piano, monkey, and blue) is another commonly used method.
- *Short-term memory* involves the ability to store information for later use. Asking the patient to reproduce the three previously named items after a span of 2 to 5 minutes is a common test.
- *Long-term memory* involves the recall of past events. This is nearly impossible to test accurately at the bedside, because the examiner is rarely privy to details of remote events from the patient's life. Asking about well-known national events or people (e.g., How did JFK die?) depends on the age and educational background of the patient. Accurate assessment often requires a standardized battery of questions available in full neuropsychological testing.

Basic Aphasiology

Type	Repetition	Comprehension	Speech
Gobal	Impaired	Impaired	Nonfluent
Wernicke's	Impaired	Impaired	Fluent
Broca's	Impaired	Intact	Nonfluent
Conduction	Impaired	Intact	Fluent
Transcortical			
Motor	Intact	Intact	Nonfluent
Sensory	Intact	Impaired	Fluent

Figure 5–3. Differential diagnosis of the main types of aphasias.

Visual-Spatial Skills

Writing: Ask the patient to write his or her name, address, and a sentence about the weather. Look for grammatical errors, as well as errors in spacing and overall presentation.

Clock-drawing: Have the patient fill in a circle with numbers in the form of a clock; when completed, ask the patient to set the hands at 10 minutes to 2. Abnormalities can occur in planning (e.g., manifested by poor spacing between numbers) or in positioning of the hands (with a style that reflects being stimulus-bound) that may belie a frontal lobe lesion. Complete absence of detail on one side of the clock (usually the left side) may represent a hemineglect syndrome associated with a (right) parietal lobe lesion.

Output

Although there are many potential responses to environmental stimuli, including subtle changes in the internal hormonal or neurochemical milieu, most often the response requires some type of motor output. The examination of this output can be divided into a motor (or muscular) component and a coordination component.

Motor (III, IV, VI, XI, XII) and Sensorimotor (V, VII, IX, X) Cranial Nerves

These cranial nerves are responsible for motor function in the head and neck and are tested by examining the functionality of the muscles they subserve. For example, cranial nerves III, IV, and VI innervate the extraocular muscles that allow the eye to scan its environment. They are therefore tested by examining the range of eye movement in all directions (by having the patient track one's finger). The role and testing of other cranial nerves are listed in Table 5–1.

Motor Examination

There are three aspects evaluated in the motor examination: muscle tone, muscle bulk, and muscle strength. The three aspects may be affected separately. *Motor tone* refers to the resistance of a limb to passive movement through its normal range of motion. To examine for tone, one can have the patient fully relax the arms and legs to allow you to determine the degree of stiffness during passive motion. An increased level of tone, noted by rigidity or spasticity, is an important finding that may belie an upper motor neuron or extrapyramidal lesion (as in, e.g., parkinsonism).

Muscle atrophy is an important sign of lower motor neuron disease. Assessment of muscle bulk can be extraordinarily difficult, even for the seasoned clinician, because of natural variations in body habitus and the role of weightlifting or exercise (i.e., "bulking up"). Muscles that are unaffected by weightlifting or exercise (e.g., the facial muscles or the intrinsic muscles of the hand) may therefore provide the best estimate of overall muscle bulk.

In testing muscle strength, it is impractical (and unnecessary) to test each of the several hundred muscles in the human body. Should the patient have a focal motor complaint, knowledge of major muscle groups in the proximal and distal limbs becomes important. Muscle strength is graded from 0 (no motion) to 5 (normal strength).

Observation of gait is an excellent screening test for the patient without focal weakness. If the patient is able to rise briskly and independently from a seated position and

walk independently, gross motor deficits can be confidently ruled out. The ability to walk on one's heels and toes further ensures distal lower-extremity strength. Gait must be tested in all patients, particularly in older adults, for whom a fall can be a life-threatening event.

Coordination

Coordination reflects the ability to orchestrate and control movement, and it is crucial in the translation of movement into productive activity. Although the cerebellum probably plays the lead role in motor coordination, several other structures (e.g., the basal ganglia and red nucleus) are also clearly involved.

Walking is an extraordinarily complex motor skill that requires significant coordination of the trunk and limbs. Its complexity makes it an ideal screening test for coordination ability. Humans have a particularly narrow base when standing upright; with any degree of incoordination (ataxia), the patient needs to widen the base to remain upright. Balance becomes even more difficult when other sensory information is removed, forming the basis for Romberg's maneuver. The sensitivity of screening is further increased by having the patient walk heel-to-toe (as on a tightrope). The ability to do this smoothly and quickly rules out any major impairment in coordination.

Diadochokinesia refers to the alternating movements made possible by the paired nature of agonist and antagonist muscle activity in coordinated limb movement. Abnormalities of this function are given the lengthy label *dysdiadochokinesia* and are detected by several simple maneuvers, including finger-to-nose, heel-to-shin, and rapid alternating movements (rapid pronation or supination of the forearm [e.g., screwing in a light bulb], finger tapping, or toe tapping). Having the patient tap out a rhythm is an excellent way to assess coordination ability. With cerebellar damage, the rhythm is poorly timed, with emphases in the wrong places.

CONCLUSION

The brain is an organ that is unmatched in its eloquence. Unlike the anginal grip of cardiac disease or the choking dyspnea of respiratory dysfunction, illness of the brain can send many different messages. Deciphering these messages using the neurologic examination can be complex and at times bewildering. This should not discourage the practicing psychiatrist from using the examination described in this chapter as a routine part of every patient evaluation.

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6 Limbic Music

George B. Murray, B.S., Ph.L., M.S., M.Sc., M.D., S.J.
Nicholas Kontos, M.D.

"Limbic Music" is a strange title for a chapter in a handbook of psychiatry in the general hospital. However, it is meant to be clinically relevant. This chapter is primarily heuristic. Some license is taken with philosophic assumptions not adequately substantiated, there are arguable statements, and the anatomy and physiology on which this structure is based may change, although probably not in a major way, in the coming years. Mesulam[1] mentions that the concept of the limbic system has ebbed and flowed to fit the preference of individual authors. This is another case of it. It is hoped that the use of *limbic music* will aid the clinician in assessing the affective component in the patient.

In academic institutions, the limbic system has historically played the ugly stepsister to the cerebral hemispheres and the arousal system. Several factors might account for this. First, the limbic system is difficult to reach within the brain; one has to traverse much cortex to get to it. Second, the limbic system is not a neatly discrete structure; some, such as Brodal,[2] would say that it does not exist as a system at all. A third factor, not usually stated, but detectable in casual discussion, is that the limbic system does not subserve "higher function" and as a result has the bias associated with it as mediating "lower functions" in humans. Academics usually pride themselves not on their pro-football muscles but on their higher functions, and they therefore do not usually feel that the study of the "lower functions" (the four Fs) in human beings is an especially worthy, clean, intellectual, and liberalizing endeavor.

MIND–BRAIN

First, let us briefly review some aspects of the mind–body arena. *Psychobiology* was a word coined by Adolph Meyer to compress and unite the concept of mind–brain. Those of us who had an interest in the mind–brain connection thought that this concept of psychobiology would contain the kernel that would dispel the problems involved with mind–brain. Unfortunately, after carefully reading Meyer's works, we find that kernel is still difficult to attain. In today's iteration of the tradition of psychosomatic medicine, a word again tries to compress the two ideas of mind and brain (and the rest of the body) into one word, implying a unity therein. As one reads the literature in this area and discusses the term with experts in the field, one finds much left to be desired for an understanding of the relationship of mind to brain and vice versa – especially for the kind of understanding that the pragmatic and action-oriented physician needs in his or her daily work. Psychosomatic concepts may be quite interesting, and even true, in themselves, but as a collected fund of knowledge, they do not allow the physician to do much.

On the other hand, there is a certain animosity among psychosomaticists directed toward those who would split humans into mind and brain. In traditional philosophic thinking, there are two core poles: realism and idealism. Those with a more idealistic bent strive for global unity, tend to dislike fractionation and atomization, tend to charge the realists with disuniting and reducing everything to its smallest biological parts (i.e., realists are practitioners of reductionism). The charge goes on to say that in reductionism what one reduces and gets rid of is, in fact, mind. The idealist smiles when the charge is made that the realist has a mindless brain only; however, when the idealist is charged with having a brainless mind (as a subject of study) the smile turns to a frown.

The culprit for this great supposed split between brain and mind is usually thought to be Descartes. His most famous treatise, *Discourse on the Method of Rightly Conducting the Reason and Seeking for Truth in the Sciences*,[3] outlined his philosophic approach to using methodical doubt in obtaining philosophic proof by the use of reason alone.

One often hears the phrase *Cartesian dualism*, and it is presupposed that Descartes, in isolating the mind from the body to study it more specifically, in fact initiated the great disunion of mind and brain.[4] We submit that it was primarily Descartes' followers who pragmatically operated on the premises of a split between brain and mind. Because Descartes is often quoted and rarely read, it is not difficult to see why he has been blamed for dualism. Descartes operated in no way differently than, for example, a heart surgeon does today. Heart surgeons isolate their interests and bear their intensity on how they may best make an intervention on the physiologic function of a failing heart, and they do not pay much attention to the gastrointestinal system, the endocrine system, and so forth. Similarly, Descartes set his intensity on the mind and did not, in fact, negate the importance of the body, just as the heart surgeon would not negate the importance of the endocrine system and the fact that humans live by all of their physiologic systems as well as mind. Although Descartes' criteria of clarity and distinctness of ideas led him to emphasize a real distinction between mind and body—soul and body to him—he still did not accept the idea that the soul (mind) is just lodged in the body. What he does say in his *Objections*

and Replies to Objections is "Mind and body are incomplete substances, viewed in relation to the man who is the unity which they form together."[5]

Most psychiatrists use the term *Cartesian dualism* in a pejorative sense, as if to castigate someone for not being an idealistic upholder of "holism." Most persons interested in psychosomatic medicine have an interest in how the body can influence the mind and how the mind can influence the body, but there have been no clear, distinct theories that settle this question to everyone's satisfaction.

We submit here that a partial key to the understanding of the mind–brain or mind–body meld is the limbic system. The limbic system can be considered in the Cartesian manner as part mind and part body. Mind consists of many things: intellect, imagination, affect, cognition, and motivation, among others. There is no one definition of *mind* that satisfies everybody. If the neocortex is more "intellectual," certainly the limbic system is more effectual. In fact, it is often stated that the limbic system is the substratum of emotion in humans and other animals.

HISTORY OF THE LIMBIC SYSTEM

The history of the development of the concept of the limbic system is important in psychiatry. Of the many names in the history of its development, four stand out: Broca, Papez, MacLean, and Nauta.

Paul Broca (1824–1880), a French surgeon, founded the Societé d'Anthropologie in Paris in 1859 (the year Darwin's *On the Origin of Species by Means of Natural Selection* was published). In 1861, a patient named Laborgne came under Broca's care. Laborgne had aphasia for 21 years; all he could say was "tan-tan-tan." After his death, a postmortem examination was carried out, and Broca found a softened area in the left frontal cortex, now described as *Brodmann's area 44* and more popularly known as *Broca's area*.[6] In the medical sciences, Broca is best known for his work in aphasia. (Laborgne's brain is extant, housed in L'École de Medicine in Paris, as is Broca's brain.)

Broca is less well known as an author of a remarkable 113-page monograph on the comparative neuroanatomy of mammals.[7] The title of this monograph is *Des Circonvolutions Cérébrals*. This work was published in Revue d'Anthropologie in 1878, two years before Broca's death. The monograph is a fascinating comparative neuroanatomic study of mammals and contains drawings of what the author called the *great limbic lobe* (*limbic* meaning *border*). What Broca called the *great limbic lobe* includes today the cingulate gyrus, retrosplenial cortex, and parahippocampal gyrus (gyrus fornicatus).

Neuroanatomic knowledge progressed with its characterizations of nuclei and connections, but there was no stimulating discussion of the limbic lobe until 1937, when James Papez published his classic paper, "A Proposed Mechanism of Emotion."[8] Papez (1883–1958) was a 1911 graduate of the University of Minnesota Medical School; at the time of writing the paper cited, he was a neuroanatomist at Cornell University Medical School when it was still in Ithaca, New York. When he published the paper, it did not create much stir. According to MacLean,[9] Papez wrote this paper because of some ongoing discussion in England on the subject; Papez thought that the discussion did not reflect the tradition of emotion and neuroanatomic structures already known, and thus he elaborated the idea of the limbic structures subserving the emotions.

From this paper came the popular name of the *Papez circuit* (Figure 6–1). This circuit was so called because Papez himself hypothesized that a neuroimpulse could leave the hippocampus via the fornix, travel up the fornix under the corpus callosum, and traverse the septal area into

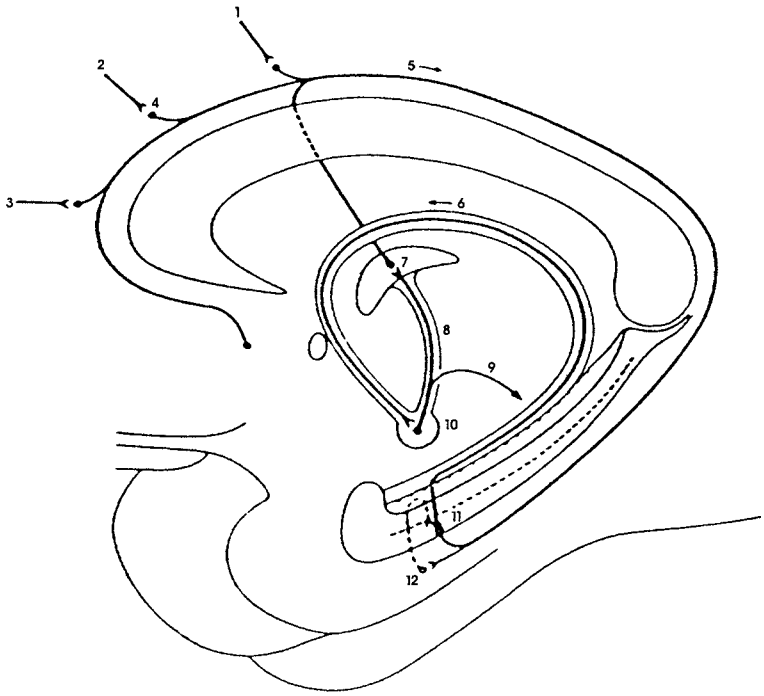

Figure 6–1. The Papez circuit. *1,* Brodmann areas 6 and 8; *2,* area 9; *3,* areas 10 and 11; *4,* area 24; *5,* cingulum; *6,* fornix; *7,* anterior nucleus of the thalamus; *8,* mamillothalamic tract; *9,* mamillotegmental tract; *10,* mamillary body; *11,* subiculum; *12,* area 28. *(From Nieuwenhuys SR, Voogd J, Van Huijzen CHR:* The human central nervous system, *New York, 1979, Springer-Verlag.)*

the mamillary bodies. At the mamillary bodies, a synaptic connection would be made to the anterior nucleus of the thalamus and then it would radiate up onto more primitive cortex, the cingulate gyrus. This impulse would then be captured at the level of the cingulate gyrus, be returned in a neurobundle, the cingulum, and be brought down and again entered into the hippocampus.[10] He did not include the amygdala in this circuit.

Papez postulated that this circuit was the basis for the feeling of emotions in humans. The cingulate gyrus in particular, not a neocortical structure, but composed of archicortex and mesocortex, allows a human to "know" that he or she is having his or her present feelings.

There was not much stir until 1947 when Paul MacLean ran across Papez's paper in the library at Massachusetts General Hospital. At this time, MacLean was a U.S. Public Health Service fellow. MacLean, with Stanley Cobb as his mentor, was making electroencephalographic recordings of the mesobasal structures of the brain in patients with temporal lobe epilepsy. Discussion with Cobb about the significance of the Papez circuit resulted in MacLean's visiting Papez (accomplished with Cobb's help).

After his discussion with Papez, MacLean wrote a paper entitled "Psychosomatic Disease and the 'Visceral Brain': Recent Developments Bearing on the Papez Theory of Emotion."[11] MacLean used the term *visceral brain* because he wanted to communicate the notion of "gut feeling." In those years, for the most part, this area of the brain was called the *rhinencephalon*, or the *nose brain*. It turned out that *visceral brain* did not catch the wind and soar effectively either.

In 1952, after further research, MacLean published another paper entitled "Some Psychiatric Implications of Physiological Studies on the Frontotemporal Portion of the Limbic System (Visceral Brain)."[12] This was the first use of the term *limbic system*. This concept did catch the wind, and it soars today as a concept for structures that subserve emotion in humans.

Walle J. H. Nauta, a neuroanatomist at Massachusetts Institute of Technology, was instrumental both in his own meticulous work and in influencing his students in careful delineation and expansion of the limbic system. In tracking down frontal lobe connections to the limbic system, he effectively expanded it forward. Connections to the midbrain indicate an expansion of the limbic concept backward or "downstream."[13,14] One of Nauta's students, Lennart Heimer, has further tracked and extended the limbic system's connections into the basal forebrain, including his ventral striatum and an extended amygdala.[15]

More important, the limbic system can serve as an integrating concept for the clinical side of psychiatry and neurology. Various approaches to the study of the limbic system can be taken: morphologic,[16] evolutionary,[17] polymodal,[1] or an overview.[18] Perhaps Nauta gave us the most contemporary view: a look at emotions and their anatomy.[19]

PSYCHOLOGISTS' VIEWS

There has been disagreement about the impact of the limbic system on the field of cognitive psychology. Some say emotion is partially independent of cognition; others say that emotions are the products of cognition. It is our position that although emotions (mediated by the limbic system) are usually conjoined with cognition, they can stand on their own without prior cognitive process. The psychologist Richard Lazarus, maintaining that emotions are the products of cognitions, said:

> *Recent years have seen a major change in the way psychologists view emotion—the rediscovery that emotions are products of cognitive processes. The emotional response is elicited by an evaluative perception in lower animals, and in humans by a complex cognitive appraisal of the significance of events for one's well-being.*[20]

The psychologist Robert Zajonc elaborated a position seemingly more in accord with how the limbic system functions:

> *Only a few years ago, I published a rather speculative paper entitled "Feeling and thinking" (Zajonc, 1980).*[21] *. . . In this paper I tried to make an appeal for more concentrated study of affective phenomena which have been ignored for decades, and at the same time to ease the heavy reliance on cognitive functions for the explanation of affect. The argument began with the general hypothesis that affect and cognition are partially independent systems and although they ordinarily function conjointly, affect could be generated without a prior cognitive process. It could, therefore, at times precede cognition in a behavioral chain.*[22]

Zajonc also believes that there exists a form of cognitive imperialism, wherein there is a disdain for affect and only the cognitive is considered to be of priority in higher animals. His position on the secondary nature of cognition recalls William James's supposition that:

> *We feel sorry because we cry, angry because we strike, afraid because we tremble, and not that we cry, strike, or tremble, because we are sorry, angry, or fearful, as the case may be. Without the bodily states following on the perception, the latter would be purely cognitive in form, pale, colourless, destitute of emotional warmth.*[23]

At the same time, Zajonc anticipates contemporary ideas such as Porges's polyvagal theory[24] and interoception[25] where limbic activation and perception of bodily states precede and influence conscious responses and experiences. Sperry has shown movies of split brain subjects who had had corpus callosotomies for intractable epilepsy. In one film, the contents of a slide were flashed into the right cortex of a woman's brain, and, of course, she could not speak about it because there is no Broca's area in the right cortex. Every slide flashed into her left cortex only was described adequately in words; in the pictures flashed to her right cortex only, the left brain chattered on in a manner not relevant to the slide shown to the right mute brain. At one point, a risqué slide was shown to the right brain and the woman flushed and showed other aspects of autonomic arousal, for example, rapid respirations, increased systolic blood pressure, increased pulse rate. Not surprisingly, her left brain did not know why. All the left brain said was "Oh my! That's something isn't it!" Even though the left brain did not know what was occurring and the right brain did, the limbic system also "knew" what was occurring to have the affectual engagement of the autonomic system. It became clear that many things can happen affectually without all of the neocortex being aware of what is going on.

EMOTIONAL VALENCE

Humans' intellects are often not formally conscious of much that goes on within them. This is no great insight to psychotherapists who emphasize the unconscious. Kihlstrom[26] stated, "People may reach conclusions about events—for example, their emotional valence—and act on these judgments without being able to articulate the reasoning by which they were reached." Behavioral activity can tell us often about the inner state of another or ourselves. For example, dogs have a visible "limbicometer," their tails. Whether a dog's tail wags or not, with what frequency, and with what vigor all tell us about the dog's feelings.

Probably the closest thing to a limbicometer in humans is the smile. In this context, a smile is the limbic recognition of reality before it is fully understood by intellect (neocortex). If someone smiles and is asked why he or she smiled or what made him or her smile, that person often cannot specify or gives an intellectual response not derived from the present smile-reality.

The traditional view of affective coloring on incoming sensory material has been that the incoming sensory signals went to thalamic relay nuclei and therein radiated to sensory receiving areas as, for example, occipital visual Brodmann area 18. From there, over many synapses, the now-modified signal went to subcortical (limbic) regions, which attached an emotional tone to the signal (schematized in Figure 6–1). It is now clear, mainly through the work of LeDoux,[27] that pathways exist from sensory receptors that bypass the neocortex and wend straight to the limbic system, specifically, the amygdala (Figure 6–2). If this bypass exists in humans, it could reshape current thinking about how the affective processing of incoming sensory material can be an unconscious function of the brain.

For example, amygdala activation was noted in white subjects exposed to unfamiliar African American faces (but not unfamiliar white faces), independent of their conscious expression of race attitudes.[28] Further, the amygdala activation correlated with indirect measures of physiologic states of alarm (e.g., a startle response). No doubt, the "high-minded" cortex steers us away from some undesirable thoughts and behaviors, but for good and for ill it shares the helm with the limbic system far more than some would like to think.

The limbic system is involved with motivation, attention, emotion, and memory. It can also be looked at in an animal way or a human way. In a cavalier fashion, it is often said that the limbic system mediates the four Fs—fear, food, fight, and fornication. This is a view from the Olympian hill of the cerebral cortex. A more noble formulation is that the limbic system mediates gender role, territoriality, and bonding.[29] For example, as far as territoriality is concerned, the limbic system mediates how one feels about family, rights, "keep off the grass," and other areas that have a spatial or relational component. In bonding, the limbic system mediates strongly how one bonds to one's spouse, family, parents, country, flag, and religion—in sum, loyalty. If this is true, most of the actions performed daily are already set limbically before humans neocortically intellectualize, and these three elements constitute much of the work of the psychiatrist.

The neocortex, with Broca's area, is the substrate for the lyrics or the words of what one thinks and feels. The limbic system has no Broca's area, has no words, but is the locus of the music of one's affect. Psychiatric interviewers hear what people verbalize, but often much more important is what one sees, what one feels, and what one hears as the affective music or tune from the person interviewed.

AMYGDALA

Some general agreement exists that the amygdala is concerned with motivation in the organism. The classic view is that the amygdala attaches motivational significance to the information elaborated by the neocortex.[30] Kagan and colleagues[31] considered increased arousal in the amygdala to be a contributor to shyness in childhood and social avoidance in adults. The late Pierre Gloor of Montreal, following his experience with implanted electrodes in the human limbic system, proposed that:

> *the site where this [the coalescence of experimental mechanisms] occurs is the limbic system, and in particular the amygdala. Visual and auditory perceptual data are first analyzed in the appropriate areas of the temporal neocortex. . . . Finally, the information is conveyed to the amygdala where affective tone is attached to it. I would like to suggest that this involvement of affect is necessary to make a perception or memory emerge into consciousness, thus enabling it to be experienced as an event one is living or has lived through.*[32]

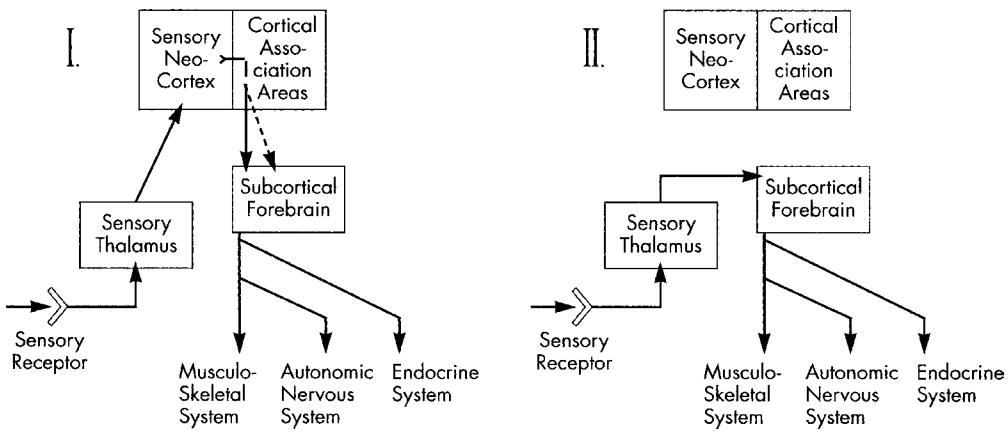

Figure 6–2. I, The traditional perceptual process. **II,** A recently found variant of the perceptual process. *(Modified from LeDoux JE:* Sensory systems and emotion: a model of affective processing, *Integr Psychiatry, 4:237–248, 1986.)*

Therefore, according to this proposal, it is primarily the amygdala and its role in affect that affects the brain's consciousness of the material. Thus, the limbic system is responsible for what enters into consciousness—a long noble step from the four Fs.

A crude analogy may be helpful in how the neocortex and limbic system might work in the human. If one views a slide of Death Valley, one perceives that slide neocortically in the primary visual area pretty much the same as all other humans do. Limbically, however, one could have at least two different feeling states on seeing the slide. One could have a subtitle or label at the bottom of the slide reading "the sparse grandeur of the West," or at the other end of the spectrum one could label the Death Valley slide as "the devil's fiery hell." The limbic system supplies the personalized affective tone when information is perceived or recalled.

HIPPOCAMPUS

The hippocampus has been termed, by O'Keefe and Nadel,[33] a *cognitive map*. The importance of the hippocampus in memory is well known since the hippocampectomies in the patient H.M., who after this surgery, and right up to his recent death, was unable to lay down new memories.[34] Knowing one's place in the world, both internally and externally, appears to be another function of the hippocampus.

Because humans are an altricial species—the infant undergoes much maturation after birth—there is a relatively enormous openness to environmental influence compared to the nonaltricial species. Some fibers to the hippocampus do not mature for years after birth. Although "the wires and the juices" have much to do in setting the individual's emotional life, it is this long maturation process that allows culture, teaching, and so forth to shape that emotional life.

CLINICAL ASPECT OF THE LIMBIC SYSTEM

At the bedside, one can use the Frank Jones story to screen for neuropsychiatric impairment. The supposition here is that the neocortex is usually affected in many conditions earlier and more severely than the limbic system. Let us say that the psychiatrist has been called because there is suspicion of a postoperative acute confusional state. One of the things the psychiatrist can do is say to the patient, "Now, how does this strike you? I have a friend, Frank Jones, whose feet are so big he has to put his pants on over his head."

Usually, one of three responses is provided by patients. The type 1—or normal—response occurs when the limbic system is grossly intact. The patient will smile or chuckle. The chuckle indicates that the patient appreciates the incongruity, and when the patient is asked, "Can he do it?" the patient usually says something like, "No, it's goofy…. The crotch—he can't go up on both sides," meaning that the patient also has intellectual insight.

The type 2 answer usually indicates that the limbic system is intact, but the neocortex is impaired. In this situation, the patient usually smiles and laughs and gives the limbic music that there's something funny to the story. However, when asked, "Can he do it?" the patient will usually say something like, "Well, whatever you say," or "Well, if he tries hard enough." This type 2 patient appreciates the incongruity but does not have intellectual insight.

The type 3 response indicates that both the limbic system and the neocortex are impaired. After hearing the story the patient does not smile, shows no facial quizzicalness, and gives no special limbic response at all. When one asks, "Can he do it?" the unsmiling answer usually is something like, "Well, doctor, he must have to have special shoes but sure he can." This patient neither appreciates the incongruity nor has intellectual insight. The patient has limbic and neocortical confusion, suggesting a more advanced or widespread pathologic process.

From a diagnostic point of view, the Frank Jones story is nonspecific, but rather sensitive.[35] Its value lies also in its vivid display of how the patient processes and responds to the world.

Quietly confused hospitalized patients are often seen after surgery. The treating physician often does not recognize that the patient has an impairment of higher cortical function. The impairment is usually missed because the patient is alert and gets along well with the physician. The patient smiles and says he or she is doing okay, but if the patient is pressed to say exactly where he or she is, or what year it is, the patient does not know. The limbic system, even without neocortical clarity, can take humans quite far in everyday life, and that is probably what really gets us through the day. That is, the limbic system and not the higher intellectual activity of the neocortex, save for the primary motor and sensory areas, is where most human mental activity occurs. Much resistance to this notion exists, especially from intellectuals, theologians, humanists, and others who, perhaps unconsciously, have a bias against the limbic system because it mediates those raw, crude, baser elements of humans: that is, the emotions.

CASE 1

One of us (GBM) was once asked to see a patient in the Massachusetts Eye and Ear Infirmary for presumed hysterical blindness. She had had an extensive work-up that included visual evoked potentials; no clinical findings were found to support an organic lesion. Unfortunately, the diagnosis of a conversion disorder is often made without primary data for the diagnosis, but only with secondary, substantive corollary data from the psychosocial realm. This woman had quite a bit of psychosocial perturbation having to do with a violent husband and an appearance in court. In fact, the day she was seen, she was to have appeared in court against her husband, but "unfortunately" she was hospitalized.

During the interview she looked away from me. Gradually, I moved in front of her again as I continued talking and noticed that her eyes gradually moved off to the other side, looking away from me again. I continued to do this, moving in front of her gaze several times; each time she shifted her gaze. I performed the usual test of threatening her eyes with my hand. She did not blink. I then moved in front of her gaze and as I continued to speak I put both of my hands on the side of my head, contorted my face, and wiggled my fingers as children do. (The incongruity of finger wiggling and serious physician's voice should evoke some response in the normal patient.) There was a brief, slight smile on her lips, and her eyes shifted away again. I repeated this maneuver

several times, and each time it was apparent that the patient revealed a small smile, which immediately disappeared. Then it was clear: This woman sees.

My interpretation of what happened was that the patient perceived in the occipital cortex my funny business with the hands and screwing-up of my face but heard in her auditory cortex a serious physician's voice. Before she could employ "neocortical squelch," her limbic system assigned a valence[32] to the incongruity of voice and pantomime, thus activating, presumably, the nucleus accumbens— the limbic basal ganglion[36]—and evoking a slight accumbens smile that appeared just beyond her immediate neocortical control.

CASE 2

One of us (NK) was once asked to see a man soon after an opiate overdose. He was large and muscular, wearing a bandana and Harley Davidson t-shirt and with abundant elaborate and somewhat macabre tattoos. He participated in the interview for only a few minutes and then quickly lapsed into a state of apparent unconsciousness when we got down to the details of his overdose and his choice of drug. He was unresponsive to voice, to loud voice, to shaking of shoulder, and all this seemed quite incongruent with his initial level of alertness. Because he looked like a man who knew how to take and to administer physical pain, I chose another route to test alertness before moving on to nail bed pressure or sternal rub. Taking a step back, I said in a slightly raised voice, "Now this is just strange. I don't know if you are really out of it or if you're just f***king with me." The patient sprang up to a seated position and angrily but affectedly shouted "Well I never!"

Yes he had, of course, as was already obvious from a casual scan of the images and words on his arms. But his limbic system would not allow my alpha-male posturing to go unchallenged, and it overrode his cortically controlled "coma." Menace ensued, but I intentionally ended the alpha male struggle via nature's nonlethal limbic means: neck-baring.[37] The patient agreed that I "would not be doing you any favors if I kept my suspicions about you a secret *just because I'm scared of you*."

CONCLUSION

There are several points to emphasize. The use of the term *limbic system* here is not a hard, scientific usage; it partakes of metaphor. The limbic system can be helpful in understanding the so-called rift between mind and body. The stuff of clinical psychiatry is primarily mediated by the limbic system and not by the nonsensory structures of the neocortex. *Limbic music* is a term that denotes the existential, clinical raw feel emanating from the patient. It is a truer rendering of the patient's clinical state than is articulate speech. Limbic music never lies.

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7 Psychological and Neuropsychological Assessment

Mark A. Blais, Psy.D.
Sheila M. O'Keefe, Ed.D.
Dennis K. Norman, Ed.D.

The intent of this chapter is to increase clinicians' knowledge of psychological and neuropsychological assessment. This will be accomplished by reviewing the scientific basis of psychological instruments, the major categories of psychological tests, and the application of these instruments in clinical assessment. The chapter also briefly touches on issues related to the ordering of psychological testing and understanding of assessment reports. The material contained in this chapter should allow clinicians to better use psychological and neuropsychological assessments in the care of patients.

Psychological tests must be reliable and valid. Reliability represents the repeatability, stability, or consistency of a subject's test score. Reliability is usually represented as a correlation coefficient ranging from 0 to 1.0. Research instruments can have reliabilities in the low .70s, whereas clinical instruments should have reliabilities in the high .80s to low .90s. A number of reliability statistics are available for evaluating a test. For example, internal consistency measures the degree to which items in a test function in the same manner, and test–retest reliability shows the consistency of a test score over time. Interrater reliability measured by the Kappa statistic reflects the degree of agreement among raters, usually corrected for chance. Unreliability, or error, can be introduced into a test score by variability in the subject (changes in the subject over time), the examiner, or the test (given with different instructions).

Validity is a more complex concept and a hard property to demonstrate. The validity of a test reflects the degree to which the test actually measures the construct it was designed to measure. Measures of validity are usually represented as correlation coefficients ranging from 0 to 1.0. Multiple types of validity data are required before a test can be considered valid. Content validity assesses the degree that an instrument covers the full range of the target construct, and predictive validity indicates how well a test predicts future occurrences of the target variable. It is important to realize that no psychological test is universally valid. Tests are considered valid or not valid for a specific purpose. The validity of psychological tests is comparable to that of most routine diagnostic tests used in medicine.

TYPES OF PSYCHOLOGICAL TESTS

Test of Intelligence

Matarazzo states, "Intelligence…is the aggregate or global capacity of the individual to act purposefully, to think rationally, and to deal effectively with the environment."[1] This definition demonstrates what the tests of intelligence measure (adaptive function) and that measured intelligence quotient (IQ) can provide important information, particularly with regard to treatment planning. In fact, measured IQ has been shown to account for approximately 25% of life success. The Wechsler tests are the most commonly used IQ tests; they cover almost the whole life span. The series starts with the Wechsler Preschool and Primary Scale of Intelligence (for ages 4 to 6 years), progresses to the Wechsler Intelligence Scale for Children-IV (for ages 5 to 16 years), and ends with the Wechsler Adult Intelligence Scale-IV (for ages 16 to 89 years).[2–4] A new abbreviated version of the Wechsler IQ test is now available (Wechsler Abbreviated Scale of Intelligence [WASI]).[5] All the Wechsler scales provide three major IQ tests scores: the full scale IQ, verbal IQ (VIQ), and performance IQ (PIQ). All three IQ scores have a mean of 100 and standard deviations (SDs) of 15. These statistical features mean that a 15-point difference between a subject's VIQ and PIQ is both statistically and clinically meaningful. Table 7–1 presents an overview of the IQ categories.

The Wechsler IQ tests are composed of 10 or 11 subtests that were developed to tap into two primarily intellectual domains, verbal intelligence (as measured by Vocabulary, Similarities, Arithmetic, Digit Span, Information, and Comprehension) and nonverbal visual–spatial intelligence (as measured by Picture Completion, Digit Symbol, Block Design, Matrix Reasoning, and Picture Arrangement). Empirical studies have suggested that the Wechsler subscales can be reorganized into three cognitive domains: verbal ability, visual–spatial ability, and attention and concentration (which is assessed by the Arithmetic, Digit Span, and Digit Symbol subtests). All the Wechsler subtests have a mean score of 10 and an SD of 3. Given this statistical feature, we know that if two subtests differ by 3 or more scaled score points, the difference is significant. All IQ scores and

TABLE 7–1 IQ Categories with Their Corresponding IQ Scores and Percentile Distribution

IQ CATEGORIES		
FULL SCALE IQ SCORE	**CATEGORIES**	**NORMAL DISTRIBUTION PERCENTILE**
≥ 130	Very superior	2.2
120-129	Superior	6.7
110-119	High average	16.1
90-109	Average	50.0
80-89	Low average	16.1
70-79	Borderline	6.7
≤ 69	Extremely low	2.2

IQ, Intelligence quotient.

subtest scaled scores are adjusted for age. It is important to understand that IQ scores represent patients' ordinal position, their percentile ranking as it were, on the test relative to the normative sample. These scores do not represent a patient's innate intelligence, and there is no good evidence that they measure a genetically determined intelligence. They do, to a considerable degree, reflect the patient's current level of adaptive function.

At times it is difficult to sort out whether dysfunction in affect, behavior, or cognition can be primarily assessed with psychological instruments of psychiatric consultation or whether they require neuropsychological assessment. Requests for psychological assessment might be conveyed as follows:

Please conduct a psychological assessment on Ms. B, a 28-year-old, right-handed, single attorney to help determine "if Ms. B was really depressed and suicidal or just character-disordered."

When the emergency department physician found her to be mildly confused and disoriented, Ms. B was admitted to the medical service. By the next morning, her mental status had improved; however, she continued to complain of extreme back pain and made vague suicidal statements. A pain workup and psychiatric consultation were both ordered.

Ms. B got into frequent struggles with the nursing staff over the hospital's smoking rules. A review of the medical chart revealed that she had graduated from a prestigious university and law school and was employed at a large legal firm. She had developed severe back pain secondary to multiple equestrian injuries that occurred while riding competitively in college. She had received various diagnoses for her pain, and she had failed to respond to several medication trials, surgery, and one stay on an inpatient pain rehabilitation unit. Ms. B's current medications included diazepam 5 mg bid, amitriptyline 100 mg qhs, and oxycodone–acetaminophen (Percocet) one tablet qhs. The pain service consultant was unsure about the diagnosis. The psychiatric consultant found her to be guarded (with regard to her mood and the level of her suicidal ideation). She reported no history of depression or suicide attempts; later that same day, Ms. B completed a brief but fairly comprehensive psychological assessment.

The test battery for Ms. B consisted of several tests, including the WASI (which was given first); it was followed by the Rorschach inkblot test, four Thematic Apperception Test (TAT) cards, and the Personality Assessment Inventory (PAI). The WASI was selected for its brief administration time (20 to 30 minutes) and its ability to provide accurate IQ data (assessing cognitive function). The Rorschach was selected as the second test to be administered for two reasons: Given Ms. B's guardedness, projective test data seemed crucial for the personality assessment, and it was felt that the novelty of the Rorschach might help maintain Ms. B's involvement in the assessment. A self-report test of psychopathology was desired, but it seemed likely that Ms. B would neither complete one nor portray herself in an exceedingly favorable light. The PAI was selected for use because of its shorter length (344 items) and its ability to be scored with a short form of the test using only the first 160 items. Also, the PAI contains a number of treatment planning scales that can provide important information.

Ms. B's assessment was conducted in her semiprivate room. Although this was not an ideal situation, hospital evaluations are commonly performed in this fashion. Surprisingly, Ms. B completed all of the testing without complaint or fuss. The WASI data assessed the quality and consistency of her cognitive function. Her WASI scores were full scale IQ 102, VIQ 120, and PIQ 87. The WASI data can be thought of as providing an estimate of the patient's current best possible level of function. Her visual–spatial skills were weak relative to her verbal ability. In general, Ms. B's cognitive functioning was not as effective as one might have assumed, given her verbal abilities and her level of education. The VIQ > PIQ difference of an 18-point split could have represented either a long-standing learning disability (somewhat less likely given her strong high school, college, and law school performance) or cognitive disruption secondary to depression, pain, the effects of her current medications, or a combination thereof.

The Rorschach revealed Ms. B's implicit psychological function. The Rorschach depression index was positive and suggested either current depression or a propensity to depressive experiences. The suicide constellation was negative. Although her adaptive psychological resources were adequate, situational stress was overwhelming her ability to cope. Her affective experience was dominated by helplessness, painful internalized affect, and unmet dependency–nurturance needs. Together these findings suggested a possible depression resulting from situational factors. She was not psychotic, but her thinking was overpersonalized and idiosyncratic. The experience of anger also decreased her reasoning and judgment. She had an immature, self-centered personality style and a narcissistic character style. She did not process her feelings but instead tried to minimize them through intellectualization or externalize them (projection).

The PAI could be considered to provide a picture of her explicated psychological world. The PAI profile was valid. She reported minimal psychopathology. Her mean elevation on the 10 clinical scales was only 53 (T-score, well within the range of nonpatients), suggesting either that she was experiencing little overt distress or that she was reluctant to express emotional pain. Either way, she did not appear to others, including her caregivers, to

be psychologically impaired. She reported mild clinical depression (T-score = 71) and excessive concern about her physical function (T-score = 85). Further, on clinical interview her excessive physical complaints and concerns overshadowed her depressive symptoms. A grandiose sense of self, consistent with the pronounced signs of a narcissistic character style on the Rorschach, was also indicated by one of the PAI subscales. On the treatment consideration scales, she indicated minimal interest in psychologically oriented treatments, a perception of high levels of social stress, and minimal suicidal ideation (T-score = 54).

Impressions and recommendations: Overall the assessment strongly suggested the presence of a clinical depression. Depression was likely masked to some extent by both the patient's focus on her physical function (the back pain) and her inability or unwillingness to express her emotional pain. As a result, her depression was likely more significant and disruptive to her function than she was reporting. In addition, character issues (Axis II pathology) in the form of an immature self-centered view of the world and narcissistic character traits complicated Ms. B's treatment. Ms. B's function was greatly reduced because of both her depression and her situational stressors. These stressors affected both her emotional and intellectual function. Her ability to organize, plan, and initiate coping strategies was limited. As such, the advisability of her immediate return to full-time employment needed to be carefully reviewed. Her caregivers may have overestimated her level of function because of her strong verbal communication skills. On testing she did not appear to be actively suicidal (either on the self-report or projective tests). However, given her state of being emotionally overwhelmed and depressed and her reduced coping ability, Ms. B should be considered at an increased risk (over and above being depressed) for impulsive self-harm. Her safety should be monitored closely. Her psychotherapy, which will be challenging given her personality style, should first focus on practical efforts to improve her coping and function. Once her function stabilizes, the therapy focus might profitably expand to include her interpersonal style.

Tests of Personality, Psychopathology, and Psychological Function

Objective psychological tests, also called *self-report tests*, are designed to clarify and quantify a patient's personality function and psychopathology. Objective tests use a patient's response to a series of true/false or multiple-choice questions to broadly assess psychological function. These tests are called *objective* because their scoring involves little speculation. Objective tests provide excellent insight into how patients see themselves and how they want others to see and treat them. Self-report tests allow the patient to directly communicate their psychological difficulties to their caregivers.

The Minnesota Multiphasic Personality Inventory–2 (MMPI-2)[6] is a 567-item true/false, self-report test of psychological function. It was designed to provide an objective measure of abnormal behavior, basically to separate subjects into two groups (normal and abnormal) and then to further categorize the abnormal group into specific classes.[7] The MMPI-2 contains 10 clinical scales that assess major categories of psychopathology and 3 validity scales designed to assess test-taking attitudes. MMPI-2 validity scales are (L) lie, (F) infrequency, and (K) correction. The MMPI-2 clinical scales include (1) Hs—hypochondriasis, (2) D—depression, (3) Hy—conversion hysteria, (4) Pd—psychopathic deviate, (5) Mf—masculinity–femininity, (6) Pa—paranoia, (7) Pt—psychasthenia, (8) Sc—schizophrenia, (9) Ma—hypomania, and (10) Si—social introversion. More than 300 new or experiential scales have also been developed for the MMPI-2. MMPI raw scores are transformed into T-scores; a T-score greater than or equal to 65 indicates clinical levels of psychopathology. The MMPI-2 is interpreted by determining the highest two or three scales, called a code type. For example, a 2–4–7 code type indicates the presence of depression (scale 2), impulsivity (scale 4), and anxiety (scale 7), along with the likelihood of a personality disorder (PD).[7]

The Millon Clinical Multiaxial Inventory–III (MCMI-III) is a 175-item true/false, self-report questionnaire designed to identify both symptom disorders (Axis I conditions) and PDs.[8] The MCMI-III is composed of 3 modifier indices (validity scales), 10 basic personality scales, 3 severe personality scales, 6 clinical syndrome scales, and 3 severe clinical syndrome scales. One of the unique features of the MCMI-III is that it attempts to assess both Axis I and Axis II psychopathology simultaneously. The Axis II scales resemble but are not identical to the Axis II disorders given in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV). Given its relatively short length (175 items versus 567 for the MMPI-2), the MCMI-III has an advantage in the assessment of patients who are agitated, whose stamina is significantly impaired, or who are just suboptimally motivated.

The PAI[9] is one of the newest objective psychological tests available. The PAI uses 344 items and a 4-point response format (false, slightly true, mainly true, and very true) to make 22 nonoverlapping scales. These 22 scales include 4 validity scales, 11 clinical scales, 5 treatment scales, and 2 interpersonal scales. The PAI covers a wide range of Axis I and Axis II psychopathology and other variables related to interpersonal function and treatment planning (including suicidal ideation, resistance to treatment, and aggression). The PAI possesses outstanding psychometric features and is an ideal test for broadly assessing multiple domains of relevant psychological function.

A subject's response style can have an impact on the accuracy of his or her self-report. Validity scales are incorporated into all major objective tests to assess the degree to which a response style may have distorted the findings. The three main response styles are careless or random responding (which may indicate that someone is not reading or cannot understand the test), attempting to "look good" by denying pathology, and attempting to "look bad" by overreporting pathology (a cry for help or malingering).

Projective tests of psychological function differ from objective tests in that they are less structured and require more effort on the part of the patient to make sense of, and to respond to, the test stimuli. As a result, the patient has a greater degree of freedom to demonstrate his or her own unique personality characteristics. Projective tests are more like problem-solving tasks, and they provide us with insights into a patient's style of perceiving, organizing, and responding to external and internal stimuli. When data

from objective and projective tests are combined, they can provide a fairly complete picture or description of a patient's range of function.

The Rorschach inkblot test[10] consists of 10 cards that contain inkblots (five are black and white; two are black, red, and white; and three are various pastels), and the patient is asked to say what the inkblot might be. The test is administered in two phases. First, the patient is presented with the 10 inkblots one at a time and asked, "What might this be?" The patient's responses are recorded verbatim. In the second phase, the examiner reviews the patient's responses and inquires where on the card the response was seen (known as *location* in Rorschach language) and what about the blot made it look that way (known as the *determinants*). For example, a patient responds to Card V with "A flying bat." The practitioner asks, "Can you show me where you saw that?" The patient answers, "Here. I used the whole card." The practitioner asks, "What made it look like a bat?" The patient answers, "The color, the black made it look like a bat to me." This response would be coded as follows:

Wo FMa.FC'o A P1.0.

The examining psychologist reviews these codes rather than the verbal responses to evaluate the patient's performance. Rorschach "scoring" has been criticized for being subjective. However, over the last 20 years, Exner[11] has developed a Rorschach system (called the *Comprehensive System*) that has demonstrated acceptable levels of reliability. For example, inter-rater Kappas of .80 or better are required for all Rorschach variables reported in research studies. Rorschach data are particularly valuable for quantifying a patient's reality contact and the quality of his or her thinking.

The TAT is useful in revealing a patient's dominant motivations, emotions, and core personality conflicts.[12] The TAT consists of a series of 20 cards depicting people in various interpersonal interactions. The cards were intentionally drawn to be ambiguous. The TAT is administered by presenting 8 to 10 of these cards, one at a time, with the following instructions: "Make up a story about this picture. Like all good stories, it should have a beginning, a middle, and an ending. Tell me how the people feel and what they are thinking." Although there is no standard scoring method for the TAT (making it more of a clinical technique than a psychological test proper), when a sufficient number of cards are presented, meaningful information can be obtained. Psychologists typically assess TAT stories for emotional themes, level of emotional and cognitive integration, interpersonal relational style, and view of the world (e.g., whether it is seen as a helpful or hurtful place). This type of data can be particularly useful in predicting a patient's response to psychotherapy.

Psychologists sometimes use projective drawings (freehand drawings of human figures, families, houses, and trees) as a supplemental assessment procedure. These are clinical techniques rather than tests because there are no formal scoring methods. Despite their lack of psychometric grounding, projective drawings can sometimes be very revealing. For example, psychotic subjects may produce a human figure drawing that is transparent and shows internal organs. Still, it is important to remember that projective drawings are less reliable and less valid than the tests reviewed in this chapter.

NEUROPSYCHOLOGICAL ASSESSMENT

The request for neuropsychological testing might be framed as follows:

Please perform a neuropsychological evaluation on Mr. A, a 20-year-old, right-handed, white single male, to assess his current cognitive function, to establish a baseline profile, to aid in diagnosis, and to guide treatment. Help figuring out whether his current problems are a result of psychiatric or neurologic conditions would be greatly appreciated.

Mr. A was recently discharged from a psychiatric unit, where he was being treated for schizophrenic symptoms that included hallucinations (in multiple perceptual systems) and dysregulated behavior. He was on the medical service for treatment of diabetic ketoacidosis. Despite a long history of psychiatric and emotional problems (including a diagnosis of attention-deficit/hyperactivity disorder at the age of 9 and visual hallucinations that first developed at the age of 16), he has completed some college courses. During his mid- to late teens, he was treated with a variety of antidepressants and antianxiety agents. Antipsychotics were started in the past year. Two years before this admission, he sustained a closed head injury (CHI) in a motor vehicle accident. A question has arisen as to whether he has residual cognitive deficits resulting from the CHI. Although he denied use of substances within the past 4 months, he had regularly smoked marijuana, taken hallucinogenic mushrooms, and used inhalants.

Mr. A's evaluation included a review of his recent hospital discharge summary, an interview with Mr. A and his mother, and a discussion with his outpatient treaters. The following tests were also administered: WASI, Wechsler Memory Scale–IV (WMS-IV), Trails A & B, Boston Naming Test, Hooper Visual Organization Test, Rey-Osterrieth Complex Figure, Stroop Color Word Test, Digit Vigilance, and PAI. Mr. A cooperated fully with the evaluation. Overall, his performance appeared to be a valid reflection of his current behavior and level of function. All the psychological tests were valid and interpretively useful. His WASI IQ scores were as follows: Full Scale IQ 76 (borderline range fifth percentile), VIQ 83 (low average range, thirteenth percentile), and PIQ 68 (second percentile). Age-adjusted scaled scores earned during this assessment were as follows:

VERBAL	SCALED SCORE	PERFORMANCE	SCALED SCORE
Vocabulary	8	Block design	5
Similarities	10	Matrix reasoning	6

Further analysis of Mr. A's WASI performance indicated a likely substantial decline from his premorbid level of function. Even if his estimated premorbid IQ had been just average (100), his current measured IQ has fallen 1.5 SDs. As such, the quality of his current function had also likely dropped substantially. Furthermore, his WASI profile revealed a significant 15-point difference between his VIQ and PIQ, favoring the former. A difference of this magnitude was unexpected and indicated that his nonverbal abilities suffered more of a decline than his verbal/language-based abilities. Because nonverbal intellectual abilities are typically associated with right-hemisphere function, these findings pointed to a relative inefficiency in his right hemisphere.

Memory Function: His performance on the WMS-IV was generally consistent with the WASI findings. His logical memory score (recalling a just-read paragraph) was at the fifty-seventh percentile on immediate recall (better than would have been expected given his current VIQ), and it fell to the eighteenth percentile after a 30-minute delay (more consistent with his measured IQ). However, the quality of his memories was not as good as the percentile scores suggest. On this test credit was given for any detail of a story recalled, and no credit was lost if the details were recalled out of order or if errors were introduced into the stories. Mr. A's recall of these two stories was disjointed, and some facts were misrepresented. His functional verbal memory was likely less adequate than his test scores suggested. His visual memory (ability to recall designs) fell at the twelfth percentile on immediate recall and at the eighteenth percentile after a 30-minute delay. Although weaker than his verbal memory scores, his recall of visual material was consistent with his current measured (nonverbal) PIQ. However, the quality of his visual memories was also quite poor. His pattern of memory scores again pointed to possible greater right-hemisphere dysfunction.

Language: On the Boston Naming Test, he was able to correctly name 52 items (out of 60) spontaneously. This score was just slightly below the level expected for his age. However, when provided with a phonemic cue, he was able to improve his score to a 58 (out of 60). This degree of improvement suggested some mild word retrieval problems. He was able to comprehend complex instructions, suggesting that his receptive language skills were intact. His reading and writing abilities were not formally tested.

Visual–Spatial: Mr. A performed weakly, but inconsistently, on tests of visual–spatial function. His performance on the WASI Block Design subtest was weak (scaled score of 5), and he frequently broke the "gestalt" of the design he was trying to copy. On the Hooper Visual Organization Test, he obtained a score of 24, which was on the border of normal and impaired. However, his copy of the Rey Complex Figure was basically accurate. His inconsistent performance across these tests (all thought to tap basically the same function) suggested that fluctuations in his level of attention and motivation accounted for some of his poor performance.

Executive Function: On tests that tapped his ability to use abstract reasoning and to plan and change his behavior on the basis of external feedback, Mr. A again performed inconsistently. On the Trail Making Test Part B, a test that required him to draw a line that alternately connected numbers and letters in increasing order, he made three impulsive errors suggesting problems with inhibition of his behavior. Yet on the Stroop Color Word Test, he scored at the expected level. Again, it is likely that alterations in his attention and motivation contributed to his inconsistent performance on these tasks that were thought to tap into frontal lobe function.

Emotional Function: The patient's PAI profile revealed elevations on the depression and schizophrenia scales. All three of the depression subscales (cognitive, affective, and physiological) were elevated (indicating a strong likelihood of major depression), as were all three schizophrenia subscales (psychotic experiences, social isolation, and thought disorder).

Mr. A likely suffers from both a mood disorder and a psychotic condition. However, it is not clear whether these are independent conditions. Mr. A also reported having a stimulus-seeking personality style and little motivation for psychological treatment. Both of these features will complicate his treatment.

Impressions and Recommendations: The neuropsychological evaluation revealed three principal findings: (1) Mr. A's overall functional capacity (efficiency of his function) was greatly reduced from his premorbid level. (2) There were some consistent findings that point to a greater relative decline in right-hemisphere function. (3) However, most of the areas tested revealed inconsistent findings that likely reflect minute-to-minute fluctuations in his attention, concentration, and level of motivation. The overall profile appears most consistent with the types of cognitive deficits usually associated with schizophrenia and also point to a possible independent (but mild) problem that affects his right-hemisphere function. Perhaps this mild right-hemisphere impairment is a residual effect resulting from his CHI. Still, the majority of difficulties seen on this testing (and likely in his daily function) appear related to his psychiatric condition (schizophrenia).

Neuropsychological function assessment is a relatively recent development within applied psychology. In fact, it is only in the last 2 or 3 decades that neuropsychology has become established as a clinical specialty. Neuropsychologists assess brain–behavior relationships using standardized psychological instruments. The main goal of a neuropsychological evaluation is to relate a patient's test performance to both the status of his or her central nervous system and real-world functional capacity. In addition to assessing general intelligence, a complete neuropsychological assessment evaluates five major cognitive abilities: attention and concentration, language (expressive and receptive), memory (immediate and delayed), visual–spatial intelligence, and executive function and abstract thinking. This assessment is similar to the mental status examination used in neurology; it differs mainly in that it provides a deeper, more comprehensive, and better-quantified assessment. The application of a battery of tests covering these major cognitive areas allows for a broad assessment of the patient's strengths and deficits and provides some indication as to how these strengths and deficits will affect real-world adaptation.

Types of Neuropsychological Assessment

The Halstead-Reitan (H-R) Battery is the oldest standardized neuropsychological assessment battery currently in use. The H-R Battery is an elaborate and time-intensive set of neuropsychological tests. Analysis of an H-R Battery is almost exclusively quantitative. The H-R profile is interpreted at four levels: an impairment index (a composite score reflecting the subject's overall performance), lateralizing signs, localizing signs, and a pattern analysis for inferences of causal factors.[13] The Boston process approach to neuropsychological assessment is a newer and more flexible style of neuropsychological assessment.[14] The Boston process approach starts with a small core test battery (usually containing one of the Wechsler IQ tests); subsequently, hypotheses regarding cognitive deficits are developed on

the basis of the patient's performance. Other instruments are administered to test and refine these hypotheses about the patient's cognitive deficits. The Boston approach focuses on both the quantitative and qualitative aspects of a patient's performance. By *qualitative*, we mean the manner or style of the patient's performance, not just the accuracy. In fact, reviewing how a patient failed an item can be more revealing than knowing which items were missed. In this way the Boston approach reflects an integration of features from behavioral neurology and psychometric assessment.

Many neuropsychologists use a composite battery of tests in their day-to-day clinical work. A composite battery is usually composed of an IQ test (one of the Wechsler scales) and a number of selected tests matched to the patient and to the disorder being evaluated. Here we review some of the specific neuropsychological tests that might be used to compose a battery or to assess specific cognitive functions. For a description of these tests, see Spreen and Strauss.[15]

Attention and concentration are central to most complex cognitive processes; therefore it is important to adequately measure these functions in a neuropsychological test battery. In fact, some patients who complain of memory disorders turn out to have impaired attention and concentration rather than pure memory dysfunction. Tests of attention and concentration include Trail Making Test Parts A & B and the mental control subtests of the WMS-IV and the WAIS-IV digit span, digit symbol, and arithmetic subtests. It is important to assess language from a number of perspectives, including simple word recognition, reading comprehension, verbal fluency, object-naming ability, and writing. Frequently used measures of language function are the WAIS Verbal IQ subtests, the Boston Naming Test, the Verbal Fluency Test, Reading (word recognition and reading comprehension), and Written Expression (a writing sample). The accurate measurement of reading ability (often using the North American Adult Reading Test) can provide an estimation of premorbid intelligence and allow the examiner to gauge the degree of overall cognitive decline. The assessment of memory is extremely important in a neuropsychological battery because impaired memory is both a major reason for referral and a strong predictor of poor treatment outcome. An evaluation of memory should cover both visual and auditory memory systems, measure immediate and delayed recall, assess the pattern and rate of new learning, and explore for differences between recognition (memory with a retrieval cue) and unaided recall. The WMS-IV[4] is one of the primary memory inventories. Like the Wechsler IQ scales, this memory test is well standardized. The WMS-IV produces major memory scores that have a mean of 100 with an SD of 15. The memory subscales all have a mean of 10 and an SD of 3. These statistical properties allow for a detailed evaluation of memory function. In fact, the most recent revision of the Wechsler IQ and Memory Scales was jointly normed, allowing for more meaningful comparisons between IQ and memory. The Three Shapes and Three Words Memory Test[16] is a less demanding test of verbal (written) and nonverbal immediate and delayed memory. Unfortunately, it is not well normed. Visual–spatial tests (usually with a motor component—drawing) help evaluate right-hemisphere functions in most (right-handed) adults. Because these deficits are nonverbal (sometimes called *silent*), they are often overlooked in briefer nonquantitative cognitive evaluations. Tests that tap visual–spatial function include the Rey-Osterrieth Complex Figure, the Hooper Visual Integration Tests, the Draw-a-Clock Test, and the Performance IQ subtests of the WAIS. *Executive function* refers to higher-order cognitive processes, such as judgment, planning, logical reasoning, and the modification of behavior on the basis of external feedback. All these functions are thought to be associated with the frontal and prefrontal lobes and are extremely important for effective real-world function. One of the most frequently used tests of executive function is the Wisconsin Card Sorting Test (WCST), which requires the patient to match 128 response cards to one of four stimulus cards using three possible dimensions (color, form, and number). While the patient matches these cards, the only feedback he or she receives is the response "right" or "wrong." After 10 consecutive correct matches, the matching rule shifts to a new dimension (unannounced) and the patient must discover the new rule. One of the primary scores from the WCST is the number of perseverative errors committed (a perseverative error is scored when the patient continues to sort to a dimension despite clear feedback that the strategy is incorrect). Other tests of executive functioning include the Booklet Format Category Test, the Stroop Color Word Test, and the similarities and comprehension subtests of the WAIS (tapping abstract reasoning).

Typically, neuropsychologists are interested in both the absolute magnitude of patients' performance (how well they performed in comparison with the test's norms) and any differences between the two body sides (the left–right discrepancies). Tests of motor function include the Finger Tapping Test (the average number of taps per 10 seconds with the index finger of each hand) and a test of grip strength (using the hand dynamometer). Sensory tests include Finger Localization Tests (naming and localizing fingers on the subject's and examiner's hand) and Two-Point Discrimination and Simultaneous Extinction Test (measuring two-point discrimination threshold and the extinction or suppression of sensory information by simultaneous bilateral activation).

It is becoming more evident that many psychiatric conditions are associated with cognitive impairment. Therefore a complete neuropsychological assessment should also include a self-report test of psychopathology, such as the MMPI-2. Including such a test in the battery allows the neuropsychologist to assess the possible contribution of psychopathology to the cognitive profile. One of the main advantages of neuropsychological assessment is the ability to compare a patient's performance to that of a normative sample. This allows the physician to determine how well the patient performed relative to a comparison group. However, the usefulness of neuropsychological test data can be limited by the quality of such norms. Unfortunately, the quality of norms varies greatly from test to test. Tests such as the Wechsler IQ and Memory Scales have excellent norms, whereas other frequently used tests (e.g., Boston Naming Test) have more limited norms. With regard to older adults, it is most helpful to have age- and education-adjusted norms because both these variables have a substantial mediating effect on the normal (age-appropriate) decline of cognitive function.

A number of brief neuropsychological assessment tools are used in clinical practice. Brief assessment tools are not a substitute for a comprehensive neuropsychological assessment, but they can be useful as screening instruments or when patients cannot tolerate a complete test battery. One such brief test is the Dementia Rating Scale–2 (DRS-2).[17] This test provides a brief but reasonable assessment of the major areas of cognitive function (attention, memory, language, reasoning, and construction). The test employs a screening methodology in evaluating these cognitive domains; the patient is first presented with a moderately difficult item, and if that item is passed, the rest of the items in that domain are skipped (with the examiner moving on to the next domain). However, if the screening item is failed, then a series of easier items are given to more fully evaluate the specific cognitive ability.

The DRS-2 is a useful tool for assessing patients 55 and older who are suspected of having dementia of the Alzheimer's type (DAT). It takes between 10 and 20 minutes to administer, and it provides six scores. The total score and the scores from the Memory and Initiation/Perseveration subscales have been useful in the identification of patients with DAT. The DRS was designed to have a deep floor. This means that the test contains many items that tap low levels of function and allow the test to track patients as their function declines. This quality makes the DRS a useful tool for monitoring patients with DAT along the course of their illness.

The differentiation of depression from dementia in older adults is the most common neuropsychological referral question. Depression in older adults is often accompanied by mild cognitive deficits, making the diagnostic picture somewhat confused with that of early dementia. By evaluating the profile of deficits obtained across a battery of tests, a neuropsychologist can help distinguish between these two illnesses. For example, depressed patients tend to have problems with attention, concentration, and memory (new learning and retrieval), whereas patients with early dementia have problems with delayed recall memory (encoding) and word-finding or naming problems. Both groups of patients can display problems with frontal lobe/executive function. However, the function of the depressed patient often improves with cues or suggestions about strategies; this typically does not help patients with dementia. Although this general pattern does not always hold true, it is this type of contrasting performance that allows neuropsychological assessment to aid differential diagnosis.

Whether a patient is capable of living independently is a complex and often emotionally charged question. Neuropsychological test data can provide one piece of the information needed to make a reasonable medical decision in this area. In particular, neuropsychological test data regarding memory function (both new learning rate and delayed recall) and executive function (judgment and planning) have been shown to predict failure and success in independent living. However, any neuropsychological test data should be thoughtfully combined with information from an occupational therapy evaluation, assessment of the patient's psychiatric status, and input from the family (when available) before rendering any judgment about a patient's capacity for independent living.

Neuropsychological assessment has a role in the diagnosis and treatment of adults and children with attention-deficit disorder (ADD). However, as in the question of independent living status, it provides just a piece of the data necessary for making this diagnosis. The evaluation of ADD should include a detailed review of academic performance, including report cards and school records. When possible, living parents should also be interviewed for their recollections of the patient's childhood behavior. The neuropsychological evaluation should focus on measuring intelligence, academic achievement (expecting to see normal or better IQ with reduced academic achievement), and multiple measures of attention and concentration (with tests of passive, active [shifting], and sustained attention). Although the neuropsychological testing profile might aid in the diagnosis of ADD in adulthood, the diagnosis is usually based on historic data. The neuropsychological test data or profile is often more useful in helping the patient, family, and treater understand the impact of ADD on the patient's current cognitive abilities, as well as ruling out co-morbid disorders (e.g., learning disabilities, which are very common in ADD).

Neuropsychological assessments can often aid in treatment planning for patients with moderate to severe psychiatric illness. Although this aspect of neuropsychological testing is somewhat underutilized at present, in the years to come this may prove to be the most beneficial use of these tests. Neuropsychological assessment benefits treatment planning by providing objective data (a test profile) regarding the patient's cognitive skills (deficits and strengths). The availability of such data can help clinicians and family members develop more realistic expectations about the patient's functional capacity.[18] This can be particularly helpful for patients suffering from severe disorders, such as schizophrenia. The current literature indicates that neuropsychological deficits are more predictive of long-term outcome in schizophrenic patients than are either positive or negative symptoms.

OBTAINING AND UNDERSTANDING TEST REPORTS

Referring a patient for an assessment consultation should be like referring a patient to any professional colleague. Psychological and neuropsychological testing cannot be done "blind." The psychologist will want to hear relevant information about the case and will explore with the referring practitioner what questions need to be answered (this is called the referral question). On the basis of this case discussion, the psychologist will select an appropriate battery of tests designed to obtain the desired information. It is helpful if the referrer prepares the patient for the testing by reviewing with him or her why the consultation is desired and telling him or her that it will likely take 3 or more hours to complete. The referrer should expect the psychologist to evaluate the patient in a timely manner and provide verbal feedback, a "wet read," quickly. The written report should follow shortly thereafter (inpatient reports should be produced within 48 hours and outpatient reports should be available within 2 weeks).

The psychological assessment report is the written statement of the psychologist's findings. It should be understandable and should plainly state and answer the referral

question(s). The report should contain relevant background information, a list of the tests used in the consultation, a statement about the validity of the results and the confidence the psychologist has in the findings, a detailed integrated description of the patient, and clear recommendations. It should contain raw data (e.g., IQ scores) as appropriate to allow for meaningful follow-up testing. To a considerable degree, the quality of a report (and the assessment consultation) can be judged from the recommendations provided. A good assessment report should contain a number of useful recommendations. The referrer should never read just the summary of a test report; this leads to the loss of important information, because the whole report is really a summary of a very complex consultation process.

In contrast to the written report from a personality assessment, the written neuropsychological testing report tends to be less integrated. The test findings are provided and reviewed for each major area of cognitive function (intelligence, attention, memory, language, reasoning, and construction). These reports typically contain substantial amounts of raw data to allow for meaningful retesting comparison. However, the neuropsychological assessment report should provide a brief summary that reviews and integrates the major findings and also contains useful and meaningful recommendations. As with all professional consultations, the examining psychologist should be willing to meet with the referrer and/or the patient to review the findings.

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Diagnostic Rating Scales and Laboratory Tests

8

Joshua L. Roffman, M.D.
Benjamin C. Silverman, M.D.
Theodore A. Stern, M.D.

Although the interview and the mental status examination compose the primary diagnostic tools in psychiatry, the use of standardized rating scales and laboratory tests provides important adjunctive data. In addition to ruling out medical and neurological explanations for psychiatric symptoms, the quantitative instruments described in this chapter play important clinical roles in clarifying disease severity, identifying patients who meet subsyndromal criteria within a particular diagnosis, assessing response to treatment, and monitoring for treatment-related side effects. Rating scales are similarly applied in research studies to enroll patients and are often developed initially for this purpose.

DIAGNOSTIC RATING SCALES

Diagnostic rating scales (or rating instruments) translate clinical observations or patient self-assessments into objective measures. Clinically, rating scales can screen for individuals who need treatment, evaluate the accuracy of a diagnosis, determine the severity of symptoms, or gauge the effectiveness of a given intervention. In clinical research, rating scales ensure the diagnostic homogeneity of subject populations, essentially helping to define phenotypic categories, and assess outcomes of study interventions. Ideal rating instruments in both settings should demonstrate good reliability (i.e., the ability to relate consistent and reproducible information) and validity (i.e., the ability to measure what they intend to measure). Although clinician-administered instruments are generally more reliable and valid, self-completed patient instruments are less time-consuming and more readily utilized. In either case, careful consideration should be given to the clinical meanings and consequences of their results, as well as to cultural factors that could affect performance. The following sections summarize commonly used rating scales for general psychiatric diagnosis as well as specific disorders and treatment-related conditions.

GENERAL PSYCHIATRIC DIAGNOSTIC INSTRUMENTS

The Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), (SCID)[1,2] is the most commonly used clinician-administered diagnostic instrument in psychiatry. An introductory segment relies on open-ended questions to elucidate demographic, medical, and psychiatric histories, as well as medication use. The remainder employs standardized questions in nine modules that reflect DSM-IV, criteria for most major Axis I disorders: mood episodes, psychotic symptoms, psychotic disorders, mood disorders, substance use, anxiety, somatoform disorders, eating disorders, and adjustment disorders. Based on patient responses, the rater determines the likelihood that criteria for a DSM-IV diagnosis will be met. The SCID is reliable but time-consuming; for this reason, it is used primarily in research. The derivative SCID-clinical version (SCID-CV) provides a simplified format more suitable for clinical use. A similar, but more compact and easily administered, structured diagnostic interview is the Mini International Neuropsychiatric Interview (MINI).[3] Also administered by the clinician, the MINI uses "yes/no" questions that cover the major Axis I disorders, as well as antisocial personality disorder and suicide risk. Following administration of a diagnostic instrument, the seven-point Clinical Global Improvement (CGI) scale may be used to determine both severity of illness (CGI-severity [S]) and degree of improvement following treatment (CGI-improvement [I]).[4] On the CGI-S, a score of 1 indicates normal, whereas a score of 7 indicates severe illness; a 1 on the CGI-I corresponds to a high degree of improvement, whereas a 7 means the patient is doing much worse.

Mood Disorders

Considered the "gold standard" for evaluating the severity of depression in clinical studies, the Hamilton Rating Scale for Depression (HAM-D)[5] may be used to monitor the patient's progress during treatment, after the diagnosis of major depression has been established. This clinician-administered scale exists in several versions, ranging from 6 to 31 items; answers by patients are scored from 0 to 2 or 0 to 4 and tallied to obtain an overall score. Standard scoring for the 17-item HAM-D-17 instrument, frequently used in research studies, is listed in Table 8–1. A decrease of 50% or more in the HAM-D score is often considered to indicate a positive treatment response, whereas a score of 7 or less is considered equivalent to a remission. The HAM-D was developed before publication of the DSM-III and does not evaluate more recent criteria for depression (e.g., anhedonia); it also favors somatic signs and symptoms and can miss atypical symptoms, such as overeating and oversleeping.

TABLE 8–1 Scoring the HAM-D

SCORE	INTERPRETATION
0–7	Not depressed
7–15	Mildly depressed
15–25	Moderately depressed
>25	Severely depressed

HAM-D, Hamilton Rating Scale for Depression.

The Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item clinician-administered scale, designed to be particularly sensitive to antidepressant treatment effects in patients with major depression.[6] The HAM-D and the MADRS are well correlated with each other, with the MADRS sampling a smaller symptom set, but including anhedonia and concentration difficulties not collected in the HAM-D. The MADRS provides a short but reliable scale, optimized for rapid clinical use.

The Beck Depression Inventory (BDI)[7] is a widely used 21-item patient self-rating scale that can be completed in a few minutes. Scores on the BDI can be used both as a diagnostic screen and as a measure of improvement over time. For each item, patients choose from among four answers, each corresponding to a severity rating from 0 to 3. The correlation between total scores and the severity of depression is provided in Table 8–2. Although easy to administer and to score, the BDI also excludes atypical neurovegetative symptoms.

Fewer rating scales have been designed to assess mania. Two instruments for assessing manic symptoms, the Manic State Rating Scale (MSRS)[8] and Young Mania Rating Scale (Y-MRS)[9] have been designed for use on inpatient units; they demonstrate high reliability and validity. Whereas the 26-item MSRS gives extra weight to grandiosity and to paranoid–destructive symptoms, the Y-MRS examines primarily symptoms related to irritability, speech, thought content, and aggressive behavior. Neither scale has been as extensively evaluated for reliability and validity as have its counterparts geared toward depression. Newer scales, such as the Bipolar Depression Rating Scale (BDRS), have been designed to capture episodes of bipolar depression, focusing more on mixed symptoms than the above noted studies designed for unipolar depression.[10]

Psychotic Disorders and Related Symptoms

Instruments for assessing psychotic symptoms are nearly always administered by clinicians. Two of the broader and more frequently used instruments are the Brief Psychiatric Rating Scale (BPRS)[11] and Positive and Negative Syndrome Scale (PANSS).[12] The BPRS was designed to address symptoms common to schizophrenia and other psychotic disorders, as well as severe mood disorders with psychotic features. Items assessed include hallucinations, delusions, and disorganization, as well as hostility, anxiety, and depression. The test is relatively easy to administer and takes about 20 to 30 minutes. The total score, often used to gauge the efficacy of treatment, provides a global assessment and therefore lacks the ability to track subsyndromal items (e.g., positive versus negative symptoms). Alternatively, the PANSS includes separate scales for positive and negative symptoms, as well as a scale for general psychopathology. The PANSS requires more time to administer (30 to 40 minutes); related versions for children and adolescents are available.

TABLE 8–2 Scoring the BDI

SCORE	INTERPRETATION
0–7	Normal
7–15	Mild depression
15–25	Moderate depression
>25	Severe depression

BDI, Beck Depression Inventory.

More focused attention to positive and negative symptoms characterize the Scale for the Assessment of Positive Symptoms (SAPS)[13] and the Scale for the Assessment of Negative Symptoms (SANS),[14] respectively. The 30-item SAPS is organized into domains that include hallucinations, delusions, bizarre behavior, and formal thought disorder; the 20-item SANS covers affective flattening and blunting, alogia, avolition-apathy, anhedonia-antisociality, and attentional impairment. The scales are particularly useful to document specific target symptoms and measure their response to treatment, but their proper administration requires more training than do the global scales.

The proclivity of neuroleptics to induce motoric side effects has driven the creation of standardized rating scales to assess these treatment-related conditions. The Abnormal Involuntary Movement Scale (AIMS)[4] is the most widely used scale to rate tardive dyskinesia. Ten items evaluate orofacial movements, limb–truncal dyskinesias, and global severity on a 5-point scale; the remaining two items rule out contributions of dental problems or dentures. The Barnes Akathisia Rating Scale[15] evaluates both objective measures of akathisia, as well as subjective distress related to restlessness. Both scales are administered easily and rapidly and may be used serially to document the effects of chronic neuroleptic use or changes in treatment.

Anxiety Disorders

A variety of rating scales are available to assess anxiety symptoms as well as specific anxiety disorders (e.g., panic disorder, social phobia, obsessive–compulsive disorder [OCD], posttraumatic stress disorder [PTSD], and generalized anxiety disorder [GAD]). Two of the more frequently used scales, both clinically and for research purposes, are described here: the Hamilton Anxiety Rating Scale (HAM-A)[16] and Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[17,18] The HAM-A provides an overall measure of anxiety, with particular focus on somatic and cognitive symptoms; worry, which is a hallmark of GAD, receives less attention. The clinician-administered scale consists of 14 items and, when scored, does not distinguish specific symptoms of a specific anxiety disorder. A briefer 6-item version, the Clinical Anxiety Scale, is also available. The most widely used scale for assessing severity of OCD symptoms, the Y-BOCS, is also clinician-administered and yields global as well as obsessive and compulsive subscale scores. Newer self-report and computer-administered versions have compared favorably to the clinician-based gold standard. The Y-BOCS has proven useful both in initial assessments and as a longitudinal measure.

Attention Disorders

Rating scales for attention disorders in children are numerous and include clinician-administered instruments, along with self-reports and scales completed by teachers, parents, and other caregivers.[19] Current (DSM-IV) diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD) in children and adolescents require impairment across multiple settings, necessitating a multi-informant assessment. The Conners Rating Scales are the most popular and well researched of the DSM-IV–based rating scales and exist in several versions, including parent and teacher questionnaires, an adolescent self-report scale, and both full and abbreviated length scales.[20] The full scale is limited in use by its length (20-30 minutes to administer), but it provides a large normative base and well tested reliability. Completed by parents or teachers, the ADHD Rating Scale-IV (ADHD RS-IV) derives directly from DSM-IV symptom criteria and provides a faster (5-10 minutes), reliable screening that can help to identify children in need of additional evaluation and monitor treatment effects in children treated for ADHD.[21] The Adult ADHD Self-Report Scale (ASRS) is an 18-item self-rating scale focusing on difficulties with concentration, organization, and psychomotor restlessness.[22] The checklist takes about 5 minutes to complete and can alert the treating clinician of the need for a more in-depth interview and assessment. A 6-item screening tool, taken out of the full ASRS, provides a rapid (less than 2 minutes) method for screening general clinic populations.

Substance Abuse Disorders

The CAGE Questionnaire (Table 8–3)[23] is a brief, clinician-administered tool used to screen for alcohol problems in many clinical settings. CAGE is an acronym for the four "yes/no" items in the test, which requires less than 1 minute to administer. "Yes" answers to two or more questions indicate a clinically significant alcohol problem (sensitivity has been measured at 0.78 to 0.81, specificity at 0.76 to 0.96), and positive screening suggests the need for further evaluation. The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire designed to detect problem drinkers at the less severe end of the spectrum, prior to the development of alcohol dependence and associated medical illnesses and major life problems from drinking.[24] The AUDIT can quickly screen for hazardous alcohol consumption (sensitivity 0.92 and specificity 0.94) in outpatient settings and permit early intervention and treatment for alcohol-related problems, often before the brief CAGE questions would be positive. A widely used scale to assess past or present clinically significant drug-related diagnoses, the Drug Abuse Screening Test (DAST)[25] is a 28- or 20-item self-administered instrument that takes several minutes to complete. If the subject answers "yes" to five or more questions, a drug abuse disorder is likely. The instrument includes consequences related to drug abuse (without being specific about the drug); it is most useful in settings where drug-related problems are not the patient's chief complaint.

TABLE 8–3 The CAGE Questionnaire

C	Have you ever felt you should **C**ut down on your drinking?
A	Have people **A**nnoyed you by criticizing your drinking?
G	Have you ever felt bad or **G**uilty about your drinking?
E	Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye opener)?

Cognitive Disorders

Cognitive scales are useful for screening out organic causes for psychopathological conditions and can help the clinician determine whether more formal neuropsychological, laboratory, or neuroimaging work-ups are warranted. It is important to consider the patient's intelligence, level of education, and literacy before interpreting results. The Folstein Mini-Mental State Examination (MMSE) (Table 8–4)[26] is used ubiquitously in diagnostic interviews as well as to follow cognitive decline over time in neurodegenerative disorders. The MMSE is administered by the clinician. It includes items that test orientation to place (state, county, town, hospital, and floor) and time (year, season, month, day, and date), registration and recall of three words, attention and concentration (serial 7s or spelling the word *world* backward), language (naming two items, repeating a phrase, understanding a sentence, following a three-step command), and visual construction (copying a design). The total score ranges from 0 to 30, with a score of 24 or lower indicating possible dementia. Although highly reliable and valid, the MMSE demonstrates less sensitivity early in the course of Alzheimer's disease and other dementing disorders, and pays little attention to executive function. In clinical practice, the MMSE is often supplemented by clock drawing and Luria maneuvers to more fully assess frontal function.

The clock drawing test is a simple, bedside assessment of general cognitive dysfunction.[27] When asked to draw a clock face with the hands set to a specified time (e.g., 10 minutes to 2), the patient must demonstrate several cognitive processes, including auditory comprehension of the instructions, access to the semantic representation of a clock,

TABLE 8–4 Scoring the MMSE

5 points	Orientation to state, country, town, hospital, floor
5 points	Orientation to year, season, month, day, date
3 points	Registration of three words
3 points	Recall of three words after 5 minutes
5 points	Serial 7s or spelling *world* backward
2 points	Naming two items
1 points	Understanding a sentence
1 points	Writing a sentence
1 points	Repeating "No *if's*, *and's*, or *but's*"
3 points	Following a three-step command
1 points	Copying a design
30 points	Total

Adapted from Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician, *J Psychiatr Res* 12:189–198, 1975.

planning ability, and visual–spatial and visual–motor skills, to successfully complete the task. Although performance can be assessed informally, several structured scoring measures have been described in the literature.[27–29]

Earlier detection of neurodegenerative disorders can be achieved with the Mattis Dementia Rating Scale (DRS).[30] Administered by a trained clinician, the DRS consists of questions in five domains: attention, initiation and perseveration, construction, conceptualization, and memory. Subscale items are presented hierarchically, with the most difficult items presented first; if the subject can perform these correctly, many of the remaining items in the section are skipped and scored as correct. The total score ranges from 0 to 144 points. In addition to early detection, the DRS can be used in some cases to differentiate dementia that results from different neuropathological conditions, including Alzheimer's disease, Huntington's disease, Parkinson's disease, and progressive supranuclear palsy. We refer the reader to Chapter 11 in this text for additional details on the work-up, assessment, and quantification of dementia.

LABORATORY TESTS

Although primary diagnoses in psychiatry are based on clinical phenomenology, physical examination and laboratory studies are often essential to rule out organic causes in the differential diagnosis for psychiatric symptoms.[31,32] Consideration should be given to dysfunction in multiple organ systems, toxins, malnutrition, infections, vascular abnormalities, neoplasm, and other intracranial problems (Table 8–5 organizes many of these using the mnemonic VICTIMS DIE). Certain presentations are especially suggestive of an organic cause, including onset after the age of 40 years, history of chronic medical illness, or a precipitous course. Laboratory tests are also important for following serum levels of certain psychiatric medications and for surveillance for treatment-related side effects. The following sections describe routine screening tests as well as specific serum, urine, cerebrospinal fluid (CSF), and other studies that are considered in the determination of the differential diagnosis and in treatment monitoring. The use of electroencephalography and neuroimaging studies is also described later in this chapter vis-à-vis diagnosis of neuropsychiatric conditions.

Routine Screening

The decision to order a screening test should take into account its ease of administration, the likelihood of an abnormal result, and the clinical implications of abnormal results (including management). Although no clear consensus exists about which tests to order in a routine screening battery for new-onset psychiatric symptoms, in practice routine screening tests include the complete blood cell (CBC) count; serum chemistries including electrolytes, glucose, calcium, magnesium, phosphate, and tests of renal function; erythrocyte sedimentation rate; and levels of vitamin B_{12}, folate, thyroid-stimulating hormone, and rapid plasma reagin (RPR). Often urine and serum toxicology screens, liver function tests (LFTs), and urinalysis are added as well.

TABLE 8–5 Organic Causes for Psychiatric Symptoms, Recalled by the Mnemonic VICTIMS DIE

Vascular	Multi-infarct dementia
	Other stroke syndromes
	Hypertensive encephalopathy
	Vasculitis
Infectious	Urinary tract infection and urosepsis
	Acquired immunodeficiency syndrome
	Brain abscess
	Meningitis
	Encephalitis
	Neurosyphilis
	Tuberculosis
	Prion disease
Cancer	Central nervous system tumors (primary or metastatic)
	Endocrine tumors
	Pancreatic cancer
	Paraneoplastic syndromes
Trauma	Intracranial hemorrhage
	Traumatic brain injury
Intoxication/withdrawal	Alcohol or other drugs
	Environmental toxins
	Psychiatric or other medications (side effects or toxic levels)
Metabolic/nutritional	Hypoxemia
	Hyper/hyponatremia
	Hypoglycemia
	Ketoacidosis
	Uremic encephalopathy
	Hyper/hypothyroidism
	Parathyroid dysfunction
	Adrenal hypoplasia (Cushing's syndrome)
	Hepatic failure
	Wilson's disease
	Acute intermittent porphyria
	Pheochromocytoma
	Vitamin B_{12} deficiency
	Thiamine deficiency (Wernicke–Korsakoff syndrome)
	Niacin deficiency (pellagra)
Structural	Normal pressure hydrocephalus
Degenerative	Alzheimer's disease
	Parkinson's disease
	Huntington's disease
	Pick's disease
Immune (autoimmune)	Systemic lupus erythematosus
	Rheumatoid arthritis
	Sjögren's syndrome
Epilepsy	Partial complex seizures/ temporal lobe epilepsy
	Postictal or intraictal states

Psychosis and Delirium

Evaluation of new-onset psychosis or delirium must include a full medical and neurological work-up; potential causes for mental status changes include central nervous system (CNS) lesions, infections, intoxication, medication effects, metabolic abnormalities, and alcohol or benzodiazepine withdrawal (Table 8–6 organizes the life-threatening causes of delirium, using the mnemonic WWHHHHHIMPS).[33] If an organic causal agent is not clearly established by virtue of the history, physical examination, and the screening studies listed previously, additional testing should include an electroencephalogram (EEG) and neuroimaging. Blood or urine cultures should be sent if there is suspicion for a systemic infectious process. Lumbar puncture is indicated (once an intracranial lesion and elevated intracranial pressure have been ruled out) if patients present with fever, headache, photophobia, or meningeal symptoms; in addition to sending routine CSF studies (e.g., opening pressure, appearance, Gram stain, culture, cell counts, and levels of protein and glucose), depending on the clinical circumstances, consideration should also be given to specialized markers (e.g., antigens for cryptococcus, herpes simplex virus, Lyme disease, and other rare forms of encephalitis, including paraneoplastic syndromes, autoimmune encephalitides, and prion diseases; acid-fast staining; and cytological examination for leptomeningeal metastases). With appropriate clinical suspicion, other tests to consider include serum heavy metals (e.g., lead, mercury, aluminum, arsenic, and copper), ceruloplasmin (which is decreased in Wilson's disease), and bromides.

Patients receiving certain antipsychotic medications (e.g., thioridazine, droperidol, pimozide, and ziprasidone [as well as haloperidol when high-dose intravenous administration is required for the treatment of agitated delirious patients]) should have a baseline electrocardiogram (ECG) as well as periodic follow-ups to monitor for QTc prolongation. Serum levels of antipsychotics can be useful both as a measure of compliance and to monitor for drug interactions (e.g., carbamazepine can decrease haloperidol levels).[34] The atypical antipsychotic clozapine causes agranulocytosis in 1% to 2% of patients taking the medication, necessitating weekly CBC testing for the first 6 months. At the initiation of treatment, a patient must have a white blood cell count (WBC) units of greater than 3500 cells/mm^3 and an absolute neutrophil count (ANC) greater than 2000 cells/mm^3. If treatment proceeds without interruption (i.e., with laboratory values remaining above these thresholds), CBC testing can be spaced to biweekly testing after 6 months and to monthly after 1 year of treatment. If the WBC or ANC drops significantly (by more than 3000 or 1500 cells/mm^3 respectively), or in the case of mild leukopenia (WBC 3000 to 3500 cells/mm^3) or granulocytopenia (ANC 1500 to 2000 cells/mm^3), the patient should be monitored closely and have biweekly CBCs checked. In the case of moderate leukopenia (WBC 2000 to 3000 cells/mm^3) or granulocytopenia (ANC 1000 to 1500 cells/mm^3), treatment should be interrupted, CBCs checked daily until abnormalities resolve, and the patient may be re-challenged with clozapine in the future. If the WBC drops below 2000 cells/mm^3 or the ANC drops below 1000 cells/mm^3, clozapine should be permanently discontinued (i.e., patients should not be challenged in the future). In this case, the patient may need inpatient medical hospitalization with required daily CBCs. Physicians and pharmacists who dispense clozapine must report laboratory values through national registries. As an aside, if a patient on clozapine develops signs of myocarditis, treaters should immediately check the WBC, troponin, and an ECG; interrupt treatment with clozapine; and refer the patient for medical evaluation.

Other adverse neuropsychiatric side effects of antipsychotic medications include the risk of seizure, changes in prolactin levels, and the onset of neuroleptic malignant syndrome (NMS). A baseline EEG can be helpful in patients taking more than 600 mg/day of clozapine because of an increased incidence of seizures at higher doses. Patients taking typical antipsychotics and risperidone should have prolactin levels checked if they manifest galactorrhea, menstrual irregularities, or sexual dysfunction. NMS should be suspected in patients who develop high fever, delirium, muscle rigidity, and elevated serum creatine phosphokinase levels while taking antipsychotic medications.

Finally, it is becoming increasingly clear that antipsychotic medications, particularly second-generation antipsychotics, are associated with weight gain and the development of metabolic syndrome. This is particularly concerning in patients with schizophrenia, who are more likely to be overweight or obese than the general population. Consensus guidelines recommend baseline and routine monitoring of weight, body mass index, waist circumference, blood pressure, and fasting glucose and lipid profiles.[35,36]

TABLE 8–6 Life-Threatening Causes of Delirium, Recalled by the Mnemonic WWHHHHIMPS

Wernicke's encephalopathy
Withdrawal
Hypertensive crisis
Hypoperfusion/hypoxia of the brain
Hypoglycemia
Hyper/hypothermia
Intracranial process/infection
Metabolic/meningitis
Poisons
Status epilepticus

Mood Disorders and Affective Symptoms

Although depressive symptoms often reflect a primary mood disorder, they may also be associated with a number of medical conditions, including thyroid dysfunction, folate deficiency, Addison's disease, rheumatoid arthritis, systemic lupus erythematosus, pancreatic cancer, Parkinson's disease, and other neurodegenerative disorders. Clinical suspicion for any of these disorders should drive further laboratory testing, in addition to the routine screening battery listed previously. First-break manic symptoms warrant especially careful medical and neurological evaluation, and patients who present with these symptoms often receive a laboratory work-up analogous to that described previously for a new-onset psychosis.

Patients who receive pharmacotherapy for mood disorders often require serum levels of the drug being prescribed (and its metabolite) to be checked periodically, as well as baseline and follow-up screening for treatment-induced organ damage. Tricyclic antidepressants (TCAs) can cause cardiac conduction abnormalities, including prolongation of the PR, QRS, or QT intervals; patients taking TCAs should have a baseline ECG to assess for conduction delays, especially if they have a history of pathologic cardiac conditions. TCA levels are useful in several clinical situations, including when the patient reports side effects at low doses, in geriatric or medically ill patients, when there is a question of compliance, or in an urgent clinical situation that requires rapid achievement of therapeutic levels (e.g., in a severely suicidal patient). Steady state levels are usually not achieved for 5 days after starting the medication or changing the dose; TCA trough levels should be obtained 9 to 12 hours after the last dose. No guidelines support routine checking of blood levels once a stable maintenance dose has been achieved, except in the noted circumstances or with changes in the clinical picture.

Lithium, a remarkably effective drug for bipolar disorder, has a bevy of adverse effects spanning numerous organ systems. Lithium can induce adverse effects on the thyroid gland, the kidney, and the heart, as well as cause a benign elevation of the WBC count; accordingly, baseline and follow-up measures of the CBC count with a differential, serum electrolytes, blood urea nitrogen (BUN), creatinine, thyroid function tests (TFTs), urinalysis, and ECG should be obtained. Pregnancy tests should also be obtained in women of childbearing years given the risk of teratogenic effects (e.g., Ebstein's anomaly) that are associated with use in the first trimester. There is general consensus that therapeutic lithium levels range from 0.8 to 1.2 mEq/L, although certain patients may have idiosyncratic responses outside of this range. Elderly patients with slower rates of drug metabolism and lower volumes of distribution, for example, may experience side effects within this typical range and may require maintenance at lower serum levels with a narrower therapeutic window. Steady state levels can be checked after 4 to 5 days. Lithium levels can change dramatically during or immediately after pregnancy or if patients are taking thiazide diuretics, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor–blockers, or in those who have deteriorating renal function or are dehydrated. Patients on a stable maintenance dose of lithium should have levels checked no less than once every 6 months, along with routine renal and thyroid function testing.

Patients taking carbamazepine or valproic acid for bipolar disorder should have baseline and follow-up CBC, electrolytes, and LFTs, in addition to routine level monitoring, typically every 6 months. In the case of carbamazepine, which can cause agranulocytosis, the CBC should be checked every 2 weeks for the first 2 months of treatment, and then at least once every 3 months thereafter. Pregnancy tests should be considered for women of childbearing age.

Anxiety

The medical differential for new-onset anxiety is broad; it includes drug effects, thyroid or parathyroid dysfunction, hypoglycemia, cardiac disease (including myocardial infarction and mitral valve prolapse), respiratory compromise (including asthma, chronic obstructive pulmonary disease, and pulmonary embolism), and alcohol or benzodiazepine withdrawal. Rare causes, such as pheochromocytoma, porphyria, and seizure disorder, should be investigated if suggested by other associated clinical features. Based on this broad differential diagnosis, laboratory work-up may include TFTs, serum glucose or glucose tolerance testing, chest x-ray examination, pulmonary function tests, cardiac work-up, urine vanillylmandelic acid or porphyrins, and an EEG.

Care of the Geriatric Population

Given the increased likelihood of medical conditions that cause psychiatric symptoms in older adults, special attention should be given to organic causal agents. Especially common are mental status changes resulting from urinary tract infections, anemia, thyroid disease, dementia, and iatrogenic effects from medications. Kolman[37] described five particularly useful tests for older adults: clean-catch urinalysis and culture, a chest x-ray examination, a serum B_{12} level, an ECG, and a BUN. Although the National Institutes of Health Consensus Development Conference identified the history and physical examination as the most important diagnostic tests in older adult psychiatric patients, they also specifically recommended checking a CBC, serum chemistries, TFTs, RPR, B_{12}, and folate levels. If clinically indicated, additional testing should include neuroimaging, an EEG, and a lumbar puncture. With suspected early dementia, in addition to the DRS (see Diagnostic Rating Scales, discussed earlier), positron emission tomography (PET) may be useful diagnostically.[38]

Substance Abuse

Substance abuse and withdrawal should always be considered in patients with mental status changes. Substances available for testing in serum and urine are summarized in Table 8–7. Alcohol levels can be quickly assessed using breath analysis (breathalyzer). It is important to remember that serum levels of alcohol do not necessarily correlate with the timing of withdrawal symptoms, especially in patients with chronically high alcohol levels (e.g., withdrawal starts well before the serum alcohol level reaches zero). Patients who present with a history of alcohol abuse should have LFTs and a CBC

TABLE 8–7 Serum and Urine Toxicology Screens

SUBSTANCE	SERUM DETECTION	URINE DETECTION
Alcohol	1–2 days	1 day
Amphetamine	Variable	1–2 days
Barbiturates	Variable	3 days to 3 weeks
Benzodiazepines	Variable	2–3 days
Cocaine	Hours to 1 day	2–3 days
Codeine, morphine, heroin	Variable	1–2 days
Delta-9-THC	N/A	~30 days, longer if chronic use
Methadone	15–29 hours	2–3 days
Phencyclidine	N/A	8 days
Propoxyphene	8–34 hours	1–2 days

N/A, Not applicable.

count checked; if macrocytic anemia is present, B_{12} and folate levels should also be assessed. Chronic liver damage can lead to coagulopathy (as manifested by an elevated prothrombin time or international normalized ratio [INR]) and other manifestations of synthetic failure (e.g., low albumin level). In the case of cocaine abuse, there should be a low threshold for obtaining an ECG with any cardiac symptom.

Eating Disorders

As part of their medical evaluation, patients who present with severe eating disorders should have routine laboratory studies to evaluate electrolyte status and nutritional measures (e.g., albumin level). Patients who are actively purging can present with metabolic alkalosis (manifested by an elevated bicarbonate level), hypochloremia, and hypokalemia. Serum aldolase levels can be increased in those who abuse ipecac; chronic emesis can also lead to elevated levels of amylase. Cholecystokinin levels can be blunted in bulimic patients, relative to controls, following ingestion of a meal. Finally, patients who abuse laxatives chronically may present with hypocalcemia.

Pharmacogenomic Testing

In recent years, research has greatly expanded knowledge of individual genetic variability, particularly as it applies to the metabolism of and response to psychotropic medications. A major focus has been on the cytochrome P450 (CYP) system, responsible for metabolism of many psychotropic agents (summarized in Table 8–8). Commercially-available tests, including one FDA-approved test, permit examination of an individual's CYP polymorphisms through gene chip technology, suggesting patients who may be slow or rapid metabolizers of the substrate drugs.[39] In theory, such knowledge might help clinicians make dosing decisions for particular patients, potentially facilitating treatment with certain medications with narrow therapeutic windows. Recent guidelines, however, have not supported the clinical use of such tests in treating nonpsychotic major depression with selective serotonin reuptake inhibitors (SSRIs), for example, because of the relatively high cost and lack of available evidence for clinical benefit.[40] Other pharmacogenomic tests work to predict clinical response to clozapine, development of agranulocytosis from clozapine, and development of antipsychotic-induced metabolic syndrome, though none are in routine clinical use at this time. Genotype testing for serotonin receptor and transporter variations are available but not yet clinically proven. Current research focuses heavily on the pharmacogenetics of antidepressants, but no tests for clinical response are yet available. The concept of personalized prescriptions, or tailoring drugs to an individual's genetic makeup, remains a future goal and research interest for psychiatry, but pharmacogenomic tests have not yet reached routine clinical practice.

THE ELECTROENCEPHALOGRAM

The EEG employs surface (and sometimes nasopharyngeal) electrodes to measure the low-voltage electric activity of the brain. Used primarily in the evaluation of epilepsy and other neurologic disorders, the EEG is often useful in evaluating organic causes of psychiatric symptoms.

TABLE 8–8 Cytochrome P450 Isoenzymes Active in Metabolizing Commonly Prescribed Psychotropic Medications

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A3/4/5
Amitriptyline	Fluoxetine	Amitriptyline	Amitriptyline	Alprazolam
Clomipramine	Moclobemide	Citalopram	Amphetamines	Amitriptyline
Clozapine	Ramelteon	Clomipramine	Aripiprazole	Aripiprazole
Duloxetine	THC	Clozapine	Atomoxetine	Buspirone
Fluvoxamine		Diazepam	Clozapine	Carbamazepine
Haloperidol		Imipramine	Codeine	Clozapine
Imipramine		Moclobemide	Desipramine	Haloperidol
Methadone		Ramelteon	Dextromethorphan	Imipramine
Mirtazapine		Sertraline	Duloxetine	Lamotrigine
Olanzapine			Fluoxetine	Methadone
Ramelteon			Mianserin	Midazolam
Tacrine			Haloperidol	Nefazodone
			Hydrocodone	Oxcarbazepine
			Methadone	Pimozide
			m-CPP	Quetiapine
			Nortriptyline	Risperidone
			Olanzapine	Trazodone
			Oxycodone	Triazolam
			Paliperidone	Zaleplon
			Paroxetine	Zolpidem
			Phenothiazines	Ziprasidone
			Risperidone	
			Sertraline	
			Thioridazine	
			Tricyclics (TCAs)	
			Venlafaxine	

Electroencephalogram signals are presumed to reflect primarily cortical activity, especially from neurons in the most superficial cortical cell layers. The frequencies of electric activity have been divided into four bands: delta (0 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 12 Hz), and beta (greater than 12 Hz). The awake state is characterized by an alpha predominance. Beta waves emerge during stage 1 sleep (drowsiness); during stage 2, vertex sharp theta and delta waves are observed. Delta waves are seen in stages 3 and 4 sleep. During rapid eye movement sleep, the EEG will record low-voltage fast waves with ocular movement artifacts. Sleep deprivation, hyperventilation, and photic stimulation can sometimes activate seizure foci. For patients with nonepileptiform EEGs but a residual high suspicion for seizure activity, serial studies, sleep-deprived studies, or long-term monitoring can produce a higher yield. Video long-term monitoring can help link often infrequent clinical events with the associated electrical patterns.

Electroencephalogram patterns associated with neuropsychiatric conditions are summarized in Table 8–9. EEG findings in generalized, absence, and partial complex seizures disorders are well characterized and are diagnostic.

TABLE 8–9 EEG Findings Associated with Neuropsychiatric Conditions

Seizure	
• Generalized	• Bilateral, symmetric, synchronous, paroxysmal spike; sharp waves followed by slow waves
• Absence	• 3-Hz spike-wave complexes
• Complex partial	• Temporal lobe spikes, polyspikes, and waves
Pseudoseizure	Normal EEG
Delirium	Generalized theta and delta activity
• Hepatic or uremic encephalopathy	• Triphasic waves
Dementia	
• Alzheimer's and vascular	• Alpha slowing of the background
• Subacute sclerosing panencephalitis and Creutzfeldt–Jakob disease	• Periodic complexes accompanying myoclonic jerks
Locked-In Syndrome	Normal EEG
Persistent Vegetative State	Slow and disorganized EEG
Death	Electrocerebral silence
Medications	
• Benzodiazepines and barbiturates	• Beta activity
• Neuroleptics and antidepressants	• Nonspecific changes
Focal Lesion	Focal delta slowing
Increased Intracranial Pressure	FIRDA

EEG, Electroencephalogram; *FIRDA*, frontal, intermittent, rhythmic delta activity.

When interpreted within the context of the clinical presentation, abnormal EEG data can help support several other broad diagnostic categories, including delirium, dementia, medication-induced mental status changes, and focal lesions. Normal data can provide support for diagnoses of pseudoseizures and locked-in syndrome, but they are not able to rule out a variety of ictal states because of limitations on the placement of surface electrodes. Although an increased number of EEG abnormalities have been described in a variety of primary psychiatric disorders, at present the EEG is not clinically useful to definitively rule in any primary psychiatric diagnosis.

NEUROIMAGING

Neuroimaging has emerged as a powerful tool in both neuropsychiatric research and in the clinical investigation of organic causal agents for psychiatric presentations; however, rarely do neuroimaging studies establish a primary psychiatric diagnosis. Although less invasive than other diagnostic tests, imaging studies come with their own risks to the patient, and they remain costly.[41] Following a thorough initial evaluation, the decision to use neuroimaging needs to be made on a case-by-case basis; at present, the major objective of neuroimaging studies in patients with psychiatric symptoms is to prevent missing a treatable brain lesion. A suggested list of indications for brain imaging in psychiatric patients is given in Table 8–10. The following sections describe the major neuroimaging techniques currently available, as well as their clinical utility.

Computed Tomography

Computed tomography (CT) scans use multiple x-rays to provide cross-sectional images of the brain. On CT films, areas of increased beam attenuation (e.g., of the skull) appear white, whereas those of low attenuation (e.g., gas) appear black, and those of intermediate attenuation (e.g., soft tissues) appear in shades of gray. Contrast material may be used to visualize areas where the blood–brain barrier has been compromised, for example, by tumors, bleeding, inflammation, and abscesses; however, up to 5% of patients can develop idiosyncratic reactions to contrast media, manifested by hypotension, nausea, flushing, urticaria, and anaphylaxis. CT scans can be obtained rapidly and are the imaging modality of choice in identifying acute hemorrhage and trauma, as well as in situations in which magnetic

TABLE 8–10 Indications for Neuroimaging in Patients With Psychiatric Symptoms

New-onset psychosis*
New-onset delirium*
New-onset dementia
Onset of any psychiatric problem in a patient > 50 years old*
An abnormal neurologic examination
A history of head trauma
During an initial work-up for ECT

*When initial history, physical examination, and laboratory studies are not definitive.

ECT, Electroconvulsive therapy.

resonance imaging (MRI) is contraindicated. CT scans are generally better tolerated by patients with anxiety or claustrophobia. Although useful in examining gross pathological conditions, CT lacks the resolution to detect subtle white matter lesions or changes in smaller structures, such as the hippocampi and basal ganglia. Because CT scans use ionizing radiation, they are contraindicated in pregnancy.

Although CT scans have a well-established role in the identification of structural abnormalities responsible for psychiatric symptoms in patients with organic lesions, they cannot be used to diagnose primary psychiatric illness. However, there are nonspecific structural changes visible on CT that have been consistently identified in the brains of psychiatric patients. Since Weinberger and coworkers[42] first described increased ventricular-to-brain ratios in patients with schizophrenia, several investigators have observed enlarged ventricles in those with eating disorders, alcoholism, bipolar disorder, dementia, and depression.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI), which provides detailed images of the brain in axial, sagittal, and coronal planes, takes advantage of the interaction between protons and an external magnetic field. In the magnetic field of the MRI scanner, hydrogen protons in the water molecules of the brain become aligned as dipoles with, or against, the field. A radiofrequency pulse is applied, shifting the spin on the protons to a higher energy level; when the signal is turned off, spin returns to the ground state and the proton releases energy. The frequency of energy release (or relaxation) depends on the chemical environment surrounding the proton. A coil that detects the energy emission generates signals that are processed by the scanner to create images. Adjusting the relaxation time parameters (known as T1 and T2) can result in images that are "weighted" differently; whereas T1-weighted images provide anatomic detail and gray–white matter differentiation, T2-weighted images highlight areas of pathological conditions.

Magnetic resonance imaging is considered superior to CT for differentiation of white and gray matter, identification of white matter lesions (e.g., in multiple sclerosis, vasculitis, and leukoencephalitis), and visualization of the posterior fossa. As with CT, contrast medium may be used to identify lesions where the blood–brain barrier has been compromised. MRI is contraindicated in patients with metallic implants (including pacemakers) and is often less tolerable to patients because of the longer length of the study, the enclosed space, and the noise.

MRI may be used clinically to rule out structural brain lesions in patients with psychiatric symptoms, including acute psychosis or delirium, severe mood disorder, and abrupt personality changes. In addition to the structural changes that CT scans are capable of detecting, MRI appears to be more sensitive at detecting atrophic changes in dementia, inflammation-induced edema, and white matter lesions. Compared with CT, MRI is capable of detecting acute strokes earlier, using a method called diffusion-weighted imaging.

Functional MRI (fMRI), which is primarily a research tool at present, uses a process of acquisition sequences to approximate cerebral blood flow; accordingly, one can infer regions of brain activation and deactivation at rest, as well as during execution of sensory, motor, or cognitive tasks. Certain patterns of activation have emerged consistently in dementia, major depression, schizophrenia, and obsessive–compulsive disorder. Although fMRI is not currently considered a diagnostic or clinical tool, it is starting to provide enhanced knowledge about psychiatric illnesses and psychotropic medications, which will likely help guide research, drug development, and clinical practice in the future.

A related imaging modality, magnetic resonance spectroscopy (MRS), permits *in vivo* measurements of certain markers of brain tissue metabolism and biochemistry. For example, using proton-based MRS, one can measure local concentrations of *N*-acetylaspartate (a putative marker of neuronal integrity), choline (a marker of membrane turnover), creatine (a marker of intracellular energy metabolism), glutamine, glutamate, and gamma-aminobutyric acid. Localized reductions in *N*-acetylaspartate have been implicated in multiple neuropsychiatric disorders, including schizophrenia, temporal lobe epilepsy, Alzheimer's disease, acquired immune deficiency syndrome dementia, and Huntington's disease. In the near future, the combined use of fMRI and MRS holds great promise for delineating abnormal structure–function relationships underlying psychopathologic conditions.[43]

PET and SPECT

Positron emission tomography (PET) employs radioactive markers to visualize directly cortical and subcortical brain functioning. Some examples of these markers include F-18 fluorodeoxyglucose (which provides a picture of brain glucose metabolism), oxygen-15 (a surrogate for regional cerebral blood flow), and receptor-specific radioligands (which indicate activity at neurotransmitter receptors). Studies can be performed only where an on-site cyclotron is present to prepare the emitter tracers. Single photon emission computed tomography (SPECT) uses photon-emitting nucleotides measured by gamma detectors to localize brain activation or pharmacological activity; commonly used tracers include xenon-133 and technetium Tc-99m hexamethylpropyleneamine (which measure cerebral blood flow) and, as in PET, radioligands with specific receptor activity. Although PET scans provide greater spatial and temporal resolution, signal-to-noise ratio, and variety of ligands, SPECT is more readily available, better tolerated, and less expensive.

Although both PET and SPECT are primarily used as research tools in delineating pathophysiology and rational drug designs, clinical use of these techniques is becoming increasingly common. PET and SPECT may be used in concert with the EEG to determine seizure foci, especially in patients with partial complex seizures; during a seizure, scans can demonstrate areas of increased metabolism, whereas interictally the focus will be hypometabolic and hypoperfused. Moreover, in both Alzheimer's disease and multi-infarct dementia, abnormal patterns of cortical metabolism and receptor function as evidenced on PET and SPECT appear to predate structural changes visible on MRI.[44,45] With the continued development of receptor-specific ligands and other functional markers, these imaging modalities may continue to find a more prominent role in clinical diagnosis and management.

CONCLUSION

Although diagnosis in psychiatry continues to rely primarily on the interview and other clinical phenomenology, diagnostic rating scales and laboratory testing serve important roles in eliminating organic causal agents from the differential diagnoses, monitoring the effects of treatment, and guiding further management decisions. Neuroimaging has provided a noninvasive means to detect subtle neurophysiological dysfunction in psychiatric patients and has begun to find meaningful clinical as well as research applications. It is clear that these quantitative measures will assume increasing prominence and importance in twenty-first century psychiatry.

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9

Mood-Disordered Patients

Paolo Cassano, M.D., Ph.D.
Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.
George I. Papakostas, M.D.
Maurizio Fava, M.D.
Theodore A. Stern, M.D.

A major depressive disorder (MDD) serious enough to warrant professional care affects approximately 16% of the general population during their lifetime.[1] Both the Epidemiological Catchment Area (ECA) study and the National Comorbidity Survey study have found that MDD is prevalent, with cross-sectional rates of up to 6.6%.[1] Although this condition ranks first among reasons for psychiatric hospitalization (23.3% of total hospitalizations), it has been estimated that 80% of all persons suffering from it are either treated by nonpsychiatric personnel or are not treated at all.[2]

Depression is second only to hypertension as the most common chronic condition encountered in general medical practice.[3] Depression is estimated to rival virtually every other known medical illness with regard to its burden of disease morbidity early in this millennium.[4] With respect to physical function, depressed patients score, on average, 77.6% of normal function, with advanced coronary artery disease (CAD) and angina being 65.8% and 71.6%, respectively, and back problems, arthritis, diabetes, and hypertension ranging from 79% to 88.1%.[5] MDD has also been characterized by increased mortality.[6–8] In the general population, suicide accounts for about 0.9% of all deaths, and depression is the most important risk factor for suicide, with about 21% and 18% of the patients with recurrent depressive disorders and dysthymic disorder, respectively, attempting suicide.

Depressed patients often have co-morbid medical illnesses (e.g., arthritis, hypertension, backache, diabetes mellitus [DM], and heart problems). Similarly, the presence of one or more chronic medical conditions raises the recent (6-month) and lifetime prevalences of mood disorder. Patients affected by chronic and disabling physical illnesses are at higher risk of depressive disorders, with rates being typically greater than 20%. Among patients hospitalized for CAD, 30% present with at least some degree of depression.[9] Patients with DM also have a twofold increased prevalence of depression, with 20% and 32% rates in uncontrolled and controlled studies, respectively, conducted with depression symptom scales.[10,11] Depression is also more common in obese persons than it is in the general population.[12] At the Massachusetts General Hospital (MGH), the psychiatric consultant called to see a medical patient makes a diagnosis of MDD in approximately 20% of cases, making MDD among the most common problems seen for diagnostic evaluation and treatment. The prevalence of chronic medical conditions in depressed patients is higher regardless of the medical context of recruitment, with an overall rate ranging from 65% to 71% of patients.[13] Several studies indicate that depression significantly influences the course of concomitant medical diseases. In general, the more severe the illness, the more likely depression is to complicate it.[14]

In acutely ill hospitalized older persons, the health status of patients with more symptoms of depression is more likely to deteriorate and less likely to improve during and after hospitalization.[15] Some degree of depression in patients hospitalized for CAD is associated with an increased risk of mortality, and also with continuing depression for at least the first year after hospitalization.[9] Proceeding to cardiac surgery while suffering from MDD, for example, is known to increase the chance of a fatal outcome.[16] Depression in the first 24 hours after myocardial infarction (MI) was associated with a significantly increased risk of early death, reinfarction, or cardiac arrest.[17] Even in depressed outpatients, the risk of mortality, chiefly as a result of cardiovascular disease, is more than doubled.[18] The increased risk of cardiac mortality has also been confirmed in a large community cohort of individuals with cardiac disease who presented with either MDD or minor depression.[19] Those subjects without cardiac disease but with depression also had a higher risk (from 1.5- to 3.9-fold) of cardiac mortality.[19]

In patients with type 1 or 2 diabetes, depression was associated with a significantly higher risk of DM-specific complications (e.g., retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction).[20] Data from the Hispanic Established Population for the Epidemiologic Study of the Elderly indicated that death rates in this population were substantially higher when a high level of depressive symptoms was co-morbid with DM (odds ratio, 3.84).[21]

Depression symptom severity is also associated with poor diet and with poor medication adherence, functional impairment, and higher health care costs in primary care patients with DM.[22] Underrecognition and undertreatment of depression in the elderly has been associated in primary care with increased medical utilization.[23] Among the elderly (age 65 years or older), a significant correlation exists between depression and the risk of recurrent falls, with an odds ratio of 3.9 when four or more depressive symptoms

are present. These data are of particular importance because falls in the elderly are a well-recognized public health problem.[24] Patients with cancer and co-morbid depression are at higher risk for mortality[25] and for longer hospital stays. Unfortunately, despite the impact of depression on overall morbidity, functional impairment, and mortality, a significant proportion of those with depression (43%) fail to seek treatment for their depressive symptoms.[26]

Failure to treat depression leaves the patient at risk for further complications and death. There is a clinical sense, moreover, that any seriously ill person who has neurovegetative symptoms, and who has given up and wishes that he or she were dead, is going to do worse than if he or she had hope and motivation. MDD, even if the patient is healthy in every other way, requires treatment. When a seriously ill person becomes depressed, the failure to recognize and to treat the disorder is even more unfortunate.

Prompt and effective treatment of medical co-morbidity is equally important for the outcome of depression. In a study of patients with DM, the severity of depression during follow-up was related to the presence of neuropathy at study entry, and to incomplete remission during the initial treatment trial.[27] By the 10th year of insulin-dependent DM, roughly 48% of a sample of young diabetics developed at least one psychiatric disorder, with MDD being the most prevalent (28%).[28] In addition to DM, other medical and neurologic conditions have been associated with an increased risk for MDD. For example, Fava and colleagues'[29] review showed that MDD is a life-threatening complication of Cushing's syndrome, Addison's disease, hyperthyroidism, hypothyroidism, and hyperprolactinemic amenorrhea, and that treatment that primarily addresses the physical condition may be more effective than antidepressant drugs for such organic affective syndromes. A study of computerized record systems of a large staff-model health maintenance organization showed that patients diagnosed as being depressed had significantly higher annual health care costs ($4246 versus $2371, $P < .001$) and higher costs for every category of care (e.g., primary care, medical specialty care, medical inpatient care, and pharmacy and laboratory costs) than patients without depression.[30] Depressive disorders are likely to cause more disability than are most other chronic diseases (e.g., osteoarthritis and DM), with a possible exception being MI.[31]

MAKING THE DIAGNOSIS OF DEPRESSION

The criteria for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)[32] should be applied to the patient with medical illness in the same way as to a patient without medical illness. The DSM-IV has a category for mood disorders "due to" a general medical condition. A stroke in the left hemisphere, for example, is commonly followed by a syndrome clinically indistinguishable from MDD. It can now be referred to as a "major depression-like" condition when full criteria are met. Our recommendation is to diagnose a mood disorder using the DSM-IV criteria. MDD can now be diagnosed as such, but there is still no term in the DSM-IV to represent what the Research Diagnostic Criteria referred to as minor depression—a distinction that is important in the medically ill.

The DSM-IV classification of MDD has traditionally had a greater focus on the psychological symptoms of depression (e.g., depressed mood, lack of interest, excessive guilt, thoughts of suicide, feelings of worthlessness, indecisiveness). Although some of the physical or somatic symptoms of MDD (primarily fatigue and disturbances of both sleep and appetite) are included in the DSM-IV classification of this disorder, it is apparent that physical symptoms are underrepresented in the current nosology, despite the fact that they represent the chief complaint for a substantial proportion of patients who suffer from MDD.

Diagnosis is crucial to treatment. Three questions face the consultant at the outset: (1) Does the patient manifest depression? (2) If so, is there an organic cause, such as use of a medication, that can be eliminated, treated, or reversed? (3) Does it arise from the medical condition (e.g., Cushing's disease), and treatment of that condition will alleviate it, or must it be treated itself (e.g., poststroke depression [PSD])?

Major Depression

Depression is a term used by most to describe even minor and transient mood fluctuations. It is seen everywhere and is often thought to be normal; therefore it is likely to be dismissed even when it is serious. This applies all the more to a patient with serious medical illness: If a man has terminal cancer and meets the full criteria for MDD, this mood state is regarded by some as "appropriate." Depression is used here to denote the disorder of MDD—a seriously disabling condition for the patient, capable of endangering the patient's life; it is not just an emotional reaction of sadness or despondency. If, while recovering from an acute stroke, a patient has a severe exacerbation of psoriasis, no one says that the cutaneous eruption is appropriate, even though the stress associated with the stroke has almost certainly caused it. Moreover, caregivers are swift to treat the exacerbation. When a patient with a history of MDD lapses into severe depression 1 month after beginning radiation therapy for an inoperable lung cancer, some may see a connection to the prior depressive illness and hasten to treat it. Far more common is the conclusion that anyone with that condition would be depressed. The majority of terminally ill cancer patients do not develop MDD no matter how despondent they feel. If a patient is hemorrhaging from a ruptured spleen, has lost a great deal of blood, becomes hypotensive, and goes into shock, no one calls this appropriate. Like shock, depression is a dread complication of medical illness that requires swift diagnosis and treatment.

Two assumptions are made here: (1) A depressive syndrome in a medically ill patient shares the pathophysiology of a (primary) major affective disorder, and (2) proper diagnosis is made by applying the same criteria. Patients who suffer from unipolar depressive disorders typically present with a constellation of psychological and cognitive (Table 9–1), behavioral (Table 9–2), and physical and somatic (Table 9–3) symptoms. Because far less epidemiologic information is available on depression in the medically ill, the requirement that the dysphoria be present for 2 weeks or longer should be regarded as only a rough approximation in the medically ill. According to the DSM-IV,[32] at least five of the following nine symptoms should be present most of the day, nearly every day, and should include either depressed mood or loss of interest or pleasure:

TABLE 9–1 Unipolar Depressive Disorders: Common Psychological and Cognitive Symptoms

Depressed mood
Lack of interest or motivation
Inability to enjoy things
Lack of pleasure (anhedonia)
Apathy
Irritability
Anxiety or nervousness
Excessive worrying
Reduced concentration or attention
Memory difficulties
Indecisiveness
Reduced libido
Hypersensitivity to rejection or criticism
Reward dependency
Perfectionism
Obsessiveness
Ruminations
Excessive guilt
Pessimism
Hopelessness
Feelings of helplessness
Cognitive distortions [e.g., "I am unlovable"]
Preoccupation with oneself
Hypochondriacal concerns
Low or reduced self-esteem
Feelings of worthlessness
Thoughts of death or suicide
Thoughts of hurting other people

TABLE 9–2 Unipolar Depressive Disorders: Common Behavioral Symptoms

Crying spells
Interpersonal friction or confrontation
Anger attacks or outbursts
Avoidance of anxiety-provoking situations
Social withdrawal
Avoidance of emotional and sexual intimacy
Reduced leisure-time activities
Development of rituals or compulsions
Compulsive eating
Compulsive use of the Internet or video games
Workaholic behaviors
Substance use or abuse
Intensification of personality traits or pathologic behaviors
Excessive reliance or dependence on others
Excessive self-sacrifice or victimization
Reduced productivity
Self-cutting or mutilation
Suicide attempts or gestures
Violent or assaultive behaviors

TABLE 9–3 Unipolar Depressive Disorders: Common Physical and Somatic Symptoms

Fatigue
Leaden feelings in arms or legs
Difficulty falling asleep (early insomnia)
Difficulty staying asleep (middle insomnia)
Waking up early in the morning (late insomnia)
Sleeping too much (hypersomnia)
Frequent naps
Decreased appetite
Weight loss
Increased appetite
Weight gain
Sexual arousal difficulties
Erectile dysfunction
Delayed orgasm or inability to achieve orgasm
Pains and aches
Back pain
Musculoskeletal complaints
Chest pain
Headaches
Muscle tension
Gastrointestinal upset
Heart palpitations
Burning or tingling sensations
Paresthesias

1. Depressed mood, subjective or observed, most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities, nearly every day
3. Significant (more than 5% of body weight per month) weight loss or gain
4. Insomnia or hypersomnia, nearly every day
5. Psychomotor agitation or retardation that is observable by others, nearly every day
6. Fatigue or loss of energy, nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional), not merely about being sick, nearly every day
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day
9. Recurrent thoughts of death (not just a fear of dying), recurrent suicidal ideation without a plan, or a suicide attempt or a specific plan for committing suicide

Two questions (does the patient suffer from depressed mood? is there diminished interest or pleasure?) have a high sensitivity (about 95%), but unfortunately a low specificity (57%), for diagnosing MDD. Consequently, posing these two questions can be useful as a first approach to the patient who presents with risk factors for depression. However, further inquiry is typically required to establish the diagnosis. Although depressive disorders are frequently associated with medical illnesses, the DSM-IV considers that potential medical illnesses underlying depressive symptoms should be excluded before making the diagnosis of MDD. This hierarchical approach is typically ignored by clinicians, who tend to make the diagnosis of MDD even in the presence of co-morbid medical conditions that may be etiologically related to the condition itself. Nevertheless, the issue of differential diagnosis with medical diseases still exists, as patients may present with transient demoralization as a result of their physical illness or of fatigue or other cognitive and neurovegetative symptoms (but not fulfilling the criteria for MDD or even minor depression). For instance, weight loss and fatigue may also be associated with a variety of disorders

(e.g., DM, cancer, thyroid disease). The medical and psychiatric history, together with the physical examination, should guide any further diagnostic work-up.

The aforementioned DSM-IV symptoms may at first seem invalid in the medically ill. If the patient has advanced cancer, how can one attribute anorexia or fatigue to something other than the malignant disease itself? Four of the nine diagnostic symptoms could be viewed as impossible to ascribe exclusively to depression in a medically ill patient: sleep difficulty, anorexia, fatigue or energy loss, and difficulty concentrating. Endicott[33] developed a list of symptoms that the clinician can substitute for, and count in place of, these four: fearful or depressed appearance; social withdrawal or decreased talkativeness; brooding, self-pity, or pessimism; and mood that is not reactive (i.e., the patient cannot be cheered up, does not smile, or does not react positively to good news). Although this method is effective, Chochinov and colleagues[34] compared diagnostic outcomes using both the regular (Research Diagnostic Criteria) and the substituted criteria in a group of medically ill patients. If one held the first two symptoms to the strict levels—that is, depressed mood must be present most of the day, nearly every day, and loss of interest applies to almost everything—the outcome for both diagnostic methods yielded exactly the same number of patients with the diagnosis of MDD.

The first help comes from discovery of symptoms that are more clearly the result of MDD, such as the presence of self-reproach ("I feel worthless"), the wish to be dead, or psychomotor retardation (few medical illnesses in and of themselves produce psychomotor retardation; hypothyroidism and Parkinson's disease are two of them). Insomnia or hypersomnia can also be helpful in the diagnosis, although the patient may have so much pain, dyspnea, or frequent clinical crises that sleep is impaired by these events. Although libidinous interests may not be high in an intensive care unit patient, some form of interest can usually be assessed, as when talk gets around to children or grandchildren, hobbies, or people. Do they still find that their affect brightens, or is it blunted? The ability to think or concentrate, like the other symptoms, needs to be specifically asked about in every case.

Unfortunately, to some a request for psychiatric consultation is tantamount to saying that physical symptoms are only "in your head" or are the result of malingering. Instead, depression is as much a somatic as a psychic disorder. The somatic manifestations of depression (e.g., insomnia, restlessness, anhedonia) may even be construed as proof to a patient that they have no "psychic" illness. "No, doctor, no way am I depressed; if I could just get rid of this pain, everything would be fine." Persistence and aggressive questioning are required to elicit the presence or absence of the nine symptoms.

If the history establishes six of nine symptoms, the consultant may not be certain that three of them have anything to do with depression but may just as likely stem from a co-morbid medical illness. If the patient were found to be hypothyroid, the treatment of choice would not be antidepressants but judicious thyroid replacement. Usually, however, everything is being done for the patient to alleviate the symptoms of the primary illness. If this appears to be the case, our recommendation is to make the diagnosis of MDD and proceed with treatment.

States Commonly Mislabeled as Depression

Up to a third of patients referred for depression have, on clinical examination, neither MDD nor minor depression. By far the most common diagnosis found among these mislabeled referrals at the MGH has been an organic mental syndrome. A quietly confused patient may look depressed. The patient with dementia or with a frontal lobe syndrome caused by brain injury can lack spontaneity and appear depressed. Fortunately, the physical and mental status examinations frequently reveal the tell-tale abnormalities.

Although much less common, mental retardation may also be mistaken for depression, especially when failure to grasp or to comply with complex instructions makes no sense to those caring for the patient ("He seems not to care"). If suspected, mental retardation can be confirmed by history from family, by review of past records, or by formal testing of intelligence.

Another unrecognized state, sometimes called depression by the consultee and easier for the psychiatrist to recognize, is anger. The patient's physician, realizing that the patient has been through a long and difficult illness, may perceive reduction in speech, smiling, and small talk on the patient's part as depression. The patient may thoroughly resent the illness, be irritated by therapeutic routines, and be fed up with the hospital environment but, despite interior smoldering rage, may remain reluctant to discharge wrath in the direction of the physician or nurses.

Excluding Organic Causes of Depression

When clinical findings confirm that the patient's symptoms are fully consistent with MDD, the consultant must still create a differential diagnosis of this syndrome. Could the same constellation of symptoms be caused by a medical illness or its treatment? Should the patient's symptoms be caused by an as yet undiagnosed illness, the last physician with the chance of detecting it is the consultant. Differential diagnosis in this situation is qualitatively the same as that described for considering causes of delirium (see Chapter 10). With depression, although the same process should be completed, certain conditions more commonly produce depressive syndromes and are worthy of comment.

Review of the medications that the patient is taking generally tells the consultant whether the patient is receiving something that might alter mood. Ordinarily, one would like to establish a relationship between the onset of depressive symptoms and either the start of, or a change in, a medication. If such a connection can be established, the simplest course is to stop the agent and monitor the patient for improvement. When the patient requires continued treatment, as for hypertension, the presumed offending agent can be changed, with the hope that the change to another antihypertensive will be followed by resolution of depressive symptoms. When this fails or when clinical judgment warrants no change in medication, it may be necessary to start an antidepressant along with the antihypertensive drug. The literature linking drugs to depression is inconclusive at best. Clinicians have seen depression following use of reserpine and steroids[35] and from withdrawal from cocaine, amphetamine, and alcohol. Despite anecdotal reports, β-blockers do not appear to cause depression. It has been suggested that depression in some cases appears

as a reaction to subclinical cardiovascular symptoms,[36] so the differential diagnosis should also take into account medical conditions. The most common central nervous system (CNS) side effect of a drug is confusion or delirium, and this is commonly mislabeled as depression because a mental status examination has not been conducted.

Abnormal laboratory values should not be overlooked, because they may provide the clues to an undiagnosed abnormality responsible for the depressive symptoms. Laboratory values necessary for the routine differential diagnosis in psychiatric consultation should be reviewed. A work-up is not complete if the evaluation of thyroid and parathyroid function is not included.

Many medical illnesses have been associated with depressive symptoms. The list is extensive, and for all practical purposes it can be included with the list of medical illnesses that can cause delirium (see Chapter 10).

MDD is never "appropriate" (e.g., "This man has inoperable lung cancer metastatic to his brain and is depressed, which is appropriate"). MDD is a common and dread complication of many medical illnesses as they become more severe. To call it anything else is to endanger the patient and neglect one of the worst forms of human suffering.

The disability associated with depressive illness is seldom recognized, yet it and mental illness in general show a stronger association with disability than with severe physical diseases.[37] One line of evidence regarding the capacity of MDD to undermine physical health is its association with decreases in trabecular bone in women (14% in the femoral neck),[38] a magnitude consistent with a 40% increase in hip fracture rates over a period of 10 years.

MDD carries its own dangers and increases the risk of cardiovascular disease. Depressed patients with CAD show a significantly higher (24% versus 4%) prevalence of ventricular tachycardia[39] and a reduction in heart rate variability,[40] both of which increase the risk of sudden death. After acute MI, the presence of MDD is the strongest predictor of death at 6 months, and depressive symptoms (defined as a Beck Depression Inventory score greater than 10) the strongest predictor of death at 18 months. Both of these predict lethality when combined with premature ventricular beats at a rate greater than 10 per hour.[41,42]

In general, the more serious the illness, the more likely the patient is to succumb to a depressive episode. Careful studies have found a high incidence of MDD in hospitalized medical patients.[14] For more than 50 years, carcinoma of the pancreas has been associated with psychiatric symptoms, especially depression, which in some cases seems to be the first manifestation of the disease.[43] Two carefully controlled studies have shown these patients to have significantly more psychiatric symptoms and major depression than patients with other malignancies of gastrointestinal origin, leading some to suspect that depression in this case is a manifestation of a paraneoplastic syndrome.[44,45]

When medical illness is localized to the CNS, the incidence of depression is dramatically higher.[14] For example, patients with acquired immune deficiency syndrome (AIDS) and possibly infection by the human immunodeficiency virus (HIV) can be expected to show higher than expected rates of depressive illness.[46,47]

Stroke

Direct injury to the brain can produce changes of affect that progress to a full syndrome of MDD. Robinson and co-workers[48–50] have intensively studied mood disorders that result from strokes. Left-hemisphere lesions involving the prefrontal cortex or basal ganglia are the most likely to be associated with poststroke depression (PSD) and to meet criteria for MDD or dysthymia.[50] Depressive symptoms appear in the immediate poststroke period in about two thirds of patients, with the rest manifesting depression by the 6th month. MDD and minor depression have different courses: MDD, left untreated, had a natural course of about 1 year, but minor depression had a more chronic (about a 2-year) course. Moreover, some untreated patients with minor depression went on to develop MDD. In depressed patients whose left-hemisphere strokes had a posterior cerebral artery distribution, depression was not only less severe but also of shorter duration, with a natural history of about 6 months. Additional risk factors for developing MDD were a prior stroke, preexisting subcortical atrophy, and a family or personal history of an affective disorder. Aphasia did not appear to cause depression, but nonfluent aphasia was associated with depression; both seemed to result from lesions of the left frontal lobe. Although the severity of functional impairment at the time of acute injury did not correlate with the severity of depression, depression appeared to retard recovery. Among patients with left-hemispheric damage, those who were depressed showed significantly worse cognitive performance, which was seen in tasks that assessed temporal orientation, frontal lobe function, and executive motor function. Successful treatment of PSD has been demonstrated by double-blinded studies with nortriptyline[51] and trazodone [52] and been reported with electroconvulsive therapy (ECT)[53] and use of psychostimulants.[54] In fact, a recent study has shown that nortriptyline was more effective than fluoxetine in treating depressive symptoms in patients with PSD.[55] Early and aggressive treatment of PSD is required to minimize the cognitive and performance deficits that this mood disorder inflicts on patients during the recovery period.

Right-hemisphere lesions deserve special attention. When the lesion was in the right anterior location, the mood disorder tended to be an apathetic, indifferent state associated with "inappropriate cheerfulness." However, such patients seldom look cheerful and may have complaints of loss of interest or even worrying. This disorder was found in 6 of 20 patients with solitary right-hemisphere strokes (and in none of 28 patients with single left-hemisphere lesions).

Prosody is also a problem for those with a right hemisphere injury. Ross and Rush[55a] focused on the presentation of aprosodia (lack of prosody or inflection, rhythm, and intensity of expression) when the right hemisphere is damaged. A patient with such a lesion could appear quite depressed and be labeled as having depression by staff and family but simply lacks the neuronal capacity to express or recognize emotion. If one stations oneself out of the patient's view, selects a neutral sentence (e.g., "The book is red"), asks the patient to identify the mood as mad, sad, frightened, or elated, and then declaims the sentence with the emotion to be tested, one should be able to identify those patients with a receptive aprosodia. Next, the patient is asked to deliver the same sentence with a series of different

emotional tones to test for the presence of an expressive aprosodia. Stroke patients can suffer from both aprosodia and depression, but separate diagnostic criteria and clinical examinations exist for each one.

Dementia

Primary dementia, even of the Alzheimer's type, increases the vulnerability of the patients to suffering MDD, even though the incidence is not as high as it is in multiinfarct or vascular dementia. The careful postmortem studies of Zubenko and colleagues[56,57] supported the hypothesis that the pathophysiology of secondary depression is consistent with theories of those for primary depression. Compared with demented patients without depression, demented patients with MDD showed a 10- to 20-fold reduction in cortical norepinephrine levels.

Multi-infarct or vascular dementia so commonly includes depression as a symptom that Hachinski and associates[58] included it in the Ischemia Scale. Cummings and co-workers[59] compared 15 patients with multi-infarct dementia with 30 patients with Alzheimer's disease and found that depressive symptoms (60% versus 17%) and episodes of MDD (4/15 versus 0/30) were more frequent in patients with the former.

Subcortical Dementias

Patients with Parkinson's disease and Huntington's disease commonly manifest MDD. In fact, Huntington's disease may present as MDD before the onset of either chorea or dementia.[60] The diagnosis is made clinically. Some have noted that as depression in the Parkinson's patient is treated, parkinsonian symptoms also improve, even before the depressive symptoms have subsided. This is especially striking when ECT is used,[61,62] although the same improvement has been reported after use of tricyclic antidepressants (TCAs). Treatment of MDD in either disease may increase the comfort of the patient and is always worth a try. Because Huntington's patients may be sensitive to the anticholinergic side effects of TCAs, anticholinergic agents should be tried first.

Another subcortical dementia worth noting is Binswanger's encephalopathy, a state of white matter demyelination presumably secondary to arteriosclerosis; it is characterized by an insidious, slowly progressive state with abulia and a paucity of focal neurologic findings.[63] Whenever affective symptoms are discovered, a trial of an antidepressant may provide striking relief for the patient.

Because the HIV-1 is neurotropic, even asymptomatic HIV-seropositive individuals, when compared with seronegative controls, demonstrate a high incidence of electroencephalographic abnormalities (67% versus 10%) and more abnormalities on neuropsychological testing.[64] The unusually high lifetime and current rates of mood disorders in HIV-seronegative individuals at risk for AIDS[65] demands an exceedingly high vigilance for their appearance in HIV-positive persons. Depression, mania, or psychosis can appear with AIDS encephalopathy, but the early, subtler signs (e.g., impaired concentration, complaints of poor memory, blunting of interests, lethargy) may respond dramatically to antidepressants, such as psychostimulants.[66,67] The selective serotonin reuptake inhibitors (SSRIs) (such as sertraline, fluoxetine, and paroxetine) have also been effective in the treatment of depression in HIV-positive patients.[68–72] A small open trial also supports the use of bupropion in these patients.[73]

We recommend that pharmacologic treatment be considered seriously whenever a patient meets criteria for either minor depression or MDD.

CHOICE OF AN APPROPRIATE ANTIDEPRESSANT TREATMENT

In Chapter 34, the properties, side effects, dosages, and drug interactions of antidepressant medications are discussed in detail. Whenever MDD is diagnosed, the effort to alleviate symptoms almost always includes somatic treatments. The consultant who understands the interactions among antidepressants, illnesses, and nonpsychotropic drugs is best prepared to prescribe these agents effectively. ECT remains the single most effective somatic treatment of depression. A nation-wide review has only sustained its merit. Indications for its use are discussed in Chapter 33.

Prescribing Antidepressants for the Medically Ill

Ever since sudden death in cardiac patients was first associated with amitriptyline,[74,75] physicians have tended to fear the use of TCAs when cardiac disease is present. However, depression itself is a life-threatening disease, and it should be treated. Choice of an agent often begins with the knowledge that a patient is especially troubled by insomnia; however, in patients with certain medical illnesses, the decision must be made on a case-by-case basis, taking into consideration the side-effect profile (risk), the anticipated benefits, and potential drug–drug interactions. In obese diabetic patients, fluoxetine has ameliorated mean blood glucose levels, daily insulin requirements, and glycohemoglobin levels,[76–80] perhaps by improving insulin sensitivity.[81,82] In contrast, TCAs, such as nortriptyline, may actually worsen glycemic control.[83] However, TCAs have been found to be superior to fluoxetine in decreasing pain secondary to diabetic neuropathy.[84]

One could also make a similar argument for patients with hypercholesterolemia, because the SSRI fluvoxamine has decreased serum cholesterol levels,[85] whereas TCAs appear to increase cholesterol levels.[86]

With respect to making a decision based on insomnia, the sedative potency of the available antidepressants can generally be predicted by their in vitro affinity for the histamine H_1 receptor. Table 9–4 shows these values.[87,88] The antihistaminic property of these drugs gives a reasonably good estimate of their sedative properties. Trazodone, which has low affinity for the H_1 receptor, is, however, a sedating agent.

This same property can also be used to predict how much weight gain may be associated with use of the antidepressant. Patients troubled by obesity may be placed at additional risk if treated with those agents higher on the list. For the most part, the SSRIs, bupropion, nefazodone, trazodone, and venlafaxine have negligible antihistaminic potency. The monoamine oxidase inhibitors (MAOIs) generally have low sedative potency, although

TABLE 9–4 Relationship of Antidepressants to Neurotransmitter Receptors

ANTIDEPRESSANT	EFFECT ON BIOGENIC AMINE UPTAKE: POTENCY*		SELECTIVITY FOR BLOCKING UPTAKE OF 5-HT OVER NE	AFFINITIES† FOR NEUROTRANSMITTER RECEPTORS							
				HISTAMINE		ADRENERGIC		SEROTONIN		MUSCARINIC	DOPAMINE
	5-HT	NE		H_1	H_2	α_1	α_2	S_1	S_2	ACh	D-2
Doxepin	0.36	5.3	0.068	420	0.6	4.2	0.091	0.34	4.0	1.2	0.042
Amitriptyline	1.5	4.2	0.36	91	2.2	3.7	0.11	0.53	3.4	5.5	0.10
Imipramine	2.4	7.7	0.31	9.1	0.4	1.1	0.031	0.011	1.2	1.1	0.050
Clomipramine	18	3.6	5.2	3.2	—	2.6	0.031	0.014	3.7	2.7	0.53
Trimipramine	0.040	0.20	0.2	370	33.3	4.2	0.15	0.012	3.1	1.7	0.56
Protriptyline	0.36	100	0.0035	4	0.05	0.77	0.015	0.011	1.5	4.0	0.043
Nortriptyline	0.38	25	0.015	10	0.12	1.7	0.040	0.32	2.3	0.67	0.083
Desipramine	0.29	110	0.0026	0.91	0.08	0.77	0.014	0.010	0.36	0.50	0.030
Amoxapine	0.21	23	0.0094	4	—	2	0.038	0.46	170.0	0.10	0.62
Maprotiline	0.030	14	0.0022	50	—	1.1	0.011	0.0083	0.83	0.18	0.29
Trazodone	0.53	0.020	26	0.29	—	2.8	0.20	1.7	13.0	0.00031	0.026
Fluoxetine	8.3	0.36	23.0	0.016	—	0.017	0.008	0.0042	0.48	0.050	—
Bupropion	0.0064	0.043	0.15	0.015	—	0.022	0.0012	0.0059	0.0011	0.0021	0.00048
Sertraline	29	0.45	64.0	0.0041	—	0.27	—	—	—	0.16	0.0093
Paroxetine	136.0	3	45.0	0.0045	—	0.029	—	—	—	0.93	0.0031
Fluvoxamine	14.0	0.2	71.0	—	—	—	—	—	—	—	—
Venlafaxine	2.6	0.48	5.4	0	—	0	—	—	—	0	0
Nefazodone	0.73	0.18	4.2	—	—	—	—	—	—	—	—
Mirtazapine	—	—	—	200.00	—	0.2	5	—	0.2	0.040	—
(Dextromphetamine)‡	2	—	—	—	—	—	—	—	—	—	—
(Diphenhydramine)‡	—	—	—	7.1	—	—	—	—	—	—	—
(Phentolamine)‡	—	—	—	—	—	6.7	—	—	—	—	—
(Yohimbine)‡	—	—	—	—	—	—	62	—	—	—	—
(Methysergide)‡	—	—	—	—	—	—	—	—	7.8	—	—
(Atropine)‡	—	—	—	—	—	—	—	—	—	42	—
(Haloperidol)‡	—	—	—	—	—	—	—	—	—	—	23

Adapted from Richelson E: Pharmacology of antidepressants—characteristics of the ideal drug, *Mayo Clin Proc* 69:1069–1081, 1994.

*$10^7 \times 1/K_i$, where K_i = inhibitor constant in molarity.

†$10^7 \times 1/K_d$, where K_d = equilibrium dissociation constant in molarity.

‡Drugs in parentheses are not antidepressants.

ACh, Acetylcholine; *HT*, serotonin; *NE*, norepinephrine.

phenelzine sulfate can produce complaints of drowsiness. Mirtazapine,[89] a powerful antagonist of the H_1 receptor, is quite sedating and can be associated with significant weight gain.

All antidepressants in the cyclic, SSRI, and MAOI categories usually correct sleep disturbances (insomnia or hypersomnia) when these are symptoms of depression, a therapeutic effect not thought to be related to their effects on brain histamine. Therefore, this discussion highlights a sedative effect of the drugs that occurs in addition to, and independent of, these agents' ability to correct the specific sleep disturbances of MDD (e.g., to lengthen rapid-eye-movement sleep latency).

Occasionally, the consultant may encounter a patient in whom antihistamines have been tried and have failed to achieve a therapeutic effect, such as in the treatment of an urticarial rash or the itching associated with uremia. Doxepin hydrochloride, possibly the most potent antihistamine in clinical medicine, has demonstrated superiority with a 10-mg dose when compared with 25 mg of diphenhydramine hydrochloride.[90]

Threatening the successful use of antidepressants is the presence of unwanted side effects. The three groups of side effects that are particularly relevant for the treatment of depression in the acute medical setting are orthostatic hypotension (OH), anticholinergic effects, and cardiac conduction effects. The clinical ratings for these three side-effect groups with current antidepressants are presented in Table 9–5. We will discuss side effects specific to each antidepressant class, and side effects associated with abrupt discontinuation of antidepressant treatment. When these side effects are understood, safe clinical prescription of antidepressant drugs is far more likely.

Orthostatic Hypotension

OH is not directly related to each drug's in vitro affinity for the α_1-noradrenergic receptor. Table 9–5 presents the drugs with a clinical rating of their likelihood of causing an orthostatic drop in blood pressure (BP). In general, among the TCAs, tertiary amine agents are more likely to cause an orthostatic fall in BP than are secondary amines. For reasons that are not clearly understood, imipramine, amitriptyline, and desipramine are the TCAs most commonly associated with clinical mishaps, such as falls and fractures. The orthostatic effect appears earlier than the therapeutic effect for imipramine and is objectively verifiable at less than half the therapeutic plasma level. Hence the drug may have to be discontinued long before a therapeutic plasma level is reached. Once postural symptoms develop, increasing the dosage of the antidepressant may not make the symptoms worse.

Paradoxically, a pretreatment fall of more than 10 mm Hg in orthostatic BP actually predicts a good response to antidepressant medication in older adult depressed patients.[91,92] Naturally, younger patients may tolerate a fall in BP more easily than older patients, so an orthostatic fall in BP may not produce symptoms serious enough to require discontinuation of the drug. The presence of cardiovascular disease increases the likelihood of OH. When patients with no cardiac disease take imipramine, the incidence of significant OH is 7%. With conduction disease, such as a bundle-branch block (BBB), the incidence rises to 33%, and with congestive heart failure (CHF), it reaches 50%.[93] Of the traditional TCAs, nortriptyline has been shown to be the least likely to cause OH, an extremely valuable factor when depression in cardiac or older adult patients requires treatment.[94] MAOIs cause significant OH with about the same frequency as imipramine (i.e., often). Moreover, the patient starting on an MAOI usually does not experience OH until the medication is having a significant therapeutic effect, roughly 2 to 4 weeks later.

Among other agents, trazodone is associated with OH moderately often, as is mirtazapine. Fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, bupropion, venlafaxine, and psychostimulants are essentially free of this side effect. Bupropion, psychostimulants, and venlafaxine may raise systolic BP slightly in some patients. Some have noted that even though the objective fall in standing BP continues for several months, some patients with initial symptoms accommodate subjectively and no longer complain of the side effect.

Anticholinergic Effects

The anticholinergic effects of TCAs are a nuisance for many patients. Urinary retention, constipation, dry mouth, confusional states, and tachycardia are the most common. The increase in heart rate is usually manifested as a sinus tachycardia that results from muscarinic blockade of vagal tone on the heart. As many as 30% of normal individuals respond to amitriptyline with tachycardia.[95] This side effect correlates nicely with the in vitro affinity of each drug for the acetylcholine muscarinic receptor (see Table 9–4). As seen in the table, amitriptyline is the most anticholinergic of the antidepressants, with protriptyline a close second. These two agents regularly cause tachycardia in the medically ill, and one should monitor the heart rate as the dosage is increased. If significant tachycardia results, another agent may have to be used. Many hospitalized patients, particularly those with ischemic heart disease, are already being treated with β-blockers, such as propranolol. When this is the case, the β-blocker usually protects the patient from developing a significant tachycardia.

All of the cyclic agents except trazodone are anticholinergic. If one switches from, for example, imipramine to desipramine because the patient developed urinary retention, the patient is quite likely to develop urinary retention again on desipramine. Amoxapine and maprotiline are not significantly less anticholinergic than desipramine. Trazodone is almost devoid of activity at the muscarinic receptor, and it is a reasonable choice when another agent has caused unwanted anticholinergic side effects.

Fluoxetine, bupropion, venlafaxine, and the MAOIs exert minimal activity at the acetylcholine muscarinic receptor; hence, they can also be useful alternatives when these side effects impair a patient's access to an antidepressant. There is laboratory evidence (see Table 9–4) with anecdotal clinical support that paroxetine is more anticholinergic, close in in vitro potency to imipramine. Likewise, in Richelson's[88] laboratory, sertraline and maprotiline appear to have quite similar anticholinergic effects. For maprotiline, this effect is clinically noticeable (e.g., dry mouth) but usually mild. Similar mild effects seem to accompany the use of mirtazapine. Effects of fluvoxamine and nefazodone are generally mild.

TABLE 9–5 Characteristics of Antidepressant Drugs

	ELIMINATION HALF-LIFE (hr)	SEDATIVE POTENCY	ANTICHOLINERGIC POTENCY	ORTHOSTATIC HYPOTENSION	CARDIAC ARRHYTHMIA POTENTIAL	TARGET DOSAGE (mg/day)	DOSAGE RANGE (mg/day)
Tricyclics							
Doxepin	17	High	Moderate	High	Yes	200	75-400
Amitriptyline	21	High	Highest	High	Yes	150	75-300
Imipramine	28	Moderate	Moderate	High	Yes	200	75-400
Trimipramine	13	High	Moderate	High	Yes	150	75-300
Clomipramine	23	High	High	High	Yes	150	75-300
Protriptyline	78	Low	High	Moderate	Yes	30	15-60
Nortriptyline	36	Moderate	Moderate	Moderate	Yes	100	40-150
Desipramine	21	Low	Moderate	Moderate	Yes	150	75-300
Others							
Citalopram	33	Low	Low	Low	Low	20	20-80
Escitalopram	22	Low	Low	Low	Low	10	10-20
Maprotiline	43	High	Moderate	Moderate	Yes	150	75-300
Trazodone	3.5	High	Lowest	Moderate	Yes	150	50-600
Fluoxetine	87	Low	Low	Lowest	Low	20	40-80
Sertraline	26	Low	Low	Lowest	Low	50	50-200
Paroxetine	21	Low	Low-Moderate	Lowest	Low	20	20-60
Fluvoxamine	19	Low	Low	Low	Low	200	50-300
Bupropion	15	Low	Low	Lowest	Low	200	75-300
Venlafaxine	3.6	Low	Low	Low	Low	300	75-375
Desvenlafaxine	10	Low	Low	Low	Low	50	50-400
Duloxetine	12	Low	Low	Low	Low	40	40-120
Nefazodone	3	Moderate	Low	Low	Low	300	300-600
Mirtazapine	30	High	Low	Low	Low	15	15-45
Selegiline (transdermal)	18	Low	Low	Moderate	Low	6	6-12
Monoamine oxidase inhibitors	—	Low	Low	High	Low	—	—

Cardiac Conduction Effects

All TCAs appear to prolong ventricular depolarization. This tends to produce a lengthening of the P-R and QRS intervals as well as of the Q-T interval corrected for heart rate (QTc) on the electrocardiogram (ECG). When the main effect of these agents is measured by His-bundle electrocardiography, the His-ventricular portion of the recording is preferentially prolonged. That is, these drugs, which are sodium-channel blockers, tend to slow the electric impulse as it passes through the specialized conduction tissue known as the His-Purkinje system. This makes them resemble in action the class IA arrhythmic drugs, such as quinidine and procainamide hydrochloride. In practical terms, this means that depressed cardiac patients with ventricular premature contractions, when started on an antidepressant, such as imipramine, are likely to experience improvement or resolution of their ventricular irritability, even if the abnormality is as serious as inducible ventricular tachycardia. Both imipramine and nortriptyline have proved efficacy as antiarrhythmics and share the advantage of a half-life long enough to permit twice-daily doses.[96–98]

Ordinarily, this property does not pose a problem for the cardiac patient who does not already have disease in the conduction system. The patient who already has conduction system disease is the focus of concern. First-degree heart block is the mildest pathologic form and probably should not pose a problem for antidepressant treatment. When the patient's abnormality exceeds this (e.g., right BBB, left BBB, bifascicular block, BBB with a prolonged P-R interval, alternating BBB, or second- or third-degree atrioventricular [AV] block), extreme caution is necessary in treating the depression. Cardiology consultation is almost always already present for the patient. Electrolyte abnormalities, particularly hypokalemia or hypomagnesemia, increase the danger to these patients, and they require careful monitoring.

Occasionally, the question arises clinically whether one of the cyclic agents is less likely than another to cause a quinidine-like prolongation in conduction, particularly when the patient already shows some intraventricular conduction delay. Maprotiline should be regarded as similar to the TCAs in its effects on cardiac conduction. Amoxapine has been touted to have fewer cardiac side effects, based on patients who had taken overdoses. Although these patients were noted to have suffered seizures, coma, and acute renal failure, the authors thought it worth noting that less cardiac toxicity resulted,[99,100] but atrial flutter and fibrillation have been reported in patients taking amoxapine.[101,102] Trazodone does not prolong conduction in the His-Purkinje system, but aggravation of the preexisting ventricular irritability has been reported.[103] Hence clinical caution cannot be abandoned.

MAOIs are remarkably free of arrhythmogenic effects, although there are several case reports of atrial flutter or fibrillation, or both, with tranylcypromine. Consultees tend to dread them, fearing drug and food interactions.

How, then, should the consultant approach the depressed patient with conduction disease? Depression can itself be life-threatening and more damaging to cardiac function than a drug. Therefore, it must be treated. In the case of a depressed patient with cardiac conduction problems, one can begin with an SSRI, bupropion, venlafaxine, nefazodone, or mirtazapine. Should the depression not remit completely, reasonable options include augmentation with a psychostimulant or switching to a psychostimulant. Should the patient improve, the stimulant can be continued as long as it is helpful. By starting with a low dosage (2.5 mg of either dextroamphetamine or methylphenidate), one is reasonably assured that toxicity will not result. The fragile patient can have heart rate and BP monitored hourly for 4 hours after receiving the drug. If no beneficial response is noted, the next day the dosage should be raised to 5 mg (our usual starting dosage), then to 10, 15, and 20 mg on successive days, if necessary. Some response to the stimulant should be seen, even a negative one (e.g., feeling more tense, "wired," or agitated). It makes little sense to stop a stimulant trial if no response is seen, or unless the patient can report some subjective verification of a drug effect. Of course, an elevation of heart rate or BP may be a reason to stop the trial. The degree of clinical vigilance must match the clinical precariousness of the patient. Discussion of the type and intensity of monitoring takes place with the consultee.

The role of the psychiatric consultant is to recommend aggressive treatment for depression, with the consultee helping to decide what means is appropriate and to detect possible side effects. If the patient's depression fails to remit despite a number of adequate antidepressant trials, an MAOI is reasonable even with an unstable cardiac condition, provided that the patient can tolerate the OH that may result. The adage, "start low, go slow," which is so appropriate in the treatment of older adult patients, is also a good rule for medically unstable patients.

If the depression has left the patient dangerously ill, suicidal, or catatonic, ECT is the treatment of choice. When an antidepressant can be used, monitoring must take into account both the development of a steady state (which typically takes about five half-lives of the drug) and the rate at which the dosage is being increased. When the patient requires a daily dosage increase, a daily rhythm strip may be necessary as well as another one, five half-lives after reaching the level thought to represent the therapeutic dosage. Plasma levels are especially useful when a 4- to 8-week drug trial is judged worthwhile. Reliable levels have been established only for nortriptyline hydrochloride (50 to 150 ng/mL), desipramine hydrochloride (>125 ng/mL), and imipramine hydrochloride (>200 ng/mL).

Myocardial Depression

Antidepressants have not been shown to impair left ventricular function significantly in depressed or nondepressed patients with either normal or impaired myocardial contractility.[104–107] Even with TCA overdose, impairment of left ventricular function is generally mild.[108] Hence, CHF is not an absolute contraindication to antidepressant therapy.[106–108] The patient with heart failure is far more vulnerable to OH; hence the SSRIs, bupropion, venlafaxine, and nortriptyline, are the preferred agents.

A severely depressed patient could suffer an acute MI. Both conditions are a threat to survival, and the MI is no contraindication to antidepressant treatment. ECT or drugs may be mandatory. Using the previously mentioned principles, psychiatrists and cardiologists must combine their efforts to restore the patient's health.

Other Side Effects (Specific to Each Antidepressant Class)

Other common side effects of bupropion include anxiety and nervousness, agitation, insomnia, headache, nausea, constipation, and tremor. Bupropion is contraindicated in the treatment of patients with a seizure disorder or bulimia, because the incidence of seizures is approximately 0.4% at dosages up to 450 mg/day, and increases almost 10-fold at higher dosages.

Common side effects of venlafaxine include nausea, lack of appetite, weight loss, excessive sweating, nervousness, insomnia, sexual dysfunction, sedation, fatigue, headache, and dizziness.

Mirtazapine's side effects include dry mouth, constipation, weight gain, and dizziness. The relative lack of significant drug–drug interactions with other antidepressants makes mirtazapine a good candidate for combination strategies (i.e., combining two antidepressants together at full dosages).

Trazodone's most common side effects are drowsiness, dizziness, headache, and nausea, with priapism being an extremely rare but potentially serious side effect in men.

Antidepressant Discontinuation Syndrome

Several reports have described discontinuation-emergent adverse events with abrupt cessation of SSRIs and venlafaxine,[109,110] including dizziness, insomnia, nervousness, nausea, and agitation. The likelihood of developing these symptoms may be inversely related to the half-life of the SSRI used, because these symptoms are more likely to develop after abrupt discontinuation of paroxetine and to a lesser degree with sertraline, with few symptoms seen with fluoxetine discontinuation.

Psychostimulant Use

Earlier MGH experience with the use of dextroamphetamine and methylphenidate, which showed them to be safe and effective in depressed mentally ill patients,[111] has been reconfirmed.[54] Their use as therapeutic agents was gradually discontinued a number of years ago,[112] but when patients with symptoms of MDD and minor depression continued to respond to stimulants, often achieving remission of their symptoms, these agents once again became used as independent antidepressants in our consultation practice. Their effects on heart rate and BP have been trivial, even though any patient with hypertension or unstable cardiac rhythm requires monitoring of vital signs when started on these agents. The most common fear expressed about their use was that they would reduce appetite in patients who were already anorectic from their illness or their depression or both. However, this was not the case. Instead, increased appetite has been reported by the patients—another striking and important benefit associated with their use.

Finally, in those patients who suffered both depressive symptoms and either dementia or an organic brain syndrome (e.g., from head injury), there was a fear that use of a stimulant would result in agitation, confusion, or psychosis. In 17 patients with an associated diagnosis of dementia, only two showed a worsening of confusion, which disappeared within 24 hours of discontinuation of the drug.[111] Hence, our practice is now to begin with a stimulant. If it helps (as it did to a moderate or marked degree in 48% of the patients), it does so within a short time: Approximately 93% of the patients who responded positively reached their maximum benefit by the second day. As long as it helps, the stimulant is maintained. Tolerance was not found in our patient sample. The same dosage of the stimulant was maintained until the depressive symptoms cleared or the patient was discharged. A small group of patients were discharged with instructions to continue taking the agent at home. The majority stopped the medication within 2 or 3 weeks. A few continued for 1 year or longer.

There is a strong bias against stimulants (dextroamphetamine more so than methylphenidate), because of associated street abuse. In the MGH review cited, neither tolerance nor abuse was found in the patients for whom these agents were prescribed.[112]

Hepatic Metabolism

Essentially all antidepressants are metabolized by the hepatic P450 microsomal enzyme system. The interactions produced by the competition of multiple drugs for these metabolic pathways are complex (see Chapter 34). For example, mirtazapine is a substrate for, but not an inhibitor of, the 2D6, 1A2, and 3A4 isoenzymes.

How long antidepressants need to be maintained in patients with MDD associated with medical illness is not known. Even though patients with primary affective disorder should be maintained on their antidepressant for more than 6 months, the same requirement is not clear for patients with MDD in the medical setting. In patients with PSD, and possibly in other instances in which primary brain disease or injury appears to cause depression, antidepressants should be continued for 6 months or longer.

Secondary Mania

Occasionally, a clinician is asked to see a patient with mania or hypomania of 1 week's duration (or longer), in whom no history of affective disorder can be obtained. Described by Krauthammer and Klerman,[113] this phenomenon results from an organic dysfunction. Table 9–6 lists some causes of secondary mania. The emergence of mania or hypomania usually signifies the presence of bipolar disorder, but cases such as those in Table 9–6 continue to accumulate in the literature, indicating that alteration of brain states can lead to a clinical picture indistinguishable from primary mania.[114–123] Of clinical note was the report that in HIV-positive patients with mania, an abnormal magnetic resonance imaging (MRI) scan predicted poor response to lithium and neuroleptics but a beneficial response to anticonvulsants.[122]

Use of Lithium Carbonate in the Medically Ill

The treatment of secondary mania is the same as that for primary mania. Neuroleptics, lithium carbonate, or anticonvulsants are required in most cases, although lorazepam and clonazepam may prove to be helpful in the acute phase.

A word of caution is appropriate when lithium is used in older adults or in patients with cardiac disease. On the ECG of a patient taking lithium, a benign and reversible T-wave flattening is seen in approximately 50% of cases. Lithium

TABLE 9–6 Reported Causes of Secondary Mania

Drugs	Alcohol intoxication, alprazolam, captopril, cimetidine, corticosteroids, cyclobenzaprine, cyproheptadine, disulfiram, felbamate, isoniazid, levodopa, L-glutamine, L-tryptophan, lysergic acid diethylamide, methylphenidate, metrizamide, metoclopramide, procainamide, procarbazine, propafenone, sympathomimetics, thyroxine, tolmetin, triazolam, yohimbine, zidovudine
Drug withdrawal	Clonidine, diltiazem, atenolol, isocarboxazid, propranolol
Metabolic	Hemodialysis, postoperative state, hyperthyroidism, vitamin B_{12} deficiency, Cushing's syndrome, cerebral hypoxia
Infection	Influenza, Q fever, post–St. Louis type A encephalitis, cryptococcosis, human immunodeficiency virus, neurosyphilis
Neoplasm	Meningiomas, gliomas, thalamic metastases, brainstem tumor
Epilepsy	Complex partial seizures with right temporal focus
Surgery	Right hemispherectomy
Cerebrovascular accident	Thalamic stroke
Other	Cerebellar atrophy, head trauma, multiple sclerosis, Wilson's disease

appears to have some inhibitory effects on impulse generation and transmission in the atrium. Hence, the reports of adverse cardiac effects of lithium have been those of sinus node dysfunction and first-degree AV block.[124–126] Because older adults seem particularly prone to these effects, caution is essentially reserved for them and for patients who have preexisting disturbances of atrial conduction.[127]

Ordinarily, lithium's effects on the heart can be assumed to be benign, but as any serious illness becomes more complicated and as treatments increase, patients are at greater risk. Mania, like depression, can seldom be tolerated by the patient or by caregivers. Whether the alternative treatments (such as use of calcium channel blockers, or use of adjunctive measures, such as lorazepam) are useful in secondary mania remains to be established.

Thioridazine

A final caution about cardiovascular toxicity should include discussion of thioridazine. Notorious among neuroleptics for its potential cardiac side effects, this drug should not be used in combination with TCAs unless there is a special need. It, too, possesses quinidine-like properties, has been associated with reports of sudden death that antedate similar reports with TCAs,[128] and was more recently implicated in the causation of ventricular tachycardia alone[129] and in combination with desipramine.[130] Thioridazine's anticholinergic potency is high (roughly equivalent in vitro to that of desipramine), which can be troublesome. This property, however, might make it particularly useful to treat the delirium of a patient with Parkinson's disease. As little as 5 to 10 mg can be helpful in such a patient. Again, it is important to avoid hypokalemia and hypomagnesemia, which predispose patients to cardiac rhythm disturbances.

OTHER DSM-IV DIAGNOSES OF DEPRESSION

Dysthymic Disorder

For the diagnosis of dysthymia (300.40), DSM-IV specifies a chronic state of depression that does not meet the full criteria for MDD. To qualify, the patient must have depressed (or, for children and adolescents, irritable) mood for most of the day, and on more days than not, for more than 2 years, and have two or more of the following six symptoms: (1) poor appetite or overeating, (2) insomnia or hypersomnia, (3) low energy or fatigue, (4) low self-esteem, (5) poor concentration or difficulty making decisions, and (6) feelings of hopelessness. For medically ill patients, this diagnosis could be used, dropping the duration requirement, to specify minor depression. Use of antidepressants is necessary in minor depression after stroke, but there are few if any other studies to guide treatment.

In DSM-IV the diagnostic criteria for MDD can be applied even when the depression follows the medical condition (and is therefore secondary). The terminology states that the mood disturbance is "due to," for example, stroke, MI, or HIV infection. The mood can be described as "with depressive features," "with major depressive-like episode," "with manic features," or "with mixed features."

Adjustment Disorder with Depressed Mood

Adjustment disorder with depressed mood (309.00) is probably the most overused diagnosis by consultation psychiatrists. It should not be given to a medical patient unless the depressive reaction is maladaptive, either in intensity of feeling (an overreaction) or in function (e.g., when a despondent patient interacts minimally with caregivers and family).

Bereavement

Bereavement (V62.82) refers to the death of a loved one. In the case of the medical patient, of course, it is the self that is mourned after a narcissistic injury (e.g., an MI). DSM-IV unnecessarily restricts bereavement to loss of a loved one. In acute grief, MDD can be a difficult diagnosis, but, when it is present, it requires treatment (perhaps even more than when it is present without acute grief). Clues helpful to determine the presence of MDD include (1) guilt beyond that about actions taken around the time of the death of the loved one, (2) thoughts of death (other than wanting to be with the lost person) or feeling one would be better off dead—suicidal ideation should count in favor of MDD, (3) morbid preoccupation with worthlessness, (4) marked psychomotor retardation, (5) prolonged and marked functional impairment, (6) hallucinations other than seeing, hearing, or being touched by the deceased person.

Prigerson and associates[131] developed two useful empirical constructs: bereavement depression (depressive symptoms in wake of a loss) and complicated grief. The first predicts future medical burden of the person, and the latter predicts functional impairment at 18-month follow-up. The symptoms related to the bereavement-depression factor are hypochondriasis, apathy, insomnia, anxiety, suicidal ideation, guilt, loneliness, depressed mood, psychomotor retardation, hostility, and low self-esteem. The symptoms that are the principal components of the complicated grief factor are yearning for, and preoccupation with, thoughts of the deceased, crying, searching for the deceased, disbelief about the death, being stunned by the death, and inability to accept the death. When patients with a Hamilton depression scale score higher than 17 were treated with nortriptyline, at dosages that averaged a low but therapeutic level of 68.1 ng/mL, those treated lowered their bereavement-depression scores substantially. This supports our clinical recommendation that any person who meets criteria for MDD should be treated. There is no evidence that antidepressants retard the grieving process.

DESPONDENCY CONSEQUENT TO SERIOUS ILLNESS

Despondency in serious illness appears to be a natural response and is here regarded as the psychic damage done by the disease to the patient's self-esteem. Bibring's[132] definition of depression is "response to narcissistic injury." The response is here called *despondency* and not *depression* because depression is reserved for those conditions that meet the research criteria for primary or secondary affective disorder. In any serious illness, the mind sustains an injury of its own, as though the illness, for example, MI, produces an ego infarction. Even when recovery of the diseased organ is complete, recovery of self-esteem appears to take somewhat longer. In patients who had an MI, for example, although the myocardial scar has fully formed in 5 to 6 weeks, recovery of the sense of psychological well-being seems to require 2 to 3 months.

Management of the Acute Phase of Despondency

A mixture of dread, bitterness, and despair, despondency presents the self as broken, scarred, and ruined. Work and relationships seem jeopardized. Now it seems to the patient too late to realize career or personal aspirations. Disappointment with both what has and what has not been accomplished haunts the individual, who may now feel old and a failure. Concerns of this kind become conscious early in acute illness, and their expression may prompt consultation requests as early as the second or third day of hospitalization.[133]

Management of these illness-induced despondencies is divided into acute and long-term phases. In the acute phase, the patient is encouraged but never forced to express such concerns. The extent and detail are determined by the individual's need to recount them. Many patients are upset to find such depressive concerns in consciousness and even worry that this signals a "nervous breakdown." It is therefore essential to let patients know that such concerns are the normal emotional counterpart of being sick and that even though there will be ups and downs in their intensity, these concerns will probably disappear gradually as health returns. It is also helpful for the consultant to be familiar with the rehabilitation plans common to various illnesses, so that patients can also be reminded, while still in the acute phase of recovery, that plans for restoring function are being activated.

Paradoxically, many of the issues discussed in the care of the dying patient (see Chapter 41) are relevant here. Heavy emphasis is placed on maintaining the person's sense of self-esteem. Self-esteem often falters in seriously ill persons even though they have good recovery potential. Hence, efforts to learn what the sick person is like can help the consultant alleviate the acute distress of a damaged self-image. The consultant should learn any "defining" traits, interests, and accomplishments of the patient so that the nurses and physicians can be informed of them. For example, after learning that a woman patient had been a star sprinter on the national Polish track team preparing for the 1940 Olympics, the consultant relayed this both in the consultation note and by word of mouth to her caregivers. "What's this I hear about your having been a champion sprinter?" became a common question that made her feel not only unique but appreciated. The objective is to restore to life the real person within the patient who has serious organic injuries or impairment.

Few things are more discouraging for the patient, staff, or consultant than no noticeable sign of improvement. When there is no real progress, all the interventions discussed in Chapter 41 are necessary. At other times, progress is being made, but so slowly that the patient cannot feel it in any tangible way. By using ingenuity, the consultant may find a way to alter this. Many of the following suggestions apply, and knowledge of the physiology of the illness is essential. Psychological interventions, however, can also be helpful. For example, getting a patient with severe CHF out of bed and into a reclining chair (known for 25 years to produce even less cardiovascular strain than the supine position)[134] can provide reassurance and boost confidence. For some patients with severe ventilatory impairments and difficulty weaning from the respirator, a wall chart depicting graphically the time spent off the ventilator each day (one gold star for each 5-minute period) is encouraging. Even if the patient's progress is slow, the chart documents and dramatizes each progressive step. Of course, personal investment in very ill persons may be far more therapeutic in itself than any gimmick, but such simple interventions have a way of focusing new effort and enthusiasm on each improvement.

Management of Post-Acute Despondencies: Planning for Discharge and After

Even when the patients are confident their illness is not fatal, they usually become concerned that it will cripple them. Such psychological "crippling" is a normal hazard of organic injury. Whether the patient had an uncomplicated MI and is still employable, or has chronic emphysema with a carbon dioxide tension of 60 mm Hg, only restoration of self-esteem can protect him or her from emotional incapacitation. Even when the body has no room for improvement,

the mind can usually be rehabilitated. Arrival home from the hospital often proves to be a vast disappointment. The damage caused by illness has been done, acute treatment is completed, and health professionals are far away. Weak, anxious, and demoralized, the patient experiences a "homecoming depression."[135] Weakness is a universal problem for any individual whose hospitalization required extensive bed rest; in fact, it was the symptom most complained of by one group of post-MI patients visited in their homes.[135] Invariably the individuals attribute this weakness to the damage caused by the disease (e.g., to the heart, lungs, and liver). A large part of this weakness, however, is the result of muscle atrophy and the systemic effects of immobilization. Bed rest includes among its ill effects venous stasis with threat of phlebitis, embolism, OH, a progressive increase in resting heart rate, loss of approximately 10% to 15% of muscle strength per week (resulting from atrophy), and reduction of approximately 20% to 25% in maximal oxygen uptake capacity in a 3-week period. This was dramatically illustrated by the study of Saltin and associates[136] of five healthy college students who, after being tested in the laboratory, were placed on 3 weeks' bed rest. Three of the men were sedentary, and two were trained athletes. As shown in Figure 9–1, after the period of bed rest, it took the three sedentary men 8, 10, and 13 days to regain their pre–bed-rest maximal oxygen uptake levels, whereas it took the two athletes 28 and 43 days to reach their initial values. The better the patient's condition, the longer it takes for the recovery of strength. Entirely unaware of the physiology of muscle atrophy, patients mistakenly believe that exercise, the only treatment for atrophy, is dangerous or impossible.

Fear can be omnipresent after discharge from the hospital. The least bodily sensation, particularly in the location of the affected organ, looms as an ominous sign of the worst recurrence (e.g., MI, malignancy, gastrointestinal bleeding, or perforation), metastatic spread, (another) infection, or some new disaster that will cripple the individual even further. Most of the alarming symptoms felt in the early post-hospital days are so trivial that they would never have been noticed before, but the threshold is far lower now, and patients may find any unusual sensation a threat. When the alarm has passed, they may feel foolish or even disgusted with themselves for being hypochondriacal. It helps to know in advance that such hypersensitivity to bodily sensations commonly occurs, that it is normal, and that it will be limited in time. Although there are wide ranges in the time it takes for this problem to disappear, a well-adjusted patient who had an uncomplicated MI requires from 2 to 6 months for these fears to resolve (far more time than the recovery of the myocardium). With specific measures, this time may be shortened.

Whether the person can improve a physical function such as oxygen consumption (e.g., as after an MI or gastrointestinal bleeding) or cannot do so at all (e.g., after chronic obstructive pulmonary disease), the mental state is basically the same—a sense of imprisonment in a damaged body that is unable to sustain the everyday activities of a reasonable life. The illness has mentally crippled the individual. Horizons have shrunk drastically, so that the person may feel literally unable or afraid to leave the house, to walk across a room, or to stray far from the phone. Moreover, such people are likely to regard routine activities like walking, riding a bike, or raking leaves as too exhausting or dangerous. For some individuals, life comes to a near standstill.

The best therapy for such psychological constriction is a program that emphasizes early and progressive mobilization in the hospital and exercise after discharge. A physician might naturally be wary of prescribing this for a person with severe chronic obstructive pulmonary disease who is dyspneic while walking at an ordinary pace. For some significantly impaired chronic pulmonary patients,[137] however, objective exercise tolerance can be increased as much

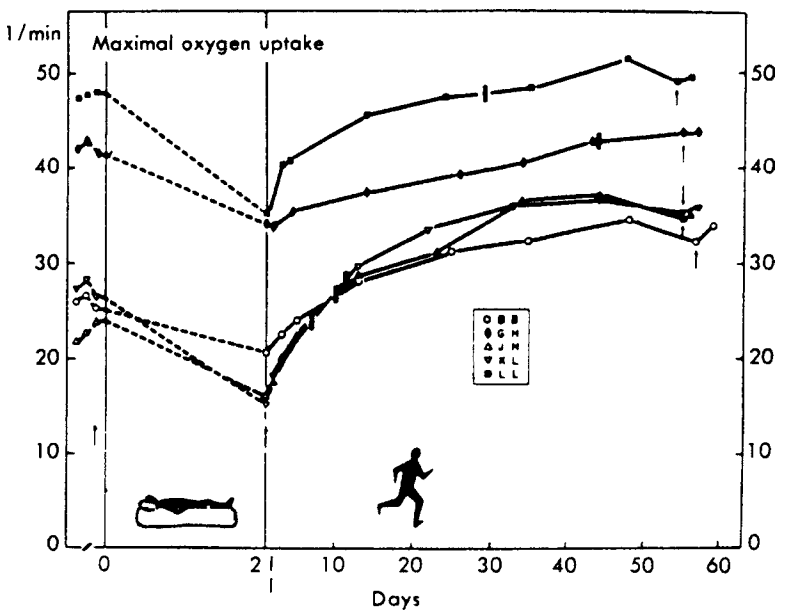

Figure 9–1. Maximal oxygen uptake in sedentary and athletic men after 3 weeks' bed rest.

as 1000-fold. The improvement is the result of better limb muscle conditioning. The patient does not have to change pulmonary function at all to experience significantly greater endurance.[138] Several self-imposed restrictions (e.g., never being far from an oxygen tank) are dramatically relieved. The psychiatric consultant should be aware that patients with chronic pulmonary disease that is considered to be irreversible can be significantly helped by a specific rehabilitation program.[139–142]

The writing of exercise regimens for the recuperation period has been greatly helped by the definition and use of the metabolic equivalent (MET). One MET is defined as the energy expenditure per kilogram per minute of the average 70-kg person sitting quietly in a chair. This amounts to approximately 1.4 cal/min or 3.5 to 4.0 mL of oxygen consumed per kilogram per minute. Table 9–7 lists activities for which measurements in METs have been determined.[143] For example, after recovery from uncomplicated MI, the average middle-aged person is capable of performing at a level of 8 to 9 METs. This includes running at 5.5 miles per hour (jogging slightly faster than 11-minute miles), cycling at 13 miles per hour, skiing at 4 miles per hour, noncompetitive squash and handball, fencing, and vigorous basketball. If, however, less-than-ordinary activity produces symptoms, the capacity of the postcoronary patient is nearer 4 METs. Despite obvious impairment, this level of capacity includes swimming the breaststroke at 20 yards per minute; cycling at 5.5 miles per hour; walking up a 5% incline at 3 miles per hour; playing table tennis, golf (carrying clubs), badminton and lawn tennis doubles, and raking leaves. For the patient, these are carefully computed, quantitated capacities. A list of activities quantified in METs is far more concrete and specific than statements such as "Use your own judgment" or "Do it in moderation." Instead, the patient can be given a list and told to select activities up to a specific level of METs. The physician who wishes to determine a tolerable level can use such devices as the step test, treadmill, and bicycle ergometer for which energy demand in METs at different levels has already been determined. Handy charts can be obtained from the American Heart Association manual.[144]

Activity levels can be gradually increased whenever appropriate. Patients should take responsibility for the extra costs that emotional involvement may require. For example, they could be told, "I am now moving you to a level of activity of 5 METs. You will find at this level all the activities that your heart (or lungs or body) is physically capable of performing. Activities you enjoy are the best. Remember that getting emotionally upset or very competitive during activity increases the energy cost to your heart. If you cannot do some of these things without getting all worked up, you will have to ease off; only you can judge that. But you now know that you are physically capable of performing at 5 METs." In this statement, vagueness remains, but only in the area of subjective emotions. Patients should be aware that they experience emotions physically and mentally even though they cannot be asked to detect changes in their left-ventricular end-diastolic pressure or arterial oxygen saturation. Moreover, emotional self-control is a fair request to make of patients who, although not responsible for detecting a rising wedge pressure on the tennis court, must try to control rising killer instincts.

Patients with chronic CAD almost always have reduced exercise capacity. Lower maximal stroke volume and heart rate decrease cardiac output and limit maximum oxygen consumption ($\dot{V}o_2max$).[145] Yet exercise training increases $\dot{V}o_2max$ for these patients, even when stroke volume cannot be enlarged (as it is in healthy persons who train). As with the chronic lung patients, the increase in exercise capacity results from changes in the muscles, especially the leg muscles. (β-Blockers, which blunt $\dot{V}o_2max$ improvement in healthy exercisers, do not prevent it in CAD patients.) Thompson[146] suggested that CAD patients as well as patients recovering from uncomplicated MI and bypass surgery walk at least 10 minutes per day and add 5 minutes per week to the walk until they are walking 45 or more minutes, four to five times a week. The patients should be instructed to walk briskly but not at a rate that causes dyspnea (which occurs at approximately 50% to 70% $\dot{V}o_2max$).

Even CHF does not necessarily proscribe exercise. In a group of patients with severely limited left-ventricular function and ejection fractions of 25% or less, Squires and associates[147] were able to produce, without morbidity or mortality, in an 8-week training program, substantial improvement in exercise capacity. Of those fully employed before CHF occurred, more than half returned to full-time work.

In any serious illness in which there are likely to be so many "don'ts" constricting the patient's world, an exercise regimen provides something to do that widens the space of existence. If a patient were limited by a maximum tidal volume of 13 L/min, an exercise program could not increase it, but it would help the patient to see that even within those limits he or she can increase exercise tolerance, venture further (e.g., away from oxygen), and perhaps experience increased freedom. Some patients suffer illnesses in which reserves wax and wane (e.g., the cancer patient with remissions and exacerbations, aplastic anemia patients between transfusions). They may view life energy as a fixed quantity that is used up by activity little by little; thus they fear activity. The psychological benefits of exercise are such that activities should bring some sense of renewed vitality (improved sleep and appetite are common effects) rather than a sense of depletion or exhaustion. As the hematocrit level decreases (or the blood urea nitrogen level increases), the capacity for exercise decreases. To continue exercising, such a person could set as a target a heart rate that was commonly experienced while exercising at his or her prescribed level of MET, or time and distance could be decreased accordingly. When his chronic CHF worsened, one man simply returned to the scene of his exercising, changed into his exercise gear, and sat talking with the regulars before returning home.

Geriatric Implications

Age further compounds the bias against encouraging physical exercise. Contrary to popular myth, vigorous exercise training in youth confers no later cardiovascular health benefits. Moderate exercise (defined as 70% to 80% of maximal heart rate) in later age does so. The trainability of older men has been shown not to depend on whether they trained in their youth. Moreover, as a person ages and functional reserve decreases, the size of the training effect becomes greater.[148]

TABLE 9–7 Energy Expenditure per Kilogram per Minute in the Average 70-kg Person

ACTIVITY	MET
Self-Care	
Rest, supine	1
Sitting	1
Standing, relaxed	1
Eating	1
Conversation	1
Dressing, undressing	2
Washing hands, face	2
Using bedside commode	3
Walking, 2.5 mph	3
Showering	3.5
Using bedpan	4
Walking downstairs	4.5
Walking, 3.5 mph	5.5
Propulsion, wheelchair	2
Ambulation with braces and crutches	6.5
Industrial Activities	
Watch repairing	1.5
Armature winding	2
Radio assembly	2.5
Sewing at machine	2.5
Bricklaying	3.5
Plastering	3.5
Tractor plowing	3.5
Wheeling barrow, 115 lb, 2.5 mph	4
Horse plowing	5
Carpentry	5.5
Mowing lawn by hand	6.5
Felling tree	6.5
Shoveling	7
Ascending stairs with 17-lb load at 27 ft/min	7.5
Planing	7.5
Tending furnace	8.5
Ascending stairs with 22-lb load at 54 ft/min	13.5
Housework Activities	
Hand sewing	1
Sweeping floor	1.5
Machine sewing	1.5
Polishing furniture	2
Peeling potatoes	2.5
Scrubbing, standing	2.5
Washing small clothes	2.5
Kneading dough	2.5
Scrubbing floors	3
Cleaning windows	3
Making beds	3
Ironing, standing	3.5
Mopping	3.5
Wringing by hand	3.5
Hanging wash	3.5
Beating carpets	4
Recreational Activities	
Painting, sitting	1.5
Playing piano	2
Driving car	2
Canoeing, 2.5 mph	2.5
Horseback riding, slow	2.5
Volleyball	2.5
Bowling	3.5
Cycling, 5.5 mph	3.5
Golfing	4
Swimming, 20 yd/min	4
Dancing	4.5
Gardening	4.5
Tennis	6
Trotting horse	6.5
Spading	7
Skiing	8
Squash	8.5
Cycling, 13 mph	9

From Cassem NH, Hackett TP: Psychological aspects of myocardial infarction, *Med Clin North Am* 61:711–721, 1977, used by permission.
MET, Metabolic equivalent.

The best measure of the effects of aging on functional activity is the $\dot{V}o_2max$. As one ages, there is a clearly demonstrated decline in $\dot{V}o_2max$, but it is much steeper for sedentary than for active men. A concrete expression of the difference between the two lifestyles is that by the time the two groups reach the decade of 50 to 59 years of age, there is already a 10-year difference between them. It is thus true, at least in terms of aerobic capacity, that exercise keeps a person younger.

All-cause mortality and physical fitness have been studied in both men and women. When fitness was divided into quintiles, the age-adjusted all-cause mortality rates declined from 64.0 and 39.5 per 10,000 person-years in the least fit men and women, to 18.6 and 8.5 per 10,000 person-years in the most fit men and women. Higher levels of fitness appeared to delay mortality, primarily as a result of lowered rates of cardiovascular disease and cancer.[149]

Even though there is no evidence that exercise in moderation is more hazardous for older adults, how often is it regularly urged for a person of 95? Fiatarone and co-workers[150] demonstrated that frail, institutionalized volunteer nonagenarians, after only 8 weeks in a supervised weightlifting program for legs only, showed a 174% increase in muscle strength and highly significant gains in muscle mass and walking speed. They concluded, "The potential for reversal of 'age-related' muscle weakness has been unexploited."[150] The most important target of conditioning in the geriatric population is the leg muscles. There are no data to prove that better conditioning would prevent falls, one of the most serious causes of morbidity in older persons, but it seems likely that improved muscle strength, tone, balance, and mobility would almost certainly help. Likewise, there may be subtle brain damage that limits an older adult's capacity to perform activities. One measure of this is the number and severity of subcortical hyperintensities seen on MRI scans.[151] Even if these are present, one should never avoid a reconditioning program for an older adult. There are no studies on the effects of such a program on these changes.

Just as the original illness or injury can be demoralizing, so can the seeming snail's pace of recovery. This normal despondency can further retard rehabilitation. Few things heal self-esteem as effectively as regaining the sense of a sound body. The consultant who helps the patient grieve for those losses beyond restoration, while correcting misconceptions about inactivity and encouraging the patient to shoulder the work of recovery, shortens the convalescence of both body and mind.

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10 Delirious Patients

Jason P. Caplan, M.D.
Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.
George B. Murray, B.S., Ph.L., M.S., M.Sc., M.D., S.J.
Jennifer M. Park, M.D.
Theodore A. Stern, M.D.

Delirium has likely replaced syphilis as "the great imitator" because its varied presentations have led to misdiagnoses among almost every major category of mental illness. Delirium is a syndrome caused by an underlying physiologic disturbance and marked by a fluctuating course, with impairments in consciousness, attention, and perception. Delirium thus is often mistaken for depression when the patient has a withdrawn or flat affect, for mania when the patient has agitation and confusion, for psychosis when the patient has hallucinations and paranoia, for anxiety when the patient has restlessness and hypervigilance, for dementia when the patient has cognitive impairments, and for substance abuse when the patient has impairment in consciousness. With so diverse an array of symptoms, delirium assumes a position of diagnostic privilege in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[1] in that almost no other diagnosis can be made in its presence.

Perhaps even more noteworthy, delirium is a signifier of often serious somatic illness.[2] Delirium has been associated with increased length of stay in hospitals[3] and with an increased cost of care.[4,5] Among intensive care unit (ICU) patients, prospective studies have noted that delirium occurs in 31% of admissions[6]; when intubation and mechanical ventilation are required, the incidence soars to 81.7%.[7]

Sometimes, delirium is refered to as an acute confusional state, a toxic-metabolic encephalopathy, or acute brain failure; unquestionably, it is the most common cause of agitation in the general hospital. Delirium ranks second only to depression on the list of all psychiatric consultation requests. Given its prevalence and its importance (morbidity and mortality), the American Psychiatric Association issued practice guidelines for the treatment of delirium in 1999.[8]

Placed in this context, the consequences of misdiagnosis of delirium can be severe; prompt and accurate recognition of this syndrome is paramount for all clinicians.

DIAGNOSIS

The essential feature of delirium, according to the DSM-IV, is a disturbance of consciousness that is accompanied by cognitive deficits that cannot be accounted for by past or evolving dementia (Table 10–1).[1] Disturbance of the sleep–wake cycle is also common, sometimes with nocturnal worsening (sundowning) or even by a complete reversal of the night–day cycle, though, despite previous postulation, sleep disturbance alone does not cause delirium.[9] Similarly, the term *ICU psychosis* has entered the medical lexicon; this is an unfortunate misnomer because it is predicated on the belief that the environment of the ICU is capable of inducing delirium and that the symptomatology of delirium is limited to psychosis.[9] Despite wide variation in the presentation of the delirious patient, the hallmarks of delirium, although perhaps less immediately apparent, remain quite consistent from case to case.

Both Chedru and Geschwind[10] and Mesulam and coworkers[11] regard impaired attention as the main deficit of delirium. This inattention (along with an acute onset, waxing and waning course, and overall disturbance of consciousness) forms the core features of delirium, whereas other related symptoms, such as withdrawn affect, agitation, hallucinations, and paranoia, serve as a frame that can sometimes be so prominent as to detract from the picture itself.

Psychotic symptoms (such as visual or auditory hallucinations and delusions) are common among patients with delirium.[12] Sometimes the psychiatric symptoms are so bizarre or so offensive (e.g., an enraged and paranoid patient shouts that pornographic movies are being made in the ICU) that diagnostic efforts are distracted. The hypoglycemia of a man with diabetes can be missed in the emergency department (ED) if the accompanying behavior is threatening, uncooperative, and resembling that of an intoxicated person.

Although agitation can distract practitioners from making an accurate diagnosis of delirium, disruptive behavior alone will almost certainly garner some attention. The hypoactive presentation of delirium is more insidious, because the patient is often thought to be depressed or anxious because of the medical illness. Studies of quietly delirious patients show the experience to be as disturbing as the agitated variant[13]; quiet delirium is still a harbinger of serious medical pathology.[14,15]

The core similarities found in cases of delirium have led to postulation of a final common neurologic pathway for its symptoms. Current understanding of the neurophysiologic basis of delirium is one of hyperdopaminergia and hypocholinergia.[16] The ascending reticular activating system (RAS) and its bilateral thalamic projections regulate alertness, with neocortical and limbic inputs to this system

TABLE 10–1 DSM-IV Diagnostic Criteria for Delirium

A disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
A change in cognition (e.g., memory deficit, disorientation, or a language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
A disturbance that develops over a short period (usually hours to days) and tends to fluctuate during the course of the day
Evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

controlling attention. Because acetylcholine is the primary neurotransmitter of the RAS, medications with anticholinergic activity can interfere with its function, resulting in the deficits in alertness and attention that are the heralds of delirium. Similarly, it is thought that loss of cholinergic neuronal activity in the elderly (e.g., resulting from microvascular disease or atrophy) is the basis for their heightened risk of delirium. Release of endogenous dopamine due to oxidative stress is thought to be responsible for the perceptual disturbances and paranoia that so often lead to mislabeling the delirious patient "psychotic." As we discuss later, cholinergic agents (e.g., physostigmine) and dopamine blockers (e.g., haloperidol) have proved efficacious in managing delirium.

Early detection of changes in cognition can be key to timely identification and treatment of delirium (and perhaps of a heretofore undiagnosed somatic illness responsible for the delirium). Unfortunately, several studies have revealed that physicians who are not psychiatrists are quite unreliable in their ability to accurately identify delirium in their patients, and most patients referred to psychiatric consultation services with purported depression are ultimately found to have delirium. Because consultation psychiatrists cannot perform repeated examinations on all patients admitted to the general hospital (even on those at high risk for delirium), a number of screening protocols designed to be serially administered by nursing staff have been developed and validated for use. Some of the most commonly used of these scales are summarized in Table 10–2.[17–23]

DIFFERENTIAL DIAGNOSIS

As useful as screening protocols may be, treatment relies on a careful diagnostic evaluation; there is no substitute for a systematic search for the specific cause of delirium. The temporal relationship to clinical events often gives the best clues to potential causes. For example, a patient who extubated himself was almost certainly in trouble before self-extubation. When did his mental state actually change? Nursing notes should be studied to help discern the first indication of an abnormality (e.g., restlessness, mild confusion, or anxiety). If a time of onset can be established as a marker, other events can be examined for a possible causal relationship to the change in mental state. Initiation or discontinuation of a drug, the onset of fever or hypotension, or the acute worsening of renal function, if in proximity to the time of mental status changes, become likely culprits.

TABLE 10–2 Delirium Assessment Tools

TOOL	STRUCTURE	NOTES
Confusion Assessment Method (CAM)[17]	Full scale of 11 items Abbreviated algorithm targeting four cardinal symptoms	Intended for use by nonpsychiatric clinicians
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[18]	Algorithm targeting four cardinal symptoms	Designed for use by nursing staff in the ICU
Intensive Care Delirium Screening Checklist (ICDSC)[19]	Eight-item screening checklist	Bedside screening tool for use by nonpsychiatric physicians or nurses in the ICU
Delirium Rating Scale (DRS)[20]	Full scale of 10 items Abbreviated seven- or eight-item subscales for repeated administration	Provides data for confirmation of diagnosis and measurement of severity
Delirium Rating Scale—Revised–98 (DRS-R-98)[21]	Sixteen-item scale that can be divided into a three-item diagnostic subscale and a thirteen-item severity subscale	Revision of DRS is better suited to repeat administration
Memorial Delirium Assessment Scale (MDAS)[22]	Ten-item severity rating scale	Grades severity of delirium once diagnosis has been made
Neecham Confusion Scale[23]	Ten-item rating scale	Designed for use by nursing staff Primarily validated for use in elderly populations in acute medical or nursing home setting

ICU, Intensive care unit.

Without a convincing temporal connection, the cause of delirium may be discovered by its likelihood in the unique clinical situation of the patient. In critical care settings, as in EDs, there are several (life-threatening) states that the clinician can consider routinely. These are states in which intervention needs to be especially prompt because failure to make the diagnosis may result in permanent central nervous system (CNS) damage. These conditions are Wernicke's disease, hypoxia, hypoglycemia, hypertensive encephalopathy, hyper- or hypothermia, intracerebral hemorrhage, meningitis or encephalitis, poisoning (exogenous or iatrogenic), and status epilepticus. These conditions are usefully recalled by the mnemonic device "WHHHHHIMPS" (Table 10–3). Other less urgent but still acute conditions that require intervention include subdural hematoma, septicemia, subacute bacterial endocarditis, hepatic or renal failure, thyrotoxicosis or myxedema, delirium tremens, anticholinergic psychosis, and complex partial seizures. If these conditions are not already ruled out, they are easy to verify. A broad review of conditions commonly associated with delirium is provided by the mnemonic "I WATCH DEATH" (Table 10–4).

Bacteremia commonly clouds a patient's mental state. In prospectively studied seriously ill hospitalized patients, delirium was commonly correlated with bacteremia.[24] In that study, the mortality of septic patients with delirium was higher than that in septic patients with a normal mental status. In the elderly, regardless of the setting, the onset of confusion should trigger concern about infection. Urinary tract infections (UTIs) and pneumonias are among the most common infections in older patients, and when bacteremia is associated with a UTI, confusion is the presenting feature nearly one third (30%) of the time.[25] Once a consultant has eliminated these common conditions as possible causes of a patient's disturbed brain function, there is time enough for a more systematic approach to the differential diagnosis. A comprehensive differential diagnosis, similar to the one compiled by Ludwig[26] (slightly expanded in Table 10–5) is recommended. A quick review of this list is warranted even when the consultant is relatively sure of the diagnosis.

To understand the acute reaction of the individual patient, one should begin by completely reviewing the medical record. Vital signs can reveal periods of hypotension or fever. The highest temperature recorded will also be key. Operative procedures and the use of anesthetics can also induce a sustained period of hypotension or reveal unusually large blood loss that requires replacement. Laboratory values should be scanned for abnormalities that could be related to an encephalopathic state.

TABLE 10–3 Life-Threatening Causes of Delirium: WHHHHIMPS

Wernicke's disease
Hypoxia
Hypoglycemia
Hypertensive encephalopathy
Hyperthermia or hypothermia
Intracerebral hemorrhage
Meningitis or encephalitis
Poisoning (exogenous or iatrogenic)
Status epilepticus

TABLE 10–4 Conditions Commonly Associated with Delirium: "I WATCH DEATH."

CATEGORY	CONDITIONS
Infectious	Encephalitis, meningitis, syphilis, pneumonia, urinary tract infection
Withdrawal	From alcohol or sedative–hypnotics
Acute metabolic	Acidosis, alkalosis, electrolyte disturbances, liver or kidney failure
Trauma	Heat stroke, burns, following surgery
CNS pathology	Abscesses, hemorrhage, seizure, stroke, tumor, vasculitis, or normal-pressure hydrocephalus
Hypoxia	Anemia, carbon monoxide poisoning, hypotension, pulmonary embolus, lung or heart failure
Deficiencies	Of vitamin B_{12}, niacin, or thiamine
Endocrinopathies	Hyper- or hypoglycemia, hyper- or hypoadrenocorticism, hyper- or hypothyroidism, hyper- or hypoparathyroidism
Acute vascular	Hypertensive encephalopathy or shock
Toxins or drugs	Medications, pesticides, or solvents
Heavy metals	Lead, manganese, or mercury

The old chart, no matter how thick, cannot be overlooked without risk. Some patients have had psychiatric consultations for similar difficulties on prior admissions. Others, in the absence of psychiatric consultations, have caused considerable trouble for their caregivers. Similar to a patient's psychiatric history, the family psychiatric history can help make a diagnosis, especially if a major mood or anxiety disorder, alcoholism, schizophrenia, or epilepsy is present.

Examination of current and past medications is essential because pharmacologic agents (in therapeutic doses, in overdose, or with withdrawal) can produce psychiatric symptoms. These medications must be routinely reviewed, especially in patients whose drugs have been stopped because of surgery or hospitalization or whose drug orders have not been transmitted during transfer between services. Of all causes of an altered mental status, use of and withdrawal from drugs are probably the most common. Some, such as lidocaine, are quite predictable in their ability to cause encephalopathy; the frequency and severity of symptoms are dose-related. Other agents, such as antibiotics, usually cause delirium only in someone whose brain is already vulnerable, as in a patient with a low seizure threshold.[27] Table 10–6 lists some drugs used in clinical practice that have been associated with delirium.

The number of drugs that can be involved either directly or indirectly (e.g., because of drug interactions) is numerous. Fortunately, certain sources provide regular review of published summaries and drug updates.[28] Although physicians are usually aware of these hazards,

TABLE 10–5 Differential Diagnosis of Delirium

GENERAL CAUSE	SPECIFIC CAUSE
Vascular	Hypertensive encephalopathy Cerebral arteriosclerosis Intracranial hemorrhage or thrombosis Emboli from atrial fibrillation, patent foramen ovale, or endocarditic valve Circulatory collapse (shock) Systemic lupus erythematosus Polyarteritis nodosa Thrombotic thrombocytopenic purpura Hyperviscosity syndrome Sarcoid
Infectious	Encephalitis Bacterial or viral meningitis, fungal meningitis (*cryptococcal, coccidioidal, Histoplasma*) Sepsis General paresis Brain, epidural, or subdural abscess Malaria Human immunodeficiency virus Lyme disease Typhoid fever Parasitic (*toxoplasma, trichinosis, cysticercosis, echinococcosis*) Behçet's syndrome Mumps
Neoplastic	Space-occupying lesions, such as gliomas, meningiomas, abscesses Paraneoplastic syndromes Carcinomatous meningitis
Degenerative	Senile and presenile dementias, such as Alzheimer's or Pick's dementia Huntington's chorea Creutzfeldt-Jakob disease Wilson's disease
Intoxication	Chronic intoxication or withdrawal effect of sedative–hypnotic drugs, such as bromides, opiates, tranquilizers, anticholinergics, dissociative anesthetics, anticonvulsants, carbon monoxide from burn inhalation
Congenital	Epilepsy Postictal states Complex partial status epilepticus Aneurysm
Traumatic	Subdural and epidural hematomas Contusion Laceration Postoperative trauma Heat stroke Fat emboli syndrome
Intraventricular	Normal pressure hydrocephalus
Vitamin deficiency	Thiamine (Wernicke–Korsakoff syndrome) Niacin (pellagra) B_{12} (pernicious anemia)
Endocrine-metabolic	Diabetic coma and shock Uremia Myxedema Hyperthyroidism, Parathyroid dysfunction Hypoglycemia Hepatic or renal failure Porphyria Severe electrolyte or acid and base disturbances Paraneoplastic syndrome Cushing's or Addison's syndrome Sleep apnea Carcinoid Whipple's disease
Metals	Heavy metals (lead, manganese, mercury) Other toxins
Anoxia	Hypoxia and anoxia secondary to pulmonary or cardiac failure, anesthesia, anemia
Depression—other	Depressive pseudodementia, hysteria, catatonia

Modified from Ludwig AM: *Principles of clinical psychiatry*, New York, 1980, The Free Press.

a common drug, such as meperidine, when used in doses greater than 300 mg/day for several days, causes CNS symptoms because of the accumulation of its excitatory metabolite, normeperidine, which has a half-life of 30 hours and causes myoclonus (the best clue of normeperidine toxicity), anxiety, and ultimately seizures.[29] The usual treatment is to stop the offending drug or to reduce the dosage; however, at times this is not possible. Elderly patients and those with mental retardation or a history of significant head injury are more susceptible to the toxic actions of many of these drugs.

Psychiatric symptoms in medical illness can have other causes. Besides the abnormalities that can arise from the effect of the patient's medical illness (or its treatment) on the CNS (e.g., the abnormalities produced by systemic lupus erythematosus or high-dose steroids), the disturbance may be the effect of the medical illness on the patient's mind (the subjective CNS), as in the patient who thinks he or she is "washed up" after a myocardial infarction, quits, and withdraws into hopelessness. The disturbance can also arise from the mind, as a conversion symptom or as malingering about pain to get more narcotics. Finally, the abnormality may be the result of interactions between the sick patient and his or her environment or family (e.g., the patient who is without complaints until the family arrives, at which time the patient promptly looks acutely distressed and begins to whimper continuously). Nurses are commonly aware of these sorts of abnormalities, although the abnormalities might go undocumented in the medical record.

TABLE 10–6 Drugs used in Clinical Practice that Have Been Associated with Delirium

Antiarrhythmics
Disopyramide
Lidocaine
Mexiletine
Procainamide
Propafenone
Quinidine
Tocainide

Antibiotics
Aminoglycosides
Amodiaquine
Amphotericin
Cephalosporins
Chloramphenicol
Gentamicin
Isoniazid
Metronidazole
Rifampin
Sulfonamides
Tetracyclines
Ticarcillin
Vancomycin

Anticholinergics
Atropine
Benztropine
Diphenhydramine
Eye and nose drops
Scopolamine
Thioridazine
Trihexyphenidyl

Tricyclic Antidepressants
Amitriptyline
Clomipramine
Desipramine
Imipramine
Nortriptyline
Protriptyline
Trimipramine

Anticonvulsants
Phenytoin

Antihypertensives
Captopril
Clonidine
Methyldopa
Reserpine

Antiviral Agents
Acyclovir
Interferon
Ganciclovir
Nevirapine

Barbiturates

β-blockers
Propranolol
Timolol

Cimetidine, ranitidine

Digitalis preparations

Disulfiram

Diuretics
Acetazolamide

Dopamine agonists (central)
Amantadine
Bromocriptine
Levodopa
Selegiline

Ergotamine

GABA agonists
Baclofen
Benzodiazepines
Zaleplon
Zolpidem

Immunosuppressives
Aminoglutethimide
Azacytidine
Chlorambucil
Cytosine arabinoside (high dose)
Dacarbazine
FK-506
5-Fluorouracil
Hexamethylmelamine
Ifosfamide
Interleukin-2 (high dose)
L-Asparaginase
Methotrexate (high dose)
Procarbazine
Tamoxifen
Vinblastine
Vincristine

Monoamine oxidase inhibitors
Tranylcypromine
Phenelzine
Procarbazine

Narcotic analgesics
Meperidine (normeperidine)
Pentazocine
Podophyllin (topical)

Nonsteroidal antiinflammatory drugs
Ibuprofen
Indomethacin
Naproxen
Sulindac

Other medications
Clozaril
Cyclobenzaprine
Lithium
Ketamine
Sildenafil
Trazodone
Mefloquine

Sympathomimetics
Aminophylline
Amphetamine
Cocaine
Ephedrine
Phenylephrine
Phenylpropanolamine
Theophylline

Steroids, ACTH

Adapted from Cassem NH, Lake CR, Boyer WF: Psychopharmacology in the ICU. In Chernow B, editor: *The pharmacologic approach to the critically ill patient*, Baltimore, 1995, Williams & Wilkins, pp 651–665; and Drugs that may cause psychiatric symptoms, *Med Letter Drugs Ther* 44:59–62, 2002.
ACTH, Adrenocorticotropic hormone; *GABA*, gamma aminobutyric acid.

THE EXAMINATION OF THE PATIENT

Appearance, level of consciousness, thought, speech, orientation, memory, mood, judgment, and behavior should all be assessed. In the formal mental status examination (MSE), one begins with the examination of consciousness. If the patient does not speak, a handy common-sense test is to ask oneself, "Do the eyes look back at me?" One could formally rate consciousness by using the Glasgow Coma Scale (Table 10–7), a measure that is readily understood by consultees in other specialties.[30]

If the patient can cooperate with an examination, attention should be examined first because if this is disturbed, other parts of the examination may be invalid. One can ask the patient to repeat the letters of the alphabet that rhyme with "tree." (If the patient is intubated, ask that a hand or finger be raised whenever the letter of the recited alphabet rhymes with "tree.") Then the rest of the MSE can be performed. The Folstein Mini-Mental State Examination (MMSE),[31] which is presented in Table 4–8, is usually included. Specific defects are more important than is the total score. Other functions (such as writing, which Chedru and Geschwind[10] considered to be one of the most sensitive indicators of impairment of consciousness) are often abnormal in delirium. Perhaps the most dramatic (though difficult to score objectively) test of cognition is the clock drawing test, which can provide a broad survey of the patient's cognitive state (Figure 10–1).[32] A more-recently developed and validated bedside test, the Montreal Cognitive Assessment (MoCA),[33] usefully incorporates some aspects of the MMSE (i.e., tests of memory, attention, and orientation) with tests of more complex visuospatial and executive function (including clock drawing and an adaptation of the trail making B task). Although not specifically validated for detecting delirium, the MoCA (available at www.mocatest.org) has been consistently shown to have greater sensitivity than the MMSE for mild cognitive impairment in a variety of conditions and typically requires less than 10 minutes to administer.

The patient's problem can involve serious neurologic syndromes as well; however, the clinical presentation of the patient should direct the examination. In general, the less responsive and more impaired the patient is, the more one should look for *hard signs*. A directed search for an abnormality of the eyes and pupils, nuchal rigidity, hyperreflexia (withdrawal), hung-up reflexes (myxedema), one-sided weakness or asymmetry, gait (normal pressure hydrocephalus), Babinski's reflexes, tetany, absent vibratory and position senses, hyperventilation (acidosis, hypoxia, or pontine disease), or other specific clues can help verify or reject hypotheses about causality that are stimulated by the abnormalities in the examination.

TABLE 10–7 Glasgow Coma Scale

CRITERION	SCORE
Eye opening (E)	
Spontaneous	4
To verbal command	3
To pain	2
No response	1
Motor (M)	
Obeys verbal command	6
Localizes pain	5
Flexion withdrawal	4
Abnormal flexion (decortication)	3
Extension (decerebration)	2
No response	1
Verbal (V)	
Oriented and converses	5
Disoriented and converses	4
Inappropriate words	3
Incomprehensible sound	2
No response	1
Coma Score = (E + M + V)	**Range 3 to 15**

From Bastos PG, Sun X, Wagner DP et al: Glasgow Coma Scale score in the evaluation of outcome in the intensive care unit: findings from the Acute Physiology and Chronic Health Evaluation III study, *Crit Care Med* 21:1459–1465, 1993.

Frontal lobe function deserves specific attention. Grasp, snout, palmomental, suck, and glabellar responses are helpful when present. Hand movements thought to be related to the premotor area (Brodmann's area 8) can identify subtle deficiencies. The patient is asked to imitate, with each hand separately, specific movements. The hand is held upright, a circle formed by thumb and first finger ("okay" sign), then the fist is closed and lowered to the surface on which the elbow rests. In the Luria sequence, one hand is brought down on a surface (a table or one's own leg) in three successive positions: extended with all five digits parallel ("cut"), then as a fist, and then flat on the surface ("slap"). Finally, both hands are placed on a flat surface in front of the patient, one flat on the surface, the other resting as a fist. Then the positions are alternated between right and left hands, and the patient is instructed to do likewise.

For verbally responsive patients, their response to the "Frank Jones story" can be gauged (I have a friend, Frank Jones, whose feet are so big he has to put his pants on over his head. How does that strike you?). Three general responses are given. Type 1 is normal: The patient sees the incongruity and smiles (a limbic response) and can explain (a neocortical function) why it cannot be done. Type 2 is abnormal: The patient smiles at the incongruity (a limbic connection), but cannot explain why it cannot be done. Type 3 is abnormal: The patient neither gets the incongruity nor can explain its impossibility.

Laboratory studies should be carefully reviewed, with special attention paid to indicators of infection or metabolic disturbance. Toxicology screens are also usually helpful in allowing the inclusion or exclusion of substance intoxication or withdrawal from the differential diagnosis. Neuroimaging can prove useful in detecting intracranial processes that can result in altered mental status. Of all the diagnostic studies available, the electroencephalogram (EEG) may be the most useful tool in the diagnosis of delirium. Engel and Romano[34] reported in 1959 their (now classic) findings on the EEG in delirium, namely, generalized slowing to the theta-delta range in the delirious patient, the consistency of this finding despite wide-ranging underlying conditions, and resolution of this slowing with effective treatment of the delirium. EEG findings might even clarify the etiology of a delirium, because delirium tremens is associated with low-voltage fast activity superimposed on slow waves, sedative–hypnotic toxicity produces fast beta activity (>12 Hz), and hepatic encephalopathy is classically associated with triphasic waves.[35]

SPECIFIC MANAGEMENT STRATEGIES FOR DELIRIUM

Thoughts about (and treatment of) delirium have changed dramatically in the past several decades. In the 1970s, atropine was routinely administered to newly admitted

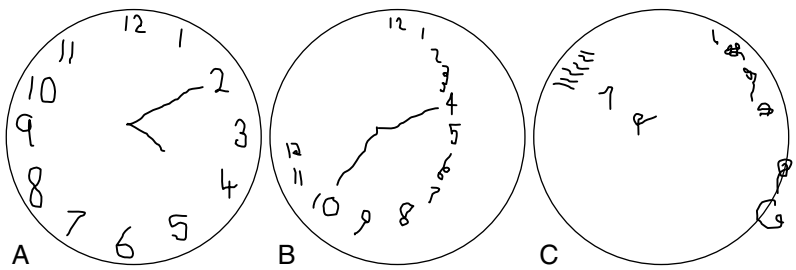

Figure 10–1. The clock drawing test. The patient is provided with a circular outline and asked to draw the numbers as they appear on the face of a clock. Once the numbering is complete, the patient is asked to set the hands to a particular time (often "ten past" the hour to test if the patient can suppress the impulse to include the number ten). **A,** This drawing demonstrates good planning and use of space. **B,** This drawing features some impulsiveness because the numbers are drawn out without regard for actual location, and the time "ten past four" is represented by hands pointing to the digits ten and four. Note the perseveration indicated by the extra loops on the digits *3* and *6*. Impulsiveness and perseveration indicate frontal lobe dysfunction. **C,** This drawing demonstrates gross disorganization, although the patient took several minutes to draw the clock and believed it to be a good representation.

coronary care unit (CCU) patients with bradycardia. Some patients, particularly older ones with preexisting organic brain disease, developed delirium. For such patients, parenteral propantheline bromide (Pro-Banthine), a quaternary ammonium compound that does not cross the blood–brain barrier and is equally effective in treating bradycardia, was substituted. This approach may still be taken, but problems are seldom so simple. Often the drugs that cause delirium (such as lidocaine or prednisone), cannot be changed without causing harm to the patient. Alternatively, pain can cause agitation in a delirious patient. Morphine sulfate can relieve pain but can unfortunately lead to decreases in blood pressure and respiratory rate.

Psychosocial or environmental measures are rarely effective in the treatment of a *bona fide* delirium of uncertain or unknown cause. Nevertheless, it is commendable to have hospital rooms with windows, calendars, clocks, and a few mementos from home on the walls[36]; soft and low lighting at night helps sundowners; and, most of all, a loving family in attendance reassures and reorients the patient. The psychiatric consultant is often summoned because psychosocial measures have failed to prevent or to treat the patient's delirium. Restraints (e.g., Posey vests; geriatric chairs; helmets; locked leather restraints for application to one or more extremities, chest, and even head) are also available and quite useful to protect patients from inflicting harm on themselves or staff. One or several of these is often in place when the consultant arrives. One hoped-for outcome of the consultation is that the use of these devices can be reduced or eliminated. The unfortunate misnomer *chemical restraint* is often applied to the most helpful class of drugs for delirium, neuroleptics. However, physicians do not use chemical restraints (i.e., tear gas, pepper spray, mace, or nerve gas) in the treatment of agitated patients.

When the cause of the delirium seems straightforward, the treatment revolves around resolution or reversal of the underlying cause. A discovered deficiency can be replaced (e.g., of blood, oxygen, thiamine, vitamin B_{12}, levothyroxine, or glucose). Pathologic conditions can be treated (e.g., volume replacement for hypotension, diuretics for pulmonary edema, antibiotics for infection, calcium for hypocalcemia, or dialysis for acute lithium toxicity). Implicated drugs, such as meperidine and cimetidine, can be stopped or reduced.

Specific antidotes can reverse the delirium caused by some drugs. Flumazenil and naloxone reverse the effects of benzodiazepines and opioid analgesics, respectively. However, caution is required because flumazenil can precipitate seizures in a benzodiazepine-dependent patient, and naloxone can also precipitate narcotic withdrawal in a narcotic-dependent patient.

Anticholinergic delirium can be reversed by intravenous (IV) physostigmine in doses starting at 0.5 to 2 mg. Caution is essential with use of this agent because the autonomic nervous system of the medically ill is generally less stable than it is in a healthy patient who has developed an anticholinergic delirium as a result of a voluntary or accidental overdose. Moreover, if there is a reasonably high amount of an anticholinergic drug on board that is clearing from the system slowly, the therapeutic effect of physostigmine, although sometimes quite dramatic, is usually short lived. The cholinergic reaction to intravenously administered physostigmine can cause profound bradycardia and hypotension, thereby multiplying the complications.[37,38] A continuous IV infusion of physostigmine has been successfully used to manage a case of anticholinergic poisoning.[39] Because of the diagnostic value of physostigmine, one might wish to use it even though its effects will be short-lived. If one uses an IV injection of 1 mg of physostigmine, protection against excessive cholinergic reaction can be provided by preceding this injection with an IV injection of 0.2 mg of glycopyrrolate. This anticholinergic agent does not cross the blood–brain barrier and should protect the patient from the peripheral cholinergic actions of physostigmine.

DRUG MANAGEMENT

Definitive treatment of delirium requires identification of the underlying somatic etiology, but all too often the cause of delirium is not readily identified or treated. These situations call for management of the symptoms of delirium until a more specific and effective treatment can be initiated. Opioids, benzodiazepines, neuroleptics, barbiturates, neuromuscular-blocking agents, inhalant anesthetics, and assorted other agents (such as propofol, ketamine, isoflurane, chloral hydrate, and clonidine), are available (alone or in creative combinations).

Benzodiazepines (e.g., diazepam 2.5 mg IV or midazolam 0.5 to 1 mg) are often effective in mild agitation in the setting of withdrawal from drugs that work at the alcohol, benzodiazepine, and barbiturate receptor. Morphine is also often used because it calms agitation and is easily reversed if hypotension or respiratory depression ensues. Especially in higher doses, these agents can cause or exacerbate confusion in older patients. This occurs much less often with neuroleptics, unless thioridazine (which has potent anticholinergic properties) is used.

Neuroleptics are the agent of choice for delirium. Haloperidol is probably the antipsychotic most commonly used to treat agitated delirium in the critical care setting; its effects on blood pressure, pulmonary artery pressure, heart rate, and respiration are milder than those of the benzodiazepines, making it an excellent agent for delirious patients with impaired cardiorespiratory status.[40]

Although haloperidol can be administered orally or parenterally, acute delirium with extreme agitation typically requires use of parenteral medication. IV administration is preferable to intramuscular (IM) administration because drug absorption may be poor in distal muscles if delirium is associated with circulatory compromise or with borderline shock. The deltoid is probably a better IM injection site than the gluteus muscle, but neither is as reliable as the IV route. Second, because the agitated patient is commonly paranoid, repeated painful IM injections can increase the patient's sense of being attacked by enemies. Third, IM injections can complicate interpretations of muscle enzyme studies if enzyme fractionation is not readily available. Fourth, and most important, haloperidol is less likely to produce extrapyramidal side effects (EPS) when given IV than when given IM or by mouth (PO), at least for patients without a prior serious psychiatric disorder.[41]

In contrast to the immediately observable sedation produced by IV benzodiazepines, IV haloperidol has a mean

distribution time of 11 minutes in normal volunteers[42]; this may be even longer in critically ill patients. The mean half-life of IV haloperidol's subsequent, slower phase is 14 hours. This is still a more rapid metabolic rate than the overall mean half-lives of 21 and 24 hours for IM and PO doses. The PO dose has about half the potency of the parenteral dose, so 10 mg of PO haloperidol corresponds to 5 mg given IV or IM.

Haloperidol has not been approved by the Food and Drug Administration (FDA) for IV administration. However, any approved drug can be used for a nonapproved indication or route if justified as "innovative therapy." For critical care units desirous of using IV haloperidol, one approach is to present this to the hospital's institutional review board (IRB) or human studies committee with a request to use the drug with careful monitoring of results based on the fact that it is the drug of choice for the patient's welfare, it is the safest drug available for this purpose, and it is justifiable as innovative therapy. After a period of monitoring, the committee can choose to make the use of the drug routine in that particular hospital.

Over decades of clinical use, IV haloperidol has been associated with few side effects on blood pressure, heart rate, respiratory rate, or urinary output and has been linked with few EPS. The reason for the latter is not known. Studies of the use of IV haloperidol in psychiatric patients have not shown that these side effects were fewer. They rarely appear after IV administration in medically ill patients probably because many of the medically ill patients have other medications in their system, especially benzodiazepines (which protect against EPS), or because patients with psychiatric disorders are more susceptible to EPS.[41]

Before administering IV haloperidol, the IV line should be flushed with 2 mL of normal saline. Phenytoin precipitates with haloperidol, and mixing the two in the same line must be avoided. Occasionally, haloperidol also precipitates with heparin, and because many lines in critical care units are heparinized, the 2-mL flush is advised. The initial bolus dose of haloperidol usually varies from 0.5 to 20 mg; usually 0.5 mg (for an elderly person) to 2 mg is used for mild agitation, 5 mg is used for moderate agitation, and 10 mg for severe agitation. A higher initial dose should be used only when the patient has already been unsuccessfully treated with reasonable doses of haloperidol. To adjust for haloperidol's lag time, doses are usually staggered by at least a 30-minute interval. If one dose (e.g., a 5-mg dose) fails to calm an agitated patient after 30 minutes, the next higher dose, 10 mg, should be administered. Calm is the desired outcome. Partial control of agitation is usually inadequate, and settling for this only prolongs the delirium or guarantees that excessively high doses of haloperidol will be used after the delirium is controlled.

Haloperidol can be combined every 30 minutes with simultaneous parenteral lorazepam doses (starting with 1 to 2 mg). Because the effects of lorazepam are noticeable within 5 to 10 minutes, each dose can precede the haloperidol dose, be observed for its impact on agitation, and be increased if it is more effective. Some believe that the combination leads to a lower overall dose of each drug.[43]

After calm is achieved, agitation should be the sign for a repeat dose. Ideally the total dose of haloperidol on the second day should be a fraction of that used on day 1. After complete lucidity has been achieved, the patient needs to be protected from delirium only at night, by small doses of haloperidol (1 to 3 mg), which can be given orally. As in the treatment of delirium tremens, the consultant is advised to stop the agitation quickly and completely at the outset rather than barely keep up with it over several days. The maximum total dose of IV haloperidol to be used as an upper limit has not been established, although IV administration of single bolus doses of 200 mg have been used,[44] and more than 2000 mg has been used in a 24-hour period. The highest requirements have been seen with delirious patients on the intra-aortic balloon pump.[45] A continuous infusion of haloperidol has also been used to treat severe, refractory delirium.[46] It has previously been argued that (despite strong empirical clinical evidence) high-dose haloperidol made little pharmacologic sense, given the high rates of dopamine receptor blockade at relatively low doses. In vitro research has revealed that the butyrophenone class of neurolpetics (haloperidol and droperidol) might protect neurons from oxidative stress resulting from interactions at the sigma receptor.[47,48] These interactions might provide the physiologic basis for the clinical benefits of high-dose haloperidol.[49]

When delirium does not respond and agitation is unabated, one might wonder if the neuroleptic (e.g., haloperidol) is producing akathisia. The best indication as to whether the treatment is causing agitation is the patient's description of an irresistible urge to move—usually the limbs, lower more often than upper. If dialogue is possible, even nodding yes or no (provided that the patient understands the question) can confirm or exclude this symptom. If the patient cannot communicate, limited options remain: to decrease the dose or to increase it and judge by the response. In our experience, it is far more common for the patient to receive more haloperidol and to improve.

Hypotensive episodes following the administration of IV haloperidol are rare and almost invariably result from hypovolemia. Ordinarily, this is easily checked in ICU patients who have in-dwelling pulmonary artery catheters, but because agitation is likely to return, volume replacement is necessary before one administers further doses. Local caustic effects on veins do not arise. IV haloperidol is generally safe for epileptic patients and for patients with head trauma, unless psychotropic drugs are contraindicated because the patient needs careful neurologic monitoring. Although IV haloperidol may be used without mishap in patients receiving epinephrine drips, after large doses of haloperidol a pressor other than epinephrine (e.g., norepinephrine) should be used to avoid unopposed β-adrenergic activity. IV haloperidol does not block a dopamine-mediated increase in renal blood flow. It also appears to be the safest agent for patients with chronic obstructive pulmonary disease.

As with all neuroleptic agents, IV haloperidol has been associated with the development of torsades de pointes (TDP).[50–54] The reasons for this are unclear, although particular caution is urged when levels of potassium and magnesium are low (because these deficiencies independently predict TDP), when a baseline prolonged QT interval is noted, when hepatic compromise is present, or when a specific cardiac abnormality (e.g., mitral valve prolapse or a dilated ventricle) exists. Progressive QT widening after administration of haloperidol should alert one to

the danger, however infrequent it may be in practice (4 of 1100 cases in one unit).[51] Delirious patients who are candidates for IV haloperidol require careful screening. Serum potassium and magnesium should be within normal range, and a baseline electrocardiogram (ECG) should be checked for the pretreatment QT interval corrected for heart rate (QTc). If necessary, potassium and magnesium shoud be repleted and the QTc and levels of potassium and magnesium should be monitored regularly for the duration of neuroleptic treatment. QT interval prolongation occurs in some patients with alcoholic liver disease; this finding is associated with adverse outcomes (e.g., sudden cardiac death).[55] Several other commonly used medications also carry the potential for QTc prolongation (Table 10–8). Medication lists should be reviewed closely for other agents that could be discontinued or therapeutically exchanged if QTc prolongation becomes a concern.

Other available parenteral first-generation neuroleptics for treatment of agitation are perphenazine, thiothixene, trifluoperazine, fluphenazine, and chlorpromazine. Perphenazine is approved for IV use as an antiemetic. Chlorpromazine is extremely effective, but its potent α-blocking properties can be dangerous for critically ill patients. When administered IV or IM, it can abruptly decrease total peripheral resistance and cause a precipitous fall in cardiac output. Nevertheless, used IV in small doses (10 mg) it can be safe and effective in the treatment of delirium.

The availability of injectable formulations of olanzapine and ziprasidone has prompted a growing interest in using the second-generation antipsychotics in managing delirium.[56] Risperidone has the most available data supporting its use, and multiple studies show it to be efficacious and safe for treating delirium[57–59]; one small randomized double-blind comparative study found no significant difference in efficacy compared with haloperidol.[60] The other members of this class (olanzapine, ziprasidone, quetiapine, clozapine, and aripiprazole) have far less supporting evidence, though some small studies seem to indicate some promise for management of delirium.[61–65] Agranulocytosis associated with clozapine and the resultant regulation of its use effectively eliminates any routine application of it in managing delirium. All drugs in this class feature an FDA black box warning indicating an increased risk of death when used to treat behavioral problems in elderly patients with dementia. Similar warnings regarding a potential increased risk of cerebrovascular events are reported for risperidone, olanzapine, and aripiprazole. One study examining the mean prolongation of the QTc for various neuroleptic agents on a per-dose-equivalent basis revealed that haloperidol was associated with the lowest increase of all the drugs tested.[66] With decades of clinical experience in the use of haloperidol, and a dearth of available data on these newer agents, haloperidol remains the agent of choice for treating delirium.

To date, there are few published data to support pharmacologic prophylaxis of delirium for the critically ill, although one randomized, double-blind, placebo-controlled study examining the preoperative use of haloperidol in elderly patients undergoing hip surgery indicated decreases in the severity and duration of delirium and length of hospital stay but no statistically significant decrease in the actual incidence of delirium.[67] A double-blind, randomized, placebo-controlled study involving the prophylactic administration of olanzapine to patients undergoing joint replacement surgery demonstrated a decreased incidence of delirium and more frequent discharge to home (as opposed to a rehabilitation hospital) when they received olanzapine before surgery.[68] There is also some limited evidence suggesting that the pro-cholinergic action of cholinesterase inhibitors provides some protection against the development of delirium.[69,70]

TABLE 10–8 Non-Neuroleptic Medications Associated with Prolongation of the QT Interval

ANTIARRYTHMICS	ANTIINFECTIOUS	OTHER
Amiodarone	Atazanavir	Alfuzosin
Disopyramide	Azithromycin	Amantadine
Dofetilide	Chloroquine	Arsenic trioxide
Flecainide	Clarithromycon	Bepridil
Ibutilide	Erythromycin	Chloral hydrate
Procainamide	Foscarnet	Cisapride
Quinidine	Gatifloxacin	Dolasetron
Sotalol	Gemifloxacin	Felbamate
	Halofantrine	Granisetron
	Levofloxacin	Indapamide
	Moxifloxacin	Isradipine
	Ofloxacin	Lapatinib
	Pentamidine	Levomethadyl
	Sparfloxacin	Lithium carbonate
	Telithromycin	Methadone
	Voriconazole	Nicardipine
		Octreotide
		Ondansetron
		Oxytocin
		Probucol
		Ranolazine
		Sunitinib
		Tacrolimus
		Tizanidine
		Vardenafil
		Venlafaxine

DELIRIUM IN SPECIFIC DISEASES

Critically ill patients with human immunodeficiency virus (HIV) infection may be more susceptible to the EPS of haloperidol and to neuroleptic malignant syndrome (NMS),[71–74] leading an experienced group to recommend use of molindone.[74] Molindone is associated with fewer of such effects; it is available only as an oral agent, and it can be prescribed from 5 to 25 mg at appropriate intervals or, in a more acute situation, 25 mg every hour until calm is achieved. Risperidone (0.5 to 1 mg per dose) is another recommended oral agent. If parenteral medication is required, 10 mg of chlorpromazine has been effective. Perphenazine is readily available for parenteral use as well, and 2-mg doses can be used effectively.

Patients with Parkinson's disease pose a special problem because dopamine blockade aggravates their condition. If oral treatment of delirium or psychosis is possible, clozapine, starting with a small dose of 6.25 or 12.5 mg,

is probably the most effective agent available that does not exacerbate the disease. With the risk of agranulocytosis attendant to the use of clozapine, quetiapine can play a valuable role in this population because its very low affinity for dopamine receptors is less likely to exacerbate this disorder.[75]

IV benzodiazepines (particularly diazepam, chlordiazepoxide, and lorazepam) are routinely used to treat agitated states, particularly delirium tremens, and alcohol withdrawal.[76] Neuroleptics have also been used successfully, and both have been combined with clonidine. IV alcohol is also extremely effective in treating alcohol withdrawal states, particularly if the patient does not seem to respond as rapidly as expected to higher doses of benzodiazepines. The inherent disadvantage is that alcohol is toxic to liver and brain, although its use can be quite safe if these organs do not show already extensive damage, and it is sometimes quite safe even when they do. Nonetheless, use of IV alcohol should be reserved for extreme cases of alcohol withdrawal when other, less-toxic measures have failed. A 5% solution of alcohol mixed with 5% dextrose in water run at 1 mL per minute often achieves calm quickly. Treatment pathways have been developed to provide nonpsychiatric clinicians with guidance on the management of alcohol withdrawal,[77] though care must always be taken to ensure that benzodiazepines are not inappropriately administered because they almost certainly exacerbate a delirium that results from any other cause.[78]

Propofol is now commonly used to sedate critically ill patients and can also be extremely effective in managing agitation.[79–81] It has moderate respiratory depressant and vasodilator effects, although hypotension can be minimized by avoiding boluses of the drug. Impaired hepatic function does not slow metabolic clearance, but clearance does decline with age, and its half-life is significantly longer in the elderly. This drug's rapid onset and short duration make it especially useful for treating short periods of stress. When rapid return to alertness from sedation for an uncompromised neurologic examination is indicated, propofol is a nearly ideal agent[82]; however, its use in treating a prolonged delirious state has specific disadvantages.[83] Delivered as a fat emulsion containing 0.1 g of fat per milliliter, propofol requires a dedicated IV line, and drug accumulation can lead to a fat-overload syndrome that has been associated with overfeeding and with significant CO_2 production, hypertriglyceridemia, ketoacidosis, seizure activity 6 days after discontinuation, and even fatal respiratory failure.[83–85] Obese patients provide a high volume of distribution, and their doses should be calculated using estimated lean, rather than actual, body mass. If the patient is receiving fat by parenteral feeding, this must be accounted for or eliminated and adequate glucose infusion must be provided to prevent ketoacidosis. Although no clear association has been demonstrated with addiction, tolerance, or withdrawal, doses seem to require escalation after 4 to 7 days' infusion. Seizures seen after withdrawal or muscular rigidity during administration are poorly understood. The drug is costly, especially when used for prolonged infusions.

Dexmedetomidine is a selective α_2-adrenergic agonist used for sedation and analgesia in the ICU setting. Its action on receptors in the locus ceruleus results in anxiolysis and sedation, and agonism of spinal cord receptors provides analgesia. This unique mechanism of action allows effective management in agitation without the risks of respiratory depression, dependence, and deliriogenesis associated with the benzodiazepines traditionally employed in the ICU.[86] Its relative lack of amnestic effect might further limit its use as monotherapy in the treatment of the delirious patient owing to an increased likelihood of distressing recollections persisting from the period of sedation.[87] In current practice, dexmedetomidine can serve as a useful (but costly) adjunct agent to quell agitation when more traditional approaches have met with limited success.

Drug infusions may be more effective and efficient than intermittent bolus dosing because the latter can intensify side effects (such as hypotension), waste time of critical care personnel, and permit more individual error. The contents of the infusion can address simultaneously multiple aspects of a patient's difficulties in uniquely appropriate ways. The report of the sufentanil, midazolam, and atracurium admixture for a patient who required a temporary biventricular assist device is an excellent example of multiple-drug infusion and creative problem-solving.[88,89]

CONCLUSION

Of all psychiatric diagnoses, delirium demands the most immediate attention because delay in identifying and treating delirium might allow the progression of serious and irreversible pathophysiologic changes. Unfortunately, delirium is all too often underemphasized, misdiagnosed, or altogether missed in the general hospital setting.[90–92] Indeed, it was not until their most recent editions that major medical and surgical texts corrected chapters indicating that delirium was the result of anxiety or depression, rather than an underlying somatic cause that required prompt investigation. In the face of this tradition of misinformation, it often falls to the psychiatric consultant to identify and manage delirium while alerting and educating others to its significance.

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11 Demented Patients

William E. Falk, M.D.
Ilse R. Wiechers, M.D., M.P.P.

As life expectancy extends, we are likely to confront an epidemic of dementia in general hospitals, with the number of cases of Alzheimer's disease (AD), the most common cause of dementia, increasing fourfold in the coming decades.[1] Unfortunately, most dementing disorders, including AD, are incurable, but progression can be slowed if the condition is identified and managed appropriately; only a few dementing illnesses are reversible. Given that a major task for consultation psychiatrists is to assist in the diagnosis and treatment of dementing disorders, this chapter provides an overview of dementing disorders and an approach to their identification and management.

Often, the request to see an inpatient on a medical or surgical floor is for a behavioral disturbance associated with a delirium (see Chapter 10), not for cognitive difficulties alone. Nonetheless, a patient who develops delirium in the hospital may have a previously undiagnosed dementing disorder. A patient with such a disorder is more likely to develop an acute confusional state than is someone without dementia. For example, a demented patient may become delirious as a result of a urinary tract infection (UTI), whereas a cognitively intact elderly patient probably would not. As a useful rule of thumb, the presence of a delirium in an elderly patient should suggest the co-existence of an underlying dementia until proved otherwise.

Another common request is for evaluation of depressive symptoms associated with dementia. It is a diagnostic challenge to determine whether the mood symptoms are causing, co-existing with, or resulting from cognitive difficulties.[2] Determining the sometimes subtle differences in the history and presentation of delirium, depression, and AD can be helpful in the diagnosis of these disorders (Table 11–1).

Other presenting problems should alert the physician to an underlying dementia. These include poor medication compliance and injuries that could be accounted for by memory impairment. For example, many elderly patients experience burns as a result of dangerous cooking methods. Another reason for referral may be the patient's difficulty in coping with the inpatient setting itself. Despite a gradual cognitive decline, the patient may have functioned adequately in his or her familiar home setting. In the alien environment of the hospital, however, unfamiliar people provide care on an unusual schedule. As a result, trusted coping mechanisms may not work; anxiety, dysphoria, agitation, or paranoia can develop.

EPIDEMIOLOGY

Improvements in public health, nutrition, and medical care for the elderly have led to dramatic increases in the United States' population over the age of 65. Furthermore, those who live beyond the age of 85, the so-called oldest old, are the fastest-growing segment of the United States' population.[3] The significance of the aging population lies in the fact that age is a risk factor for dementia. Although the results of epidemiologic studies vary depending on the subjects sampled and the method employed, dementia occurs in approximately 15% of all individuals over the age of 65 and in up to 45% of those over the age of 80.[4] On this basis, nearly 5.7 million people over age 65 in the United States are affected. The global prevalence of dementia has been estimated at over 24 million people; the number of people affected will double every 20 years and reach 81 million by the year 2040.[5]

The most common type of dementia (accounting for 50% to 70% of cases) is AD. Among the neurodegenerative dementias, dementia with Lewy bodies (DLB) is the next most common, followed by frontotemporal dementia (FTD). Vascular dementia (which can have a number of different etiologies) can exist in the absence of AD, but the two frequently co-occur. Dementias associated with Parkinson's disease and Creutzfeldt–Jakob disease (CJD) are much less common.[6]

DIAGNOSIS

The definition of dementia in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[7] emphasizes that memory impairment is a necessary, but not sufficient, sign of the syndrome. At least one of the following additional findings must also be present: aphasia (a difficulty with any aspect of language), apraxia (the impaired ability to perform motor tasks despite intact motor function), agnosia (an impairment in object recognition despite intact sensory function), or a disturbance of executive function (including the ability to think abstractly, as well as to plan, initiate, sequence, monitor, and stop complex behavior). Associated features include impaired judgment, poor insight, personality change, and psychiatric symptoms (e.g., persecutory delusions and hallucinations, particularly visual). Motor disturbances (falls, ataxia, and extrapyramidal signs) and dysarthria (slurred speech) may be associated with certain dementing disorders.

TABLE 11–1 Clinical Features of Delirium, Depression, and Alzheimer's Disease

	DELIRIUM	DEPRESSION	AD
Onset	Abrupt	Relatively discrete	Insidious
Initial Symptoms	Difficulty with attention and disturbed consciousness	Dysphoric mood or lack of pleasure	Memory deficits—verbal and/or spatial
Course	Fluctuating—over days to weeks	Persistent—usually lasting months if untreated	Gradually progressive, over years
Family history	Not contributory	May be positive for depression	May be positive for AD
Memory	Poor registration	Patchy/inconsistent	Recent > remote
Memory complaints	Absent	Present	Variable—usually absent
Language deficits	Dysgraphia	Increased speech latency	Confrontation naming difficulties
Affect	Labile	Depressed/irritable	Variable—may be neutral

AD, Alzheimer's disease.

Additional essential elements for a diagnosis of dementia include a significant impact on social or occupational function and a significant decline from a previous level of function. Finally, the impairment occurs at times when delirium is absent. These final criteria are necessary to rule out age-associated memory impairment, congenital mental retardation, and life-threatening acute confusional disorders.

Scores of specific disorders can cause dementia (Table 11–2). The consultant cannot have in-depth knowledge of all of them but can identify common or typical and rare

TABLE 11–2 Dementia: Diagnosis by Categories with Representative Examples

Degenerative
Alzheimer's disease
Frontal lobe dementia with/without motor neuron disease
Pick's disease
Diffuse cortical Lewy body disease
Corticobasal degeneration
Huntington's disease
Wilson's disease
Parkinson's disease
Multiple system atrophy
Progressive supranuclear palsy

Psychiatric
Depression
Schizophrenia

Vascular
Vascular dementia
Binswanger's encephalopathy
Amyloid dementia
Diffuse hypoxic/ischemic injury

Obstructive
Normal pressure hydrocephalus
Obstructive hydrocephalus

Traumatic
Chronic subdural hematoma
Dementia pugilistica
Postconcussion syndrome

Neoplastic
Tumor—Malignant—primary and secondary
Tumor—Benign (e.g., frontal meningioma)
Paraneoplastic limbic encephalitis

Infections
Chronic meningitis
Postherpes encephalitis
Focal cerebritis/abscesses
HIV dementia
HIV-associated infection
Syphilis
Lyme encephalopathy
Subacute sclerosing panencephalitis
Creutzfeldt-Jakob disease
Progressive multifocal leukoencephalopathy
Parenchymal sarcoidosis
Chronic systemic infection

Demyelinating
Multiple sclerosis
Adrenoleukodystrophy
Metachromatic leukodystrophy

Autoimmune
Systemic lupus erythematosus
Polyarteritis nodosa

Drugs/Toxins

Medications
Anticholinergics
Antihistamines
Anticonvulsants
β-blockers
Sedative–hypnotics

Substance abuse
Alcohol
Inhalants
PCP

Toxins
Arsenic
Bromide
Carbon monoxide
Lead
Mercury
Organophosphates

Adapted from Schmahmann JD: Neurobehavioral manifestations of focal cerebral lesions, presented at the Massachusetts General Hospital course in Geriatric Psychiatry, Boston, 1995.

HIV, Human immunodeficiency virus; *PCP*, phencyclidine.

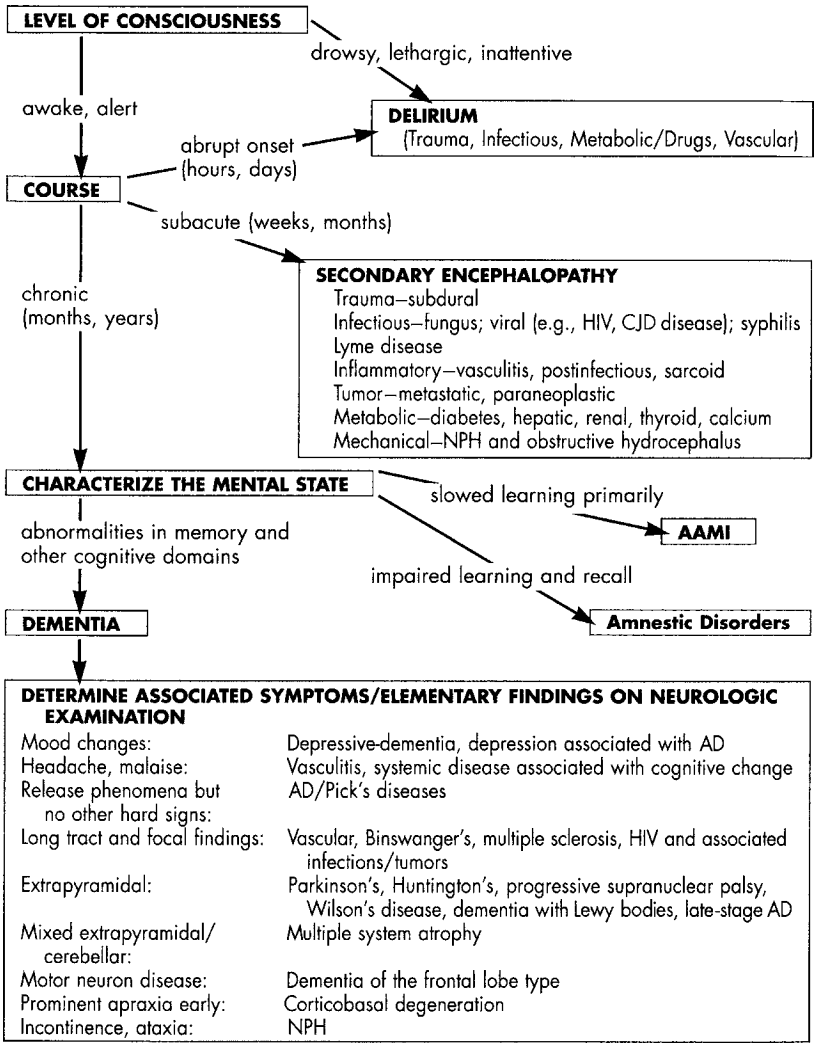


Figure 11–1. An algorithm for dementia diagnosis. *AAMI*, Age-associated memory impairment; *CJD*, Creutzfeldt-Jakob disease; *AD*, Alzheimer's disease; *HIV*, human immunodeficiency virus; *NPH*, normal pressure hydrocephalus. *(Adapted from Schmahmann JD: Neurobehavioral manifestations of focal cerebral lesions, presented at the Massachusetts General Hospital course in Geriatric Psychiatry, Boston, 1995.)*

or unusual presentations. In addition, certain associated physical findings can direct the consultant to particular diagnoses (Figure 11–1).

Many elderly individuals complain of memory difficulties, often involving learning new information or names or finding the right words. In most circumstances, such lapses are normal. The term *mild cognitive impairment (MCI)* was coined to label an intermediate category between the normal cognitive losses that are associated with aging and those linked with dementia. MCI is characterized by a notable decline in memory or other cognitive functions compared with age-matched controls. MCI is common among the elderly, although estimates vary widely depending on the diagnostic criteria and assessment methods employed; some, but not all, individuals with MCI progress to dementia. The identification of those at risk for progression of cognitive impairment is an active area of research.[8,9]

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive, irreversible, and fatal brain disease that affects memory, thinking, and behavior. The classic brain lesions of AD are known as neurofibrillary tangles (NFTs) and neuritic plaques (NPs). Although a definitive diagnosis of AD relies upon postmortem findings of these lesions,[10] detailed clinical assessments (by psychiatrists, neurologists, and neuropsychologists) in combination with use of structural and functional neuroimaging have a high concordance rate with autopsy-proven disease.

Progressive memory loss is the hallmark of AD. Other common cognitive clinical features include impairment of language, visual–spatial ability, and executive function. Patients may be unaware of their cognitive deficits, but this is not uniformly the case. There may be evidence of forgetting conversations, having difficulty with household finances, being disoriented to time and place, and misplacing items regularly. At least two domains of cognitive impairment, including progressive memory decline (that affects functional ability), are required to make a clinical diagnosis of AD.[11] In addition to its cognitive features, AD is associated with a number of neuropsychiatric symptoms, even in its mildest phases.[12] In particular, irritability, apathy, and depression are common early in the course of the disease, whereas psychosis (including delusions and hallucinations) tends to occur later.

Vascular Dementia

Vascular dementia refers to a variety of vascular-related causes of dementia, including multi-infarct dementia (MID) and small vessel disease. The pathophysiology of vascular dementia can be related to recurrent or localized embolic strokes, smaller subcortical strokes (e.g., lacunar infarcts), or cerebral hemorrhages. It is important to keep in mind that cerebral hemorrhages (resulting from hypertension or amyloid angiopathy) require a different type of clinical management than does typical vascular occlusive disease.

The clinical features of vascular dementia depend on the localization of the lesions; both the type of cognitive deficits and the time course of the cognitive changes vary. Embolic or large-vessel stroke-related dementia often progresses in a stepwise pattern, with intervening periods of stability punctuated by abrupt declines in cognitive function. Although this might be considered the classic presentation, it may not be its most common form.[13] Presentations that involve relatively isolated psychotic symptoms in the setting of preserved memory should also raise the possibility of vascular dementia. Likewise, apathy, executive dysfunction, and a relatively intact memory are suggestive of a small-vessel ischemic process.

The main difficulty that arises in the diagnosis of vascular dementia is distinguishing it from AD. Classically, vascular dementia is distinguished from AD on the basis of an abrupt onset and a stepwise course. In addition, prominent executive dysfunction and preserved recognition memory are also suggestive of vascular dementia. However, the symptoms of vascular dementia often overlap with those of AD; in fact, evidence of both conditions is often found at autopsy.

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) shares clinical features of both AD and Parkinson's disease; this makes accurate diagnosis a challenge.[14] The main pathologic features of DLB are proteinaceous deposits called Lewy bodies, composed of α-synuclein in the cortex and brainstem.[15,16] Features that suggest DLB include visual hallucinations (which often occur early in the course, in contrast to the pattern seen in AD), a fluctuating course, an extreme sensitivity to neuroleptic medications, autonomic dysfunction (with falls), disorientation, and executive and visual–spatial dysfunction (with relatively spared language and memory function). Sleep disorders are also common; in particular, rapid eye movement–behavior disorder is problematic. Other neuropsychiatric manifestations (e.g., apathy, irritability, depression, agitation) are also common. Parkinsonian symptoms are also necessary for the diagnosis of DLB; in most cases, motor symptoms occur within 1 year of the onset of cognitive problems. By contrast, in Parkinson's disease with dementia, the motor symptoms typically precede cognitive problems by several years. Although specific clinical features of the disease (e.g., hallucinations, fluctuations, visual–spatial deficits, and rapid eye movement–behavior disorder) are helpful in the identification of this disease, clinical–pathologic concordance has not been great, and postmortem pathologic findings of Lewy bodies in the cerebral cortex, amygdala, and brainstem are necessary to confirm the diagnosis.[17,18]

Frontotemporal Dementias

Frontotemporal dementias (FTDs) are a heterogeneous group of neurodegenerative disorders that involve degeneration of different regions of the frontal and temporal lobes, resulting in a variety of clinical presentations. Currently included under the category of FTDs are Pick's disease, frontotemporal lobar degeneration, primary progressive aphasia, and semantic dementia.[19] FTDs tend to manifest at younger ages than typical AD, with the majority of cases occurring in people younger than 65 years of age.

The classic hallmarks of FTDs are behavioral features, usually out of proportion to, or even preceding, memory impairment. In general, there is a subtle onset and a progression of symptoms (with loss of judgment, disinhibition, impulsivity, social misconduct, loss of awareness, and interpersonal withdrawal). Other typical symptoms are stereotypies, excessive oral–manual exploration, hyperphagia, wanderlust, excessive joviality, displays of sexually provocative behaviors, and use of inappropriate words or actions. Clinical presentations of FTD vary depending on the relative involvement of the hemisphere (right or left) or lobe (frontal or temporal) affected.[20] Patients may initially have more involvement of the right temporal lobe than the left and exhibit primarily a behavioral syndrome with emotional distance, irritability, and disruption of sleep, appetite, and libido. With greater initial left than right temporal lobe involvement, patients tend to exhibit more language-related problems, including anomia, word-finding difficulties, repetitive speech, and loss of semantic information (e.g., semantic dementia).[21] In some cases of FTD, the frontal lobes may be involved more than the temporal lobes. In these instances, patients exhibit symptoms of elation, disinhibition, apathy, or aberrant motor behavior.

Dementia Caused by Other Medical Conditions

Dementias caused by other medical conditions include a broad range of disorders that are causally associated with a dementia: structural lesions; trauma; infections; endocrine, nutritional, and metabolic disorders; and autoimmune diseases. Two notable examples include dementias caused by normal pressure hydrocephalus (NPH) and CJD.

NPH is recognized by the classic clinical features of gait disturbance, frontal systems dysfunction, and urinary incontinence.[22] Intermittent pressure increases are thought to cause ventricular expansion over time, with damage to the adjacent white matter tracts that connect the frontal lobes. Evaluation usually includes structural brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) that demonstrates ventricular enlargement that is out of proportion to the atrophy present.

CJD is a rare disorder that causes a characteristic triad of dementia, myoclonus, and distinctive periodic electroencephalographic (EEG) complexes. CJD is caused by prions, novel proteinaceous infective agents, that induce changes in the cerebral cortex and lead to the distinctive microscopic, vacuolar appearance of spongiform encephalopathy. The cerebrospinal fluid in almost 90% of CJD cases contains traces of prion proteins detected by a routine lumbar puncture. Treatment of afflicted individuals is supportive, insofar as the condition follows a characteristic course, with death arriving after an average of 6 months.[23]

Substance-Induced Persisting Dementia

To establish the diagnosis of substance-induced persisting dementia, there must be evidence from the history, physical examination, or laboratory data that cognitive deficits consistent with dementia are probably caused by exposure to a substance. The term *persisting* is important because the diagnosis cannot be made during a period of acute intoxication or during drug withdrawal. The most common cause of this type of disorder is chronic alcohol usage, but toxins, poisons, inhalants, sedative–hypnotics, and other medications are also causes.

Dementia Resulting from Multiple Causes

In the diagnostic section of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), the phrase "dementia due to multiple etiologies" serves to emphasize that a patient can have more than one cause for cognitive decline. Although many combinations can occur, perhaps the most common is the co-existence of AD and vascular disease. Some authorities refute this assertion, suggesting that diffuse DLB is the second most common primary dementing disorder and that its combination with AD is not sufficiently recognized.[24] AD can also co-exist with reversible causes of dementia (e.g., vitamin B_{12} deficiency, hypothyroidism), further emphasizing the importance of a thorough medical and neurologic work-up.

EVALUATION OF DEMENTIA

Brain failure deserves at least as careful an assessment as the failure of any other organ. Only through thoughtful evaluation can remediation of the cognitive decline be possible. Although in most cases the goal of treatment is not a cure, there is still much that can be done to help afflicted patients and their families. The evaluation requires a reliable history (cognitive, psychiatric, medical, and family), complete medical and neurologic examinations, appropriate laboratory testing, and assessments of the mental status and cognitive function.

History

A meticulous cognitive history is an extremely sensitive diagnostic tool. Onset, course, and associated symptoms must be elicited carefully because these details of history often provide critical diagnostic clues. Because of time constraints, consultants may be inclined to limit their history-taking to the patient alone. Although some mildly impaired patients may have sufficient capacity to provide an accurate account of their deficits, many (owing to their amnesia, agnosia, or failure of insight) do not. To rely solely on the patient's report is unwise; it may be inaccurate, and it will be incomplete. Additional history is best obtained from family members or close friends. It is important to interview informants away from the patient because informants are often uncomfortable discussing evidence of cognitive decline in the presence of the patient. Even a phone call to a family member or a friend can be helpful, as can a review of old medical records, when available.

A good cognitive history must establish the time at which cognitive changes first became apparent. This information provides important clues regarding the nature of the disorder because some diseases (e.g., CJD) are well known for causing a rapid rate of decline. If the time of onset of the disorder is known, the rate of decline can be estimated by seeing how long it has taken the patient to reach the current level of dysfunction. The rate of progression can only be approximated; however, it is helpful for family members to have such estimations so that plans for the future can be facilitated.

Next, it is important to determine the nature of the behavioral changes that were evident when the disease began. This information can also be helpful in the diagnostic process. For example, an early symptom of FTD is personality change, as manifested by inappropriate behavior, whereas the early symptoms of AD may involve increased passivity or apathy and a gradual, progressive decline in the ability to learn new information. Several years after the onset of the disease, when most patients are actually diagnosed, the cognitive symptoms of the two disorders may be quite similar, so information about the initial symptoms may be critical.

It is also important to determine whether the initial symptoms developed gradually or suddenly. If the onset of illness was insidious, as in AD, the family may realize only in retrospect that a decline has occurred. In contrast, a series of small strokes may produce symptoms of sudden onset, even if lesions were not evident on a CT scan or MRI of the head. Delirium generally has an acute onset as well. However, if it results from a condition such as a gradually developing drug toxicity, its onset may be subacute or insidious.

The manner in which symptoms have progressed also provides important diagnostic information. Stepwise deterioration characterized by sudden exacerbation of symptoms is typical of vascular dementia. A physical illness (e.g., pneumonia, a hip fracture) in a patient with AD, however, can also cause a sudden decline in cognitive function. Thus careful questioning is necessary to determine the underlying cause of a stepwise decline in function.

Accurate histories of cognitive function are difficult to obtain because most patients and family members are not attuned to subtle behavioral changes. Important aspects of the medical history may not be recognized. For example, the family may state that the first symptoms of the disease were the patient's anxiety and depression about work. Only after further inquiry will family members remember several episodes that preceded the onset of work-related anxiety in which the patient could not remember how to deal with a complex situation or learn how to use new equipment.

Family members may also have difficulty understanding why certain subtle distinctions are important for diagnosis. For example, they may report that the patient's first symptom was forgetfulness, but when asked to provide instances of this forgetfulness, they may explain that the patient had difficulty installing a new knob in the kitchen or had trouble finding a familiar location. Both features would suggest spatial difficulty more than memory difficulty. In addition, an unwillingness to admit that certain impairments exist may prevent family members from providing accurate information.

Finally, family members may misinterpret even direct questions. Although a history of a gradual, progressive decline is essential to the diagnosis of AD, informants

frequently state that the disorder came on suddenly because they suddenly became aware that something was wrong. This realization on the part of the family often coincides with external events (e.g., a trip to an unfamiliar place prevented the patient from employing overlearned habits and routines and thus exposed the cognitive decline). The hospital is obviously one such setting; it is not uncommon for family members to state, "He was fine until he got here!" When this misconception appears, it is necessary to determine when subtle symptoms of cognitive change first occurred. Usually, family members can recall episodes that they had previously ignored that suggest an earlier change in cognitive function. Annual family gatherings or holiday events are useful occasions about which to inquire.

It is also important to determine the patient's current functional status. This information is best obtained in an informal manner by asking about the patient's typical day. Alternatively, scales, such as the activities of daily living (ADL) and the instrumental activities of daily living (IADL) scales (Table 11–3), have been developed for this purpose. The ADL scale surveys six basic areas of function and determines whether the individual can perform these tasks independently or with assistance.[25] The IADL scale provides a sense of a patient's executive functions.[26] A substantial discrepancy between the functional and cognitive status of the patient generally suggests the presence of a psychiatric illness. For purposes of comfort, safety, rehabilitation, and determination of appropriate level of care, ADL and IADL results should be evaluated carefully.

The psychiatric history, with particular attention paid to reports of past mood or psychotic disorders, may assist in the differentiation of cognitive changes observed in depression from those of a primary dementing disorder. Although cognitive changes can be seen in depression, the history and mental status examination usually allow the physician to separate depression and dementia or suggest that both are present. Neurovegetative symptoms of depression may be difficult to link specifically to mood or cognitive disorders because anergia, sleep disturbance, and appetite changes can be seen in both depression and dementia. Thus it is important to modify the questions asked to encompass the possibility of cognitive impairment. For example, if the tasks are simplified and within the capabilities of a nondepressed, demented patient, the patient is typically able to carry them out. Similarly, if food is presented in a manner that the patient can manage, such as meat cut into bite-size pieces, the patient may show a newfound gusto in his or her appetite (see Table 11–1).

In reviewing the medical history, the physician should consider whether surgical procedures (e.g., gastrectomy predisposing to vitamin B_{12} deficiency) or medical illnesses (e.g., hypertension, systemic lupus erythematosus) contribute to the symptoms of cognitive dysfunction. It is crucial to determine whether the patient underwent blood transfusions (particularly during the early to mid-1980s, when human immunodeficiency virus testing was not readily available), was exposed to toxins (e.g., lead or other heavy metals, carbon monoxide), or has a history of head trauma. Careful questioning should cover alcohol and drug usage (not just current patterns), including a past history of abuse or overuse. Many nonpsychotropic agents, including those sold over the counter, can have negative effects on cognition. For example, antihistamines and antispasmodic drugs can cause cognitive difficulties. Valuable historical data includes information regarding impairments in hearing or vision, incontinence, falls, and gait disturbances.

The family history portion of the evaluation is also helpful. Certain dementing disorders (e.g., Huntington's disease) have definite genetic modes of transmission (e.g., autosomal dominant), whereas for others (e.g., certain vascular dementias) the specific mode of transmission may be unclear, but their prevalence is much higher in affected families than in the population at large. Several familial subtypes of AD with genetic loci have been identified. An estimated 7% of cases with an onset before the age of 60 are familial, with an autosomal dominant inheritance. Several genes, including beta-amyloid precursor protein and presenilin 1 and 2, have been associated with early-onset AD.[27] For the majority of patients with AD, there appears to be a complex interaction among genetic and other factors.[28] Variations in the gene for apolipoprotein E (APOE) may increase the risk of developing AD or predispose to earlier onset.[29] APOE remains the only documented late-onset AD gene.[30]

TABLE 11–3 Assessment of Functional Status

Activities of Daily Living (ADL)	Instrumental Activities of Daily Living (IADL)
Bathing	Ability to use telephone
Dressing	Shopping
Toileting	Food preparation
Transferring	Housekeeping
Continence	Laundry
Feeding	Mode of transportation
	Responsibility for own medications
	Ability to handle finances

Adapted from Katz S, Downs TD, Cash HR et al: Progress in the development of the index of ADL, *Gerontologist* 10:20–30, 1970; and Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living, *Gerontologist* 9: 179–186, 1969.

Medical and Neurologic Examination

The consultant should review recent examinations in the medical record to assess their adequacy and accuracy. The cognitive portion of prior examinations may note only that the patient was alert and oriented. Additionally, if notes report "disorientation," it is often unclear from the chart whether the patient could not remember the day of the week or whether he or she was confused or psychotic. Consequently, the psychiatric consultant should look for medical and neurologic findings that are associated with dementing disorders. For example, focal areas of muscle weakness and pyramidal signs may suggest vascular dementia. The presence of extrapyramidal movements may point to one of the dementias that principally affects subcortical motor areas. Mild to moderate AD, however, may also be associated with extrapyramidal symptoms (EPS) and other neurologic signs.[31] A comprehensive neurologic examination should include careful assessment of ocular function, gait, and praxis, as well as the presence of any frontal release signs.

Laboratory Examination

Table 11–4 lists hematologic and other tests that are typically ordered as part of a dementia evaluation. Whenever possible and appropriate, results of prior testing in other settings should be obtained. For example, a chest x-ray examination or CT scan should not be reordered if one was recently done unless an acute change has occurred. Additional tests (e.g., serum copper and ceruloplasmin for Wilson's disease or serum and urine porphyrins for acute intermittent porphyria) should be requested when the history and examination suggest a particular disorder.

Psychiatric Mental Status Examination

The bedside psychiatric examination covers considerable territory, but it focuses on assessments of affective and psychotic signs and symptoms. The physician should probe for mood symptoms, irritability or tearfulness, and nihilistic or suicidal thinking. Depressed elderly patients may, among their somatic complaints, describe decrements in memory. Depressed patients, as opposed to patients with AD, however, may perform better on more difficult memory tasks than on simple ones.

TABLE 11–4 Recommended Laboratory Studies in a Dementia Work-Up

Blood Studies
Complete blood cell count
Vitamin B_{12}
Folate
Sedimentation rate
Glucose
Calcium
Phosphorus
Magnesium
Electrolytes
Liver function tests
Thyroid-stimulating hormone
Creatinine, blood urea nitrogen
Cholesterol (high-density lipoprotein/low-density lipoprotein)
Triglycerides
Syphilis serology
Other Studies
Urinalysis
Electrocardiogram
CT or MRI
Representative Additional Studies Based on History and Physical Findings
Chest x-ray examination
Electroencephalogram
Noninvasive carotid studies
HIV testing
Rheumatoid factor, antinuclear antibody, and other autoimmune disorder screens
Lumbar puncture
Drug levels
Heavy metal screening

CT, Computed tomography; *HIV*, human immunodeficiency virus; *MRI*, magnetic resonance imaging.

Psychotic symptoms can be present in primary psychiatric disorders, such as psychotic depression or schizophrenia, but they can also be associated signs of delirium or dementia. The prevalence of psychosis in moderate to severe AD is estimated to be in the range of 40% to 80%.[32] Usually, delusions in patients with AD are of a paranoid nature, often involving the mistaken belief that misplaced items have been stolen. With progression of the disease, the patient may come to believe that spouses are parents or that they are actually imposters (i.e., Capgras syndrome). Illusions and hallucinations, usually of a visual nature, also occur with advanced AD. For example, some patients describe seeing "little people" entering their homes. Despite their unusual nature, not all hallucinations or delusions are troublesome to the patient. Mood and psychotic symptoms can occur as part of the clinical picture of many dementing disorders. Generally, they are nonspecific. However, taken together with other elements of the assessment, such symptoms can provide clues as to whether a psychiatric disorder or a dementing disorder is present.

Bedside Cognitive Assessment

Domains of cognitive function that require rapid and accurate bedside assessment can be remembered with the mnemonic A CALM VISAGE (the face the consultant would put forward when confronted with a patient who is difficult to diagnose). These domains include the following: Attention, Conceptualization, Appearance/behavior, Language, Memory, VISual–spatial, Agnosia and apraxia, and GEneral intelligence.

Attention is important to consider because simple attentional abilities must be preserved if any other cognitive task is to be performed adequately. If the patient has difficulty concentrating on a task for even a few minutes at a time, assessment of other domains will likely be inaccurate. For this reason, attention is often evaluated first. Auditory and visual attention can be assessed easily by means of digit span and letter cancellation tests. For the digit span test, the patient is asked to repeat a series of numbers spaced 1 second apart. The examiner provides gradually increasing spans; unimpaired individuals are able to repeat five to seven numbers. For the letter cancellation test, the patient is asked to cross off a particular letter each time he or she observes it in any series of letters. A gross assessment can be inferred from how well the patient responds to questions during an interview. The physician should note whether the level of arousal appears to fluctuate or the patient seems easily distracted during the interview.

Tasks that examine conceptualization include tests of concept formation, abstraction, set-shifting, and set-maintenance. Similarities and proverbs are useful in this regard.

Observation of appearance and behavior is helpful in determining whether patients are able to care adequately for themselves. Detecting that a patient's buttons are misaligned, for example, may suggest that he or she has spatial difficulties or an apraxia.

Language testing for aphasia should include evaluation of comprehension, repetition, reading, writing, and naming. If aphasia has been ruled out or is not suspected, confrontation naming (e.g., of objects and their parts, such as jacket and lapel or watch and stem) should be included in

an assessment of the older individual because declines in naming ability occur with age but are prominent in a number of disorders, including AD. In addition, alterations in verbal fluency (tested by having the patient name as many animals or words beginning with a certain letter as possible in a minute) are seen in many dementing diseases.[33]

The presence of memory dysfunction is essential for a diagnosis of dementia. The nature and severity of the memory impairment can serve as a guide to diagnosis, but the assessment of memory is complicated by the fact that changes in memory capacity normally occur with aging. Normal elders may require more time to retain new information. Therefore careful testing is important to differentiate normal from pathologic memory performance. Testing should include not only short-term memory but also memory of personal events (e.g., details of marriage, names of children) and significant historical dates (e.g., John F. Kennedy's assassination, September 11).

Assessment of visual–spatial abilities may be more difficult in older than in younger individuals because of the frequency of visual–sensory deficits in the elderly. It is difficult to enlarge certain test stimuli to evaluate this domain; therefore figure copying (e.g., of intersecting pentagons or a cube) is the most useful method of assessment.

When agnosia or apraxia is evident, the patient's disease is usually quite advanced. Agnosia is diagnosed when a patient fails to recognize a familiar object despite intact sensory function. With apraxia, the patient's ability to carry out motor tasks is impaired despite intact motor systems and an understanding of the tasks. For example, the patient is unable to mimic the use of common objects (e.g., use of a toothbrush) or to carry out well-learned motor behaviors (e.g., pretending to blow out a candle). A subtle finding is "organification of praxis" in which the subject, for example, uses a finger as the toothbrush.

In addition to the areas of assessment previously mentioned, the examiners should estimate general intelligence to determine whether the patient has access to previously acquired knowledge. A rough approximation can be inferred from the patient's highest level of education. Alternatively, the vocabulary subtest of *The Wechsler Adult Intelligence Scale–Revised* can be used to estimate level of intelligence.[34]

Standardized Cognitive Testing

Nonstandard testing developed by the clinician can be used to evaluate the cognitive domains noted previously, but a variety of standardized, brief mental status tests can be useful as well. However, although screening tests may identify cognitive difficulties, they are not sufficient to establish a diagnosis of dementia.

Commonly used screening tests are the Mini-Mental State Examination (MMSE),[35] the Blessed Dementia Scale,[36] and the Short Portable Mental Status Questionnaire.[37] All have high test–retest reliability, and all are relatively brief, taking 5 to 15 minutes to administer. Of these, the MMSE is most often used in clinical settings (see Table 4–8 for details) because it assesses a broad range of cognitive abilities (i.e., attention, concentration, memory, language, spatial ability, and set-shifting) in a simple, straightforward manner. Scores on the MMSE range from 0 to 30, with scores greater than 26 generally indicating normal cognitive function. Mildly impaired patients typically obtain MMSE scores of 20 to 26, moderate impairment is reflected in scores of 11 to 20, and severe impairment is indicated by scores of 10 or lower. A cutoff score of 23 is generally recommended as suggestive of cognitive dysfunction; however, the application of this cutoff score must be modified in light of the patient's education level. For example, an extremely bright, well-educated patient may score 29 or 30 despite having significant impairment.

The MMSE is a useful screening tool in the assessment of demented patients with mild to moderate cognitive impairments, but it is less helpful in the evaluation of severely impaired patients. The quantification of cognitive abilities in severely impaired patients can serve a variety of needs, including the ability to follow patients throughout an intervention trial, the assessment of spared abilities (which health care professionals can use in the development of management strategies), and the examination of the relationship among postmortem neurochemical and neuropathologic findings and cognitive status shortly before death. The Test for Severe Impairment (TSI) is a useful scale for severely impaired patients that can contribute to improved patient management.[38] It minimizes the need for the patient to use language skills because severely impaired patients often have minimal intact verbal skills. Nonetheless, the TSI can evaluate motor performance, language comprehension, language production, immediate and delayed memory, general knowledge, and conceptualization.

On the other end of the spectrum, patients with MCI often score within the normal range on the dementia screening tools discussed previously. The Montreal Cognitive Assessment (MoCA) was created as a 10-minute screening tool to assist in the detection of MCI.[39] It assesses many cognitive domains, and although somewhat more challenging than the MMSE, it assesses executive and abstract functions in a superior manner. Components of the visual–spatial and executive function testing include a brief "Trails B," copying a cube, and drawing a clock. The MoCA is available free of charge for noncommercial clinical use and available online (www.mocatest.org) in a multitude of languages (Figure 11–2).

With all structured tests, the examiner must not simply look at the total score but rather assess the qualitative areas of low and high function. The pattern of deficits may confirm a diagnostic opinion. Conversely, determining that areas of function have been preserved assists the clinician in making recommendations to the patient and the family for adaptive coping with the dementia.

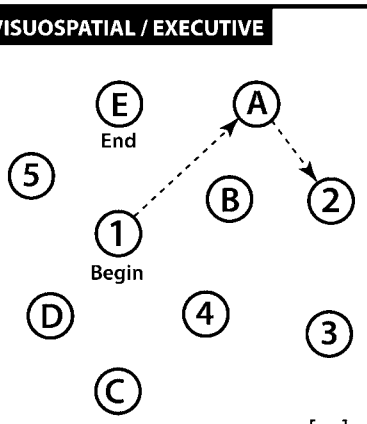
TREATMENT CONSIDERATIONS

The approach to treatment of a dementing disorder depends on the specific diagnosis established as well as on the troublesome symptoms and signs that must be managed. Treatment is divided into three broad categories: medical and surgical interventions, behavioral interventions, and pharmacotherapy. Pharmacotherapy can be divided further into treatments for cognitive symptoms and neuropsychiatric symptoms of dementia.

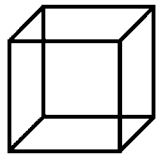
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

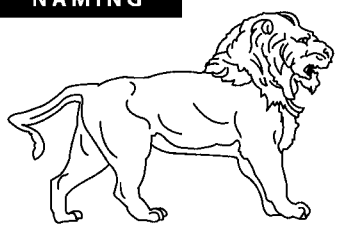


[ ] [ ]

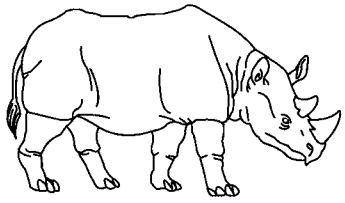
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING



[ ]



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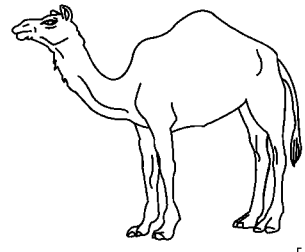

[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD Version 7.1 **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Figure 11–2. The Montreal Cognitive Assessment (MoCA). *Copyright Z. Nasreddine M.D., reproduced with permission.*

Medical and Surgical Interventions

Some dementing disorders can be helped dramatically by surgical interventions. For example, the treatment for NPH is removal of cerebrospinal fluid by way of a lumbar puncture or ventriculoperitoneal shunting. It is important to perform cognitive and motor testing before and after the removal of a large volume of cerebrospinal fluid.[40] Similarly, draining of frontal subdural hematomas can improve patients' cognition and behavior.

Other reversible medical disorders that cause dementia should be corrected. For example, thyroid repletion in the myxedematous patient improves cognitive function. In many conditions, however, damage has already been done, and repletion may provide only marginal improvement. For example, a patient who had deteriorated over several years was found to have an extremely low vitamin B_{12} level. Her dementia was profound, and it did not respond to intramuscular injections of vitamin B_{12}. Further deterioration of her cognition and other nervous system functions, however, may have been prevented by the treatment.

Sometimes the reduction or elimination of drugs can be helpful. For example, patients with Parkinson's disease and psychotic symptoms secondary to use of dopamine agonists may require dosage adjustment to reduce the psychotic symptoms. Other examples are barbiturate-induced cognitive decline and benzodiazepine-induced memory impairment. Elimination of the sedative is essential because cognitive symptoms caused by the drug are most likely to remit with cessation. Care must be taken, however, to avoid a withdrawal syndrome caused by too abrupt a discontinuation.

Searching for treatable contributors to cognitive decline is important, even when the principal diagnosis is AD. Identification of co-existing medical conditions that have a deleterious effect on the patient's cognition is critical. For example, the aggressive treatment of a urinary tract infection improves not only physical comfort but also intellectual function (because infection in the setting of AD usually causes delirium). Pain, too, may have a negative effect on cognition. A patient whose AD was manageable at home became severely aggressive and more confused owing to the discomfort of an impacted bowel. Another patient with presumed vascular dementia showed some improvement in cognition after treatment for congestive heart failure.

Behavioral Interventions

Once drug effects and contributing medical conditions are identified and managed, acute behavioral symptoms associated with dementia may subside. The environmental strangeness of the hospital, however, may be enough to trigger new psychiatric and behavioral problems, such as paranoid thinking and agitation.

Often, behavioral management alone reduces certain symptoms; such nonpharmacologic interventions should be used in every case. The basic approaches are well known but bear repeating (Table 11–5). When considering behavioral interventions, always remember the ABCs of behavioral analysis: antecedent, behavior, and consequences. For example, a patient is easily upset and confused when she cannot remember her nurse; as a result, she yells and sometimes throws things at the nurse when she comes into the room, putting both the patient and nurse in danger (e.g., from inadvertent removal of intravenous lines or being struck by thrown objects). When tailoring behavioral interventions, the physician should consider each aspect of the behavioral analysis. Possible solutions to the aforementioned case include posting the names of providers in the patient's room, removing potentially dangerous objects from within reach of the patient's bed, and reassuring the patient.

TABLE 11–5 Behavioral Management for Dementia Patients

Reorient to the environment (e.g., clock, calendar); post names of care providers
Simplify communication (e.g., yes/no questions)
Reassure, distract, and redirect (e.g., familiar pictures from home)
Use eyeglasses and hearing aids appropriately
Encourage activity and exercise
Offer soothing therapies (e.g., music therapy or aromatherapy)
Provide one-on-one supervision
Apply physical restraint (when necessary for the safety of the patient and others)

The manner in which staff members communicate with the patient is also important. Speaking loudly enough (but not too loudly) is a critical first step. Decreased hearing acuity affects all elders, but this does not mean that shouting is necessary. The content of what is said should be simple and to the point. If the patient has considerable expressive language difficulties, questions should be framed so that a yes-or-no response is adequate. Reassurance and distraction are preferred responses to patients who are paranoid or easily distressed.[41]

Pharmacotherapy for Cognitive Symptoms

Pharmacotherapies in dementia generally target both cognitive decline and the behavioral and other psychiatric consequences of disease. Because AD is associated with cholinergic dysfunction, cholinesterase inhibitors (ChE-Is) have been developed and are now widely used in treatment (Table 11–6). The commonly used ChE-Is in the United States include donepezil, rivastigmine, and galantamine. A fourth agent, tacrine, is no longer widely used because of its association with hepatotoxicity. The ChE-Is differ in their pharmacologic properties, administration regimens, drug interactions, and effect on hepatic enzymes. The most common side effects include nausea, vomiting and diarrhea; other bothersome adverse effects include insomnia or vivid dreams, fatigue, muscle cramps, incontinence, bradycardia, and syncope. As a result, these drugs may be contraindicated in the setting of bradycardia or sick sinus syndrome; severe asthma and peptic ulcer disease may also be relative contraindications.

In patients with AD, all the ChE-Is have been shown to produce improvements in cognition, functional outcomes (e.g., in ADL and IADL), and neuropsychiatric and behavioral symptoms.[42,43] Treatment with these agents should begin as early as possible in patients with AD.[44] The usefulness of these agents in other forms of dementia is not as well studied. One randomized, double-blind, placebo-controlled study comparing rivastigmine against placebo found that rivastigmine appeared to moderately improve cognition and to a

TABLE 11–6 Characteristics of Cholinesterase Inhibitors

DRUG	CHEMICAL CLASS	TOTAL DAILY DOSE	REGIMEN	ADVERSE EVENTS
Donepezil	Piperidine	5-10 mg	Daily	GI, headaches, weakness
Rivastigmine	Carbamate	6-12 mg (oral), 4.6-9.5 mg (transdermal)	Twice daily (oral) or daily (transdermal)	GI, headaches, dizziness
Galantamine	Tertiary alkaloid	16-24 mg	Once daily (extended release) or twice daily (immediate release)	GI, insomnia
Tacrine	Aminoacridine	80-160 mg	Four times daily	Elevated liver enzymes, GI

Adapted from Daly EJ, Falk WE, Brown, P: Cholinesterase inhibitors for behavioral disturbance in dementia, *Curr Psychiatry Rep* 3:251–258, 2001.
GI, Gastrointestinal.

lesser extent ADL in patients with dementia associated with Parkinson's disease.[45] Review of the literature on the use of ChE-Is in DLB found no convincing evidence for their use.[46]

Goals of therapy with ChE-Is include a delay in cognitive decline, a delay of functional decline, and treatment or prevention (or both) of the development of behavioral symptoms. It is important to note that the downhill slope of the illness will continue. ChE-Is also have a small beneficial effect on burden and active time use among caregivers of persons with AD.[47]

Memantine, an *N*-methyl-D-aspartate antagonist, has been approved by the Food and Drug Administration for treatment of moderate to severe AD. Memantine normalizes levels of glutamate, a neurotransmitter involved in learning and memory, and which in excessive quantities is thought to contribute to neurodegeneration. Common side effects include dizziness, agitation, headache, and confusion. Evidence indicates that adding memantine to the regimen of patients with moderate to severe AD (who were already receiving stable doses of donepezil) results in better outcomes on measures of cognition, ADL, and behavior.[48,49]

Initiating pharmacotherapy for cognitive symptoms is not usually in the domain of the psychiatric consultant in the general hospital; this is typically the work of outpatient treaters. However, one reason to consider starting these medications in an inpatient medical setting might be to monitor for side effects and tolerability in patients with significant co-morbid medical illnesses. Initiation of ChE-Is may also be considered in this setting for treatment of neuropsychiatric symptoms, as described later. The consultant may be asked to consider reasons to stop ChE-Is, such as side effects, new medical contraindications, poor compliance, or rapid decline in the patient's illness. Any benefits of treatment are rapidly lost upon discontinuation.

Pharmacotherapy for Neuropsychiatric Symptoms

Pharmacotherapy may also be useful for managing disruptive or distressing psychiatric or behavioral symptoms unresponsive to the medical corrections and behavioral interventions noted. However, certain symptoms are poorly responsive to drug therapies. For example, the motor restlessness and wandering behavior seen in patients with AD are typically nonresponsive to medications; in addition, some treatments (e.g., neuroleptics that cause akathisia) may actually aggravate the problem.[50] When other symptoms, such as visual hallucinations or delusions, cause no distress to the patient and are not dangerous, medication is not required. When treatment is necessary, the golden rule of geriatric pharmacotherapy is, "Start low, go slowly, but go all the way." This maxim applies whether target symptoms relate to apathy, depression, psychosis, agitation, or some combination of these domains.

Apathy is the most common behavioral change in AD.[51] It is defined as a lack of motivation relative to the prior level of function, with a decrease in goal-directed behaviors, goal-directed cognition, and emotional responsiveness.[52] The lack of motivation must not be attributable to intellectual impairment, emotional distress, or a diminished level of consciousness. It is important to distinguish apathy from depression in patients with dementia because the treatments are different (Table 11–7). Treatments for apathy include use of psychostimulants,[53] dopamine agonists (e.g., bupropion and amantadine),[54] and ChE-Is.[55]

The depressive component of any dementia should be assessed and treated aggressively. If the degree to which affective symptoms are contributing to cognitive dysfunction is unclear, a therapeutic trial of an antidepressant should be employed. Choice of an agent is based principally on the side effects it produces; other considerations include drug–drug interactions and cost. The selective serotonin reuptake inhibitors (e.g., citalopram and sertraline), bupropion, and mirtazapine have favorable side effect profiles and should be considered, despite a paucity of literature on their use in depression associated with dementia. Care should be taken to avoid those drugs with greater anticholinergic side effects (e.g., paroxetine). Nortriptyline has been used effectively in depression following strokes and is generally well tolerated.[56] Tertiary amine tricyclic antidepressants (TCAs) that are highly anticholinergic (e.g., amitriptyline,

TABLE 11–7 Apathy Versus Depression in Alzheimer's Disease

	APATHY	DEPRESSION
Mood	Blunted	Dysphoric
Attitude	Indifferent	Pessimistic, hopeless
Self-concept	Bland	Self-critical
Thoughts/ actions	Decreased initiative and persistence	Guilty, suicidal

imipramine) should be avoided. Finally, as long as they are administered in a safe manner, monoamine oxidase inhibitors (MAOIs) may be useful in the treatment of depression associated with AD.[57]

Hallucinations (particularly visual), delusions (e.g., paranoid, persecutory, somatic), and agitation (which can take the form of motor restlessness, verbal outbursts, or physical aggression) are common in patients with dementia and MCI.[58] Before any medication is instituted, reversible causes (e.g., infection, drug effects) should be investigated. If the symptoms are causing significant distress and placing the patient or caregiver at risk, and if nonpharmacological interventions have failed, the first-line treatment is an antipsychotic medication.

First-generation or typical antipsychotics (e.g., haloperidol, trifluoperazine, perphenazine, thiothixene) have been well studied and show modest improvement in target symptoms.[59,60] However, elderly patients may be particularly sensitive to the side effects of these agents (e.g., sedation, postural hypotension, EPS). Second-generation or atypical antipsychotics (e.g., risperidone) have also been well studied in patients with dementia.[61,62] Direct comparison of atypical antipsychotics in the CATIE-AD trial (which randomized patients to olanzapine, quetiapine, risperidone, or placebo) found no differences among treatments in the main outcome, time to all-cause discontinuation.[63] A meta-analysis of randomized controlled trials of atypical antipsychotics found that drop-outs and adverse events further limit effectiveness; approximately one third of patients dropped out of the studies (with no difference between drug and placebo), and cognitive scores worsened on medications.[64]

Further complicating the picture is the evidence showing an increased risk of cerebrovascular adverse events in patients with dementia taking atypical antipsychotics.[65] The risk of death in patients taking typical antipsychotics is comparable to or higher than the rates in patients taking atypical antipsychotics.[66-68] More recent data have found that the use of both typical and atypical antipsychotic drugs carries a similar, dose-related increased risk of sudden cardiac death.[69]

Thus the clinician facing the challenge of treating a dementia patient with psychosis or agitation must carefully weigh the risk of not treating neuropsychiatric symptoms against the risks of the treatment previously discussed. This requires consideration of the evidence supporting efficacy of a given agent, the morbidity and risk associated with the target symptoms, the patient's medical conditions, and the risks and benefits of the proposed antipsychotic being considered. It is essential that the clinician obtain informed consent from the patient's health care decision-maker before starting any antipsychotic medications. In general, dosing of atypical antipsychotics is lower in elderly patients than other populations (see Table 44–3). In addition to oral forms, some agents may be administered intramuscularly when required.[70,71] Usage should be reassessed periodically, particularly because target symptoms may subside with disease progression, and tardive movement disorders occur frequently in this population and typically do not resolve spontaneously.[50]

Treatment of psychosis and agitation associated with Parkinson's disease requires special mention. High-potency neuroleptics may aggravate tremor and bradykinesia. Clozapine has been found to be useful in controlling psychotic symptoms in patients with Parkinson's disease and DLB.[72,73]

Several additional medications can be used in addition to antipsychotics in patients with agitation. Benzodiazepines have also been used to treat the agitation associated with dementia; however, the risk of worsening cognition and inducing behavioral disinhibition should be weighed, particularly before prescribing a long-acting agent (e.g., diazepam, clonazepam) or prescribing them for protracted periods.[74] The short-acting lorazepam (in an oral dosage of 0.25 to 1 mg) is often quite helpful when administered before an uncomfortable or potentially frightening procedure, such as a lumbar puncture or MRI scan. The use of buspirone for treatment of agitation has been reported, but at least a few weeks are necessary to achieve a modest benefit with this agent.[75]

Among the antidepressants, trazodone has been the subject of most case reports demonstrating behavioral improvement in agitated, demented patients.[76] A small, randomized controlled trial of trazodone use in patients with FTD found a significant decrease in behavioral symptoms.[77] Similarly, a naturalistic follow-up study of patients with AD found that after 6 months, patients treated with trazodone exhibited no increase in behavioral or psychological symptom frequency or severity, nor was an increase noted in caregiver burden.[78] In our experience, it has been modestly effective for agitation but quite useful for nocturnal insomnia.[79] Starting at a dosage of 25 to 50 mg per day, trazodone can be increased to as much as 400 mg daily, as tolerated. Sedative effects are usually quite rapidly achieved. Although generally well tolerated, trazodone may induce postural hypotension and priapism.

β-blockers (e.g., propranolol, pindolol) have been beneficial in treatment of agitation associated with dementias of various causes.[80] The risk of side effects, however, may outweigh potential benefits; a gradual dosage escalation is necessary, particularly with geriatric patients.

Finally, lithium carbonate, carbamazepine, and valproic acid have reportedly been used to treat agitation associated with dementia.[81-83] Of the three, valproic acid may hold the most promise because doses found effective were low and side effects were minimal and well tolerated. In an open-label study of 10 elderly patients with AD or vascular dementia, Lott and colleagues[83] observed moderate or better improvement in eight, with doses ranging from 250 to 750 mg (yielding levels of 13 to 52 g/mL). However, a recent review of four placebo-controlled trials found conflicting and inconclusive results.[84] Hence, further research is needed to determine the optimal use of valproic acid for treatment of neuropsychiatric symptoms in this population.

There is also growing evidence that ChE-Is and memantine have modest benefit in the neuropsychiatric symptoms and behavioral disturbances in AD and possibly other related dementias with cholinergic deficits.[42,48,85] Mood symptoms and apathy have most commonly responded to ChE-Is, whereas memantine has been associated with a reduction in irritability and agitation.[55] Using ChE-Is or memantine for neuropsychiatric symptoms offers another alternative to antipsychotic medications in patients with dementia. Unfortunately, the effects of these drugs are modest and often provide only temporary improvement.

CONCLUSION

As the population ages, the number of people with dementing disorders is increasing dramatically; most have AD or vascular dementia. The role of the psychiatric consultant in the diagnosis and treatment of dementing disorders is important, particularly in the identification of treatable psychiatric and behavioral symptoms.

Family members are the hidden victims of progressive dementia. They typically appreciate the consultant's communication about the diagnosis and the expected course of the disorder. They can benefit from advice about how best to relate to the patient, how to restructure the home environment, and how to seek out legal and financial guidance if appropriate. Family members also should be made aware of the assistance available to them through such organizations as the Alzheimer's Association.

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12 Psychotic Patients

Oliver Freudenreich, M.D.
Donald C. Goff, M.D.

Psychosis, broadly defined, is a gross impairment of reality testing. Psychosis can result from a wide range of psychiatric and medical disturbances and may take several forms. The elderly woman lying quietly in bed listening to Satan whisper bears little resemblance to the wildly agitated young man who accuses the nursing staff of trying to poison him. Hallucinations and delusions are the two classic psychiatric symptoms whose presence would indicate that the patient has lost touch with reality (i.e., suffers from psychosis). Hallucinations, which are sensory perceptions in the absence of an external source, can occur in any sensory modality and may take the form of voices, visions, odors, or even complex tactile perceptions (such as electric shocks or the sensation that one is being fondled). Delusions are firmly held false beliefs. Delusional individuals cling to their beliefs with unfaltering conviction even in the face of overwhelming evidence to the contrary. Delusions range from beliefs that are plausible, albeit unlikely (such as being monitored by the Central Intelligence Agency), to bizarre convictions (e.g., that one's internal organs have been replaced with empty beer cans). Another category of psychotic symptoms comes under the rubric of a formal thought disorder, which refers to a disruption in the form, or organization, of thinking. Patients with a formal thought disorder may be incoherent; they may not be able to make sense of reality or to communicate their thoughts to others.

When called to see a patient with psychosis, the psychiatric consultant can be of immediate help by ensuring that patient and staff are safe; moreover, he or she can demystify this often-frightening condition. Psychosis can best be approached by proceeding with a well-ordered differential diagnosis, which transforms the patient's condition in the eyes of medical staff from insanity, with all its disturbing connotations, to a more comprehensible disorder of brain function.

DIAGNOSTIC EVALUATION

It cannot be stressed enough that the presence of psychotic symptoms does not always mean that a primary psychiatric disorder like schizophrenia is present. Therefore, the diagnostic assessment of a psychotic patient begins with a thorough consideration of toxic or medical conditions that can present with psychosis (Table 12–1).[1,2] A medical history, review of systems, family history, and physical examination are crucial elements of this process because most organic causes can be identified on this basis. A bedside examination of cognitive function should be performed. The Mini-Mental State Examination supplemented by the clock drawing test will usually suffice as an initial cognitive screen. Serious deficits in attention, orientation, and memory suggest delirium or dementia rather than a primary psychotic illness. Careful delineation of the temporal course of psychotic symptoms is of particular importance. One should consider whether the disorder is chronic, episodic, or of recent onset. The pattern of psychotic symptoms should be examined to determine whether a mood disorder, substance abuse, medication use, or medical or neurological illness is present. Substance abuse, such as intoxication with stimulants, is a frequent and reversible cause of psychosis. Many medications have the potential to cause psychosis; unfortunately, causality is often difficult to prove (Table 12–2). Such drug-induced psychoses should be considered if the psychosis is of new onset, if there is no personal history of psychosis, or if the psychosis starts in the hospital, particularly if a delirium is present. A urine toxicologic screening test might identify unsuspected drug use, but it would not rule out drug-induced psychosis if it were negative, nor would a positive toxicologic screening test necessarily establish a cause for the psychosis, because co-morbid substance use and abuse is common in psychotic disorders. Routine testing includes determination of a sedimentation rate, a complete blood cell count, serum electrolytes, urinalysis, and levels of calcium, glucose, creatinine, and blood urea nitrogen. In addition, liver function tests, thyroid function tests, and syphilis serology (specific, such as the fluorescent treponemal antibody absorption test), are appropriate. Human immunodeficiency virus (HIV) testing should be recommended.[3] Extended work-ups may include karyotyping for chromosomal abnormalities or urine testing for metabolic disorders.[4] The diagnostic yield from neuroimaging of the brain (magnetic resonance imaging or computed tomography) is low in the absence of localizing neurological findings.[5] Neuroimaging should be obtained, however, in cases with atypical or unresponsive psychotic symptoms when psychotic symptoms first appear and should be considered even in cases with typical psychotic features, because the long-term costs and morbidity of this disorder are potentially quite high in relation to the expense of diagnostic procedures. The electroencephalogram (EEG) can be useful when evaluating a confused patient where a delirium is suspected or when a history of serious head trauma or symptoms suggestive of a seizure disorder are present.[6–8] An EEG is rarely helpful if it is employed as a routine screening procedure. Similarly, a

TABLE 12–1 Selected Medical Conditions Associated with Psychosis

- Epilepsy
- Head trauma (history of)
- Dementias
  - Alzheimer's disease
  - Pick's disease
  - Lewy body disease
- Stroke
- Space-occupying lesions and structural brain abnormalities
  - Primary brain tumors
  - Secondary brain metastases
  - Brain abscesses and cysts
  - Tuberous sclerosis
  - Midline abnormalities (e.g., corpus callosum agenesis, cavum septi pellucidi)
  - Cerebrovascular malformations (e.g., involving the temporal lobe)
- Hydrocephalus
- Demyelinating diseases
  - Multiple sclerosis
  - Leukodystrophies (metachromatic leukodystrophy, X-linked adrenoleukodystrophy, Marchiafava–Bignami disease)
  - Schilder's disease
- Neuropsychiatric disorders
  - Huntington's disease
  - Wilson's disease
  - Parkinson's disease
  - Friedreich's ataxia
- Autoimmune disorders
  - Systemic lupus erythematosus
  - Rheumatic fever (history of)
  - Paraneoplastic syndrome
  - Myasthenia gravis
- Infections
  - Viral encephalitis (e.g., herpes simplex, measles including SSPE, cytomegalovirus, rubella, Epstein–Barr, varicella)
  - Neurosyphilis
  - Neuroborreliosis (Lyme disease)
  - HIV infection
  - CNS-invasive parasitic infections (e.g., cerebral malaria, toxoplasmosis, neurocysticercosis)
  - Tuberculosis
  - Sarcoidosis
  - Cryptococcus infection
  - Prion diseases (e.g., Creutzfeldt–Jakob disease)
- Endocrinopathies
  - Hypoglycemia
  - Addison's disease
  - Cushing's syndrome
  - Hyperthyroidism and hypothyroidism
  - Hyperparathyroidism and hypoparathyroidism
  - Hypopituitarism
- Narcolepsy
- Nutritional deficiencies
  - Magnesium deficiency
  - Vitamin A deficiency
  - Vitamin D deficiency
  - Zinc deficiency
  - Niacin deficiency (pellagra)
  - Vitamin B_{12} deficiency (pernicious anemia)
- Metabolic disorders
  - Amino acid metabolism (Hartnup disease, homocystinuria, phenylketonuria)
  - Porphyrias (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria)
  - GM-2 gangliosidosis
  - Fabry's disease
  - Niemann–Pick type C disease
  - Gaucher's disease, adult type
- Chromosomal abnormalities
  - Sex chromosomes (Klinefelter's syndrome, XXX syndrome)
  - Fragile X syndrome
  - VCFS

CNS, Central nervous system; *HIV*, human immunodeficiency virus; *SSPE*, subacute sclerosing panencephalitis; *VCFS*, velo-cardio-facial syndrome.

lumbar puncture is not necessary for a routine work-up, but it can be lifesaving if a treatable central nervous system (CNS) infection is suspected.

Several neuropsychiatric disorders in particular should be considered during the diagnostic work-up of a patient with psychosis.[9] Huntington's disease is suggested by family history of Huntington's disease, dementia, and choreiform movements; psychotic symptoms may occur before motor and cognitive symptoms become prominent.[10] Neuroimaging may be necessary to establish the diagnosis in some cases. Parkinson's disease also may present with psychosis, along with bradykinesia, tremor, rigidity, and a festinating gait. The diagnosis of Parkinson's disease can be complicated by exposure to neuroleptics—review of the time course of neurologic symptoms in relation to the use of antipsychotics should clarify this diagnostic possibility.[11] Wilson's disease may also present with psychotic symptoms, tremor, dysarthria, rigidity, and a gait disturbance.[12,13] Kayser–Fleischer rings, which are golden brown deposits that encircle the cornea, are pathognomonic for this disease. The diagnosis can be confirmed by measuring concentrations of ceruloplasmin in the urine and serum. Finally, acute intermittent porphyria is characterized by acute episodes of abdominal pain, weakness, and peripheral neuropathy; this condition may be associated with psychosis.[14,15] Because this is a hereditary (autosomal dominant) illness, a family history often points to this diagnosis. During acute attacks, levels of δ-aminolevulinic acid and porphobilinogen are elevated in the urine.

It is of course impossible to rule out all possible diseases that could potentially cause psychosis. Thankfully, a thoughtful approach that combines clinical history and a physical examination (including a neurologic examination) with selected laboratory tests will usually suffice to exclude treatable medical illnesses and provide a medical baseline for future reference.[16] Table 12–3 suggests one screening battery that accomplishes these important initial diagnostic goals.

After an organic cause has been ruled out, the psychiatric differential diagnosis of psychosis flows from the diagnostic criteria contained in the Psychotic Disorders section of the *Diagnostic and Statistical Manual of Mental Disorders*,

TABLE 12–2 Substances Associated with Psychosis

DRUGS OF ABUSE

Associated with Intoxication
Alcohol
Amphetamine
Anabolic steroids
Cannabis
Cocaine
Hallucinogens: LSD, MDMA
Inhalants: glues and solvents
Opioids (meperidine)
Phencyclidine (PCP), ketamine
Sedative-hypnotics (including withdrawal): barbiturates and benzodiazepines

Associated with Withdrawal
Alcohol
Sedative-hypnotics

Medications (Broad Classes with Selected Medications)
Anesthetics and analgesics (including NSAIDs)
Anticholinergic agents and antihistamines
Antiepileptics (with high doses)
Antihypertensive and cardiovascular medications (e.g., digoxin)
Antiinfectious medications (antibiotics [e.g., fluoroquinolones, TMP/SMX], antivirals [e.g., nevirapine], tuberculostatics [e.g., INH], antiparasitics [e.g., metronidazole, mefloquine])
Antiparkinsonian medications (e.g., amantadine, levodopa)
Chemotherapeutic agents (e.g., vincristine)
Corticosteroids (e.g., prednisone, ACTH)
Interferon
Muscle relaxants (e.g., cyclobenzaprine)
Over-the-counter medications (e.g., pseudoephedrine, caffeine in excessive doses)

Toxins
Carbon monoxide
Heavy metals: arsenic, manganese, mercury, thallium
Organophosphates

Key Diagnostic Questions to Determine Causality between a Substance and Psychosis
Does the patient have a history of psychosis?
Does the patient have a history of illicit drug use?
Did the psychosis start after a medication was started? After the patient came to the hospital?
Is there evidence of delirium?

ACTH, Adrenocorticotropic hormone; *INH*, isoniazid; *LSD*, d-lysergic acid diethylamide; *MDMA*, methylenedioxymethamphetamine; *NSAID*, nonsteroidal antiinflammatory drug; *TMP/SMX*, trimethoprim/sulfamethoxazole.

TABLE 12–3 Medical Work-up for First-Episode Psychosis

Physical exam with emphasis on neurologic exam
Vital signs
Weight and height (BMI), waist circumference
Electrocardiogram (ECG)

Laboratory Tests

Broad screening and medical baseline:
Complete blood count (CBC)
Electrolytes including calcium
Renal function tests (BUN/creatinine)
Liver function tests
Erythrocyte sedimentation rate (ESR)
Antinuclear antibody (ANA)
Fasting glucose
Fasting lipid profile
Consider prolactin level
Hepatitis C (if risk factors are present)
Pregnancy test (in women of childbearing age)
Urine drug screen

Exclude specific treatable disorders:
Thyroid stimulating hormone (TSH)
Fluorescent treponemal antibody absorbed (FTA-ABS)
HIV test
Ceruloplasmin
Vitamin B_{12}

Neuroimaging
MRI (preferred over CT)

Ancillary Tests
Expand etiological search if indicated, taking into account epidemiology: e.g., chest x-ray, electroencephalogram (EEG), lumbar puncture, karyotype, heavy metal testing, Lyme antibodies
Expand medical monitoring if indicated: e.g., eye exam (if risk factors for cataracts are present)

Modified from Freudenreich O, Schulz SC, Goff DC: Initial medical work-up of first-episode psychosis: a conceptual review, *Early Interv Psychiatry* 3:10–18, 2009.

Fourth Edition, Text Revision (DSM-IV-TR).[17] It should be emphasized, however, that these criteria are guidelines for diagnosis; they are to be used only in conjunction with a full understanding of the descriptions of disorders contained in the text (Table 12–4). A clear, longitudinal view of the illness is necessary to identify affective episodes and to determine whether the patient's level of function has declined. In addition, the range and severity of psychotic and negative symptoms must be determined and a judgment made as to whether delusional beliefs are bizarre or plausible.

Psychotic patients are often unable to provide an accurate history; therefore information must be collected from as many sources as possible. In one study, information necessary for diagnosis, such as the presence of persecutory delusions, was missed more than 30% of the time when the assessment was based on the interview only.[18] Concurrent substance abuse is also frequently missed in patients with schizophrenia if toxicologic screening is not performed.[19]

If major depression and mania are not present and have not played a prominent role in the past, the diagnosis is likely to be schizophrenia, delusional disorder, or schizotypal personality disorder (depending on the severity of the illness). To meet criteria for schizophrenia, the patient must have demonstrated a decline in function and displayed, for at least 4 weeks, symptoms of the active phase, which can consist of either bizarre delusions or typical auditory hallucinations (voices conversing or keeping up a running commentary). If neither of these psychotic symptoms is present, the active phase criteria can also be met by the presence of any two of the following: nonbizarre delusions, less typical hallucinations, disorganized speech,

TABLE 12–4 Psychiatric Disorders That May Present with Psychosis

Continuous Psychosis
Schizophrenia
Schizoaffective disorder, bipolar type (with prominent episodes of mania)
Schizoaffective disorder, depressed type (with prominent depressive episodes)
Delusional disorder (plausible, circumscribed delusions)
Shared psychotic disorder (in which delusions are induced by another person)
Episodic Psychosis
Depression with psychotic features
Bipolar disorder (manic or depressed)
Schizophreniform disorder (<6 mo duration)
Brief psychotic disorder (<1 mo duration)
Key Diagnostic Questions
Has a reversible, organic cause been ruled out?
Are cognitive deficits prominent? (delirium or dementia)
Is the psychotic illness continuous or episodic?
Have psychotic symptoms (active phase) been present for at least 4 weeks?
Has evidence of the illness been present for at least 6 months?
Is there evidence of a decline in level of functioning?
Are negative symptoms present?
Are mood episodes prominent?
Have there been episodes of major depression or mania?
Do psychotic features occur only during affective episodes?

disorganized behavior, or negative symptoms. Negative symptoms of schizophrenia fall into two main clusters: a cluster of reduced affective experience or expression (i.e., affective blunting and alogia) and an amotivation cluster (i.e., avolition, anhedonia, and asociality).[20] The diagnosis of schizophrenia is made only after evidence of the illness has been present for at least 6 months—if symptoms have been present for less than 6 months, the provisional diagnosis of schizophreniform disorder is used. Patients whose psychotic symptoms remit within 4 weeks of their onset are diagnosed as having a brief psychotic disorder if no organic cause is identified.

If the patient's condition does not meet the criteria for schizophrenia or schizophreniform disorder, but a nonbizarre (plausible) delusion is present, the diagnosis of delusional disorder is made, provided that the patient does not exhibit severe deterioration in function outside of the circumscribed delusional system. Typical delusions include the belief that one has a physical defect or medical condition or that one is being followed, poisoned, infected, loved by a famous person, or cheated on by a spouse. Patients who do not meet the active phase criteria for schizophrenia but who present with chronic, bizarre, or idiosyncratic thoughts or behaviors are classified as having schizotypal personality, which probably is a less severe form of schizophrenia.

If the patient meets criteria for major depression and has exhibited psychotic symptoms only during episodes of depression, the diagnosis is major depression with psychotic features. If psychotic features characteristic of schizophrenia have also occurred during periods when the patient was euthymic, the illness is classified as schizoaffective disorder, depressed type if depressions have been prominent throughout the course of the illness, or schizophrenia with superimposed depression if depressions have been infrequent. Patients who have experienced manic episodes and who have been psychotic only during affective episodes are diagnosed as having bipolar disorder. If psychosis has been present between manic and depressive states, the diagnosis is schizoaffective disorder, bipolar type, or schizophrenia with superimposed mood disorder; again, the diagnosis depends on how prominent a role affective episodes have played in the overall course of the illness. The proper psychiatric diagnosis of a patient who is psychotic on a cross-sectional examination requires an intimate knowledge of the patient's longitudinal course, something that is often unavailable during an inpatient admission.

CLINICAL PICTURES AND CORRESPONDING PROBLEMS ON THE MEDICAL WARD

It is often surprising to see that psychotic patients do perfectly well when admitted to a medical or surgical service; they tend to require little in the way of special treatment. One survey found that only half of patients with schizophrenia admitted to a general hospital required psychiatric consultation.[21] Interestingly, the most common reason for a psychiatric consultation in patients with schizophrenia admitted to the medical service of the Massachusetts General Hospital was "schizophrenia" (30%); there was no specific question. This may reflect a concern that is evoked by managing a patient with schizophrenia.[22] Other referrals revolve around depression (16%), capacity assessment (14%), and help with prescription of psychotropic medications (10%). For patients with psychotic disorders, the role of the consultation psychiatrist in the general hospital can be seen as threefold: conducting conventional consultations with an emphasis on making a correct diagnosis and instituting proper treatment, educating staff about the nature of schizophrenia, and serving as an advocate for the chronically mentally ill so that they can receive standard and comprehensive medical care.[23,24] In one chart review study, patients with schizophrenia who needed a medical or surgical admission had higher rates of complications in the form of infections and postoperative complications compared to patients who did not carry a schizophrenia diagnosis.[25] Effective consultation and advocacy could thus have real-life implications for some patients with schizophrenia.

The specific form of illness that a patient with schizophrenia manifests determines the nature of the staff's concerns as well as the staff's level of comfort. Studies have demonstrated that the symptoms of schizophrenia tend to cluster into at least three groups: reality distortion (e.g., delusions and hallucinations), disorganization (e.g., formal thought disorder and inappropriate affect), and negative symptoms (e.g., apathy, anhedonia, social withdrawal, alogia, and flat affect).[26,27] A fourth symptom domain, cognitive deficits, has been rediscovered.[28] Schizophrenia was once known as dementia praecox because of its prominent cognitive problems. The majority of patients with schizophrenia display symptoms from all four categories and are

classified as having an undifferentiated type. Some patients, however, exhibit prominent symptoms from only one category, and the difficulties they encounter in the general hospital are determined by which cluster of symptoms predominates.

In all cases, a question can arise as to whether the patient is competent to make treatment decisions. Some patients may already have a guardian who must be involved in treatment decisions; if not, assessment for competency and initiation of appropriate legal steps may be necessary to ensure proper medical treatment. It is crucial to assess to what degree, if at all, delusions affect the patient's decision-making. The consultant should make it clear that patients with psychosis may have the capacity to make certain decisions, such as weighing risks and benefits of proceeding with or refusing medical treatment, even when their judgment is impaired in other realms. The idiosyncratic speech manifest by some patients may give an exaggerated impression of cognitive impairment, whereas their capacity to understand aspects of their medical condition may be adequate.

The Paranoid or Delusional Patient

Patients with schizophrenia whose symptoms are restricted to complex delusional systems and hallucinations are classified as having the paranoid type, even when their delusions are not persecutory in nature. In the absence of overt disorganization and negative symptoms, individuals with paranoid schizophrenia may go unnoticed by hospital staff. These patients often conceal all psychiatric symptoms and fail to exhibit the bizarre appearance and speech that attract attention in others with schizophrenia. Patients with paranoid schizophrenia may antagonize nursing staff because of their anger, argumentativeness, or patronizing manner. Nursing staff often appreciate learning that these annoying characteristics are actually common features of the illness. Despite complex and bizarre delusional beliefs, these individuals may elude detection and complete a medical or surgical hospitalization without incident. Difficulties arise when circumstances in the hospital collide with an individual's delusions. The patient who believes that the Mafia is attempting to kill him may refuse all hospital food for fear of being poisoned. Others become convinced that their physicians are members of the conspiracy that is plotting against them or that the surgeons have implanted a microchip intended to control or monitor their thoughts. To assess safety and to anticipate potential problems with compliance, the psychiatric consultant must understand the full scope of the person's delusional system and the nature of any hallucinatory experiences.

Because paranoid patients usually are reluctant to reveal their delusional beliefs, the consultant must proceed carefully and deliberately. A direct, interrogatory approach often convinces the patient that conspirators sent the interviewer. Because delusional individuals are preoccupied and distressed by their delusional beliefs, it is usually sufficient to engage them in a neutral, nonthreatening discussion about their current interests and activities. Comments that seem out of place or inappropriate to the content may provide clues as to the subject of the delusional system, and these should be explored. Questions should never imply a judgment about psychopathology, but rather they should demonstrate the interviewer's interest and concern. Examples of such questions include, "Are you safe? Have you noticed any strange coincidences? Are you aware of anyone trying to play with your mind? How do you understand what is happening to you? What is it that you overhear from others about this?" The interviewer should neither agree with the delusion nor attempt to reality-test—impartial interest and concern are usually a welcome relief to a delusional patient. This technique is sometimes called *partial joining of perspectives*.[29] Ideally, the consultant can serve as an intermediary, listening to the concerns of both the patient and the hospital staff; as a consequence he or she can mediate misunderstandings.

In addition to persecutory delusions, somatic delusions may also pose unique problems for the patient with schizophrenia admitted to a medical service. In a retrospective chart survey, McGilchrist and Cutting found that more than half of patients with schizophrenia described somatic delusions.[30] These delusions were typically bizarre (such as the belief that a third arm is growing out of one's chest) and could usually be immediately recognized as delusional. Having heard a patient's somatic delusions, however, medical staff tend to discount other somatic complaints. The consultant may be needed to help sort out which physical complaints merit further investigation by hospital staff and which delusional concerns are best ignored.

The Disorganized Patient

The disorganized patient can be problematic on a medical service. Disordered speech may make communication about medical symptoms difficult and may interfere with discussions about treatment options. If disorganization is subtle, the patient may merely appear stubborn or oppositional, and make routine nursing tasks difficult. One major area of concern for disorganized patients is their lack of judgment and behavioral control. These patients may engage in inappropriate behaviors (such as masturbating or disrobing in public, stealing food, and smoking in restricted areas). Of even greater concern is the occasional violent or self-injurious behavior of an agitated, disorganized patient. These patients typically require aggressive pharmacotherapy and may require physical restraints or round-the-clock attendants. A review of past behavioral problems, which can be provided by outpatient caregivers or family, can help the consultant anticipate behavioral problems that are likely to arise during a medical or surgical hospitalization.

The Patient with Negative Symptoms or Neurocognitive Deficits

Individuals with schizophrenia who display prominent negative symptoms may encounter unique difficulties when admitted to medical or surgical services. Moreover, negative symptoms are often compounded by cognitive deficits, particularly in the realms of sustained attention, memory, and executive function. Patients may seem indifferent to their medical problems and unappreciative of their care. Nursing staff can easily be put off by the poor hygiene and soiled clothing. Sustaining empathy and enthusiasm for the care of a withdrawn, unmotivated patient can require unusual

efforts by nursing staff. This process may be facilitated by the psychiatric consultant, who can explain that poor hygiene, apathy, and deficits in interpersonal skills are symptoms of illness that require management and that should not be interpreted as willful or as a weakness of character. Often if the consultant can provide a description of the patient as a vibrant, healthy young adult before onset of the illness, nursing staff can find it easier to empathize. When ongoing treatment or rehabilitation is required after discharge, a comprehensive plan should be developed to provide supervision for avolitional patients, who otherwise would be unlikely to follow through with treatment. If little history about the patient's baseline level of function is available, it is important to rule out other causes of negative symptoms, such as a hypoactive delirium or a seizure disorder.[31]

The Manic Patient

Although psychotic features in patients with schizophrenia are typically bizarre and idiosyncratic, patients who are manic are much more likely to present with grandiose delusions that typically impair judgment and self-esteem. These patients may be difficult to manage because of their boundless energy and their grandiose misinterpretation of their situation. Staff may at first mistake mania for unusually high energy, talkativeness, and positive self-esteem; eventually they turn to the psychiatric consultant when the patient refuses to stop pacing or to stop talking to other patients late at night, or when he or she is belligerent or insists that he or she is free of any medical problems. Patients with irritable or dysphoric mania may present with persecutory delusions and can be superficially indistinguishable from a patient with paranoid schizophrenia. Management of the manic patient should begin with containment and isolation from distracting stimuli and behavioral temptations. Short-term behavioral control can be achieved with use of antipsychotics in combination with benzodiazepines, whereas the ultimate goal of sustained remission with the prevention of relapse requires a therapeutic blood level of lithium carbonate, valproic acid, or another mood stabilizer.[32]

The Psychotic Depressed Patient

The delusions of the psychotically depressed patient usually reflect ruminative concerns about guilt, worthlessness, or physical decrepitude. These patients may puzzle their medical or surgical caregivers with somatic delusions involving fanciful disease or dysfunction. Their overwhelming sense of hopelessness and sense of being responsible for their plight may also interfere with attempts to involve them in treatment decisions—they may seem more interested in euthanasia. Some psychotically depressed patients withdraw and may become mute. Persecutory delusions also occur in psychotic depression, but these beliefs tend to be less bizarre than those encountered in patients with schizophrenia. In fact, it may be quite difficult to discern whether strangers are actually attempting to break into the patient's house or whether family members are stealing the elderly aunt's savings. Treatment of psychotic depression typically requires either a course of electroconvulsive therapy or the use of an antipsychotic agent, plus an adequate dose of an antidepressant.[33]

The Elderly Psychotic Patient

Psychotic symptoms are relatively common among the medically ill or disabled elderly. One survey found that 21% of newly admitted nursing home patients were delusional, and approximately 4% of elderly individuals in the community suffer from persecutory delusions.[34] Isolation and sensory impairment probably contribute to the higher incidence of paranoia and agitation in the elderly. *Late paraphrenia* is an older term still used to describe such patients.[35] In addition, such individuals are at particular risk for a host of organic causes of psychosis, including dementia, medication toxicity, and depression. Late-onset schizophrenia, which occurs after the age of 45 and may first present in old age, usually occurs in women and appears as a paranoid psychosis.[36] Psychotic symptoms are quite common in patients with Alzheimer's disease; approximately one third of patients with Alzheimer's disease develop paranoid delusions, and 7% develop auditory hallucinations.[37] Management of psychosis in the elderly involves first and foremost a comprehensive screening for organic causes, plus supportive measures and the judicious use of antipsychotics. Supportive measures should be individualized but include reassurance, visits from family to alleviate isolation, strategies to maintain the sleep–wake cycle, and measures to compensate for sensory or cognitive deficits, such as providing clear and repeated instructions, to counteract misinterpretation of reality. If antipsychotics are used to treat the psychosis of Alzheimer's disease, clinicians face two problems. For one, antipsychotics must be used with great care, because they increase the risk of death in this population.[38,39] Moreover, antipsychotics might have limited efficacy for the neuropsychiatric complications of Alzheimer's disease (e.g., agitation and psychosis).[40,41]. Unfortunately, safer or more effective options may not always be available.

MANAGEMENT OF PSYCHOTIC PATIENTS

General Considerations

As has been emphasized, the first step in approaching the treatment of a psychotic patient is to clarify the diagnosis, along with any prior psychotropic medication use. Delirium, which is characterized by fluctuations in mental status and by confusion, must be recognized and the underlying cause addressed. The pharmacological management of delirium is described in Chapter 10. Specific information about individual antipsychotic agents and drug–drug interactions is provided in Chapter 34.

Target symptoms for antipsychotics fall into three categories: (1) psychotic symptoms (e.g., hallucinations, delusions, and disorganization), (2) agitation (e.g., distractibility, affective lability, tension, and increased motor activity), and (3) negative symptoms (e.g., apathy, flat affect, social isolation, and poverty of speech). The pharmacologic treatment of psychotic symptoms is similar in many ways to the treatment of infection with antibiotics—the clinician needs to choose the proper medication at a sufficient dose and then await therapeutic results while monitoring side effects. Contrary to common wisdom, a response to antipsychotics can often be seen after a few days or even after a single dose, particularly for agitation.[42]

Psychotic symptoms and agitation usually improve with antipsychotics, regardless of cause. Most causes of organic psychosis, such as stimulant intoxication (e.g., amphetamines and cocaine), respond readily to antipsychotics. The decision whether to use an antipsychotic in cases of organic psychosis should be informed by a weighing of the anticipated duration and severity of the psychosis and the potential side effects of the drug. When time-limited psychoses, such as those produced by psychoactive substances, are treated with an antipsychotic, care should be taken that this medication not be continued indefinitely after the patient is discharged from the hospital, particularly if a conventional neuroleptic is used; the risk of irreversible tardive dyskinesia (TD) must be considered.

Drug Selection

Selection of an antipsychotic agent is usually guided by efficacy considerations, side-effect profiles, and available formulations (i.e., tablet, rapidly-dissolving wafer, liquid, IM, IV, or depot preparations). First-generation antipsychotics, which act by blocking dopamine D_2 receptors, are of similar efficacy and differ primarily in their potency (i.e., the dose required for their clinical effect) and in their side effects.[43] Second-generation antipsychotics were developed based on the observation that clozapine, though an effective antipsychotic, did not cause extrapyramidal symptoms (EPS).[44] However, four large randomized treatment trials known by their acronyms, CATIE, CUtLASS, TEOSS, and EUFEST have been unable to clearly establish superior efficacy of second-generation antipsychotics as a class.[45–49] It has, however, become clear that not all second-generation antipsychotics are alike; each drug needs to be considered individually.[50] Clozapine remains the gold standard with regard to efficacy; of the other second-generation agents, evidence suggestive of enhanced efficacy is strongest for olanzapine.[51]

Although now controversial, use of the first-generation antipsychotics rapidly declined during the past decade as second-generation antipsychotics were introduced. High-potency, first-generation agents continue to have their strongest support in the short-term treatment of medically compromised agitated patients; they have been relatively free of serious medical side effects. An additional role for first-generation antipsychotics is in the treatment of patients for whom compliance is a problem. Currently, haloperidol and fluphenazine are available in depot (long-acting) IM formulations, in addition to long-acting risperidone. As many as 70% of patients with schizophrenia do not take their medications as prescribed, in part because of ongoing substance use, medication side effects, and a lack of insight, but also because of a poor response to treatment.[52,53] We could be seeing a reassessment of selected first-generation antipsychotics, like perphenazine and molindone, that served as comparators in recent trials and demonstrated good efficacy and tolerability, comparable to second-generation antipsychotics. Molindone is particularly attractive because it does not cause weight gain in most patients.[47] The issue of TD remains a concern, however.

If a patient has been taking an antipsychotic with good results, it is best not to make changes in the regimen unless medical problems or potential drug interactions necessitate a switch. Exacerbations in otherwise stable patients, particularly if related to stress and accompanied by depressive symptoms, usually improve without altering the medication or raising the dosage.[54]

First-Generation Antipsychotics

Low-potency first-generation antipsychotic agents like chlorpromazine (CPZ) are often prescribed in dosages of 300 to 600 CPZ mg-equivalents/day; they are associated with orthostatic hypotension, anticholinergic side effects, sedation, and weight gain, and they are less readily or safely administered in a parenteral fashion.[43] Thioridazine, which can produce substantial QT interval prolongation, has been discontinued by the manufacturer of the brand name product. High-potency agents, such as haloperidol, are more likely to produce EPS, such as acute dystonias, parkinsonism, and akathisia (see later discussion), except when administered intravenously. Haloperidol is available for parenteral (including IV) administration. In the setting of serious medical illness, particularly if other medications with anticholinergic or hypotensive side effects are being administered, haloperidol is typically the antipsychotic of choice. It is important to minimize the small risk of torsades de pointes from parenteral haloperidol by reducing risk factors for it (e.g., hypokalemia) and by tracking the QTc. Although considerable inter-individual variability exists, daily oral doses of haloperidol between 5 and 15 mg are adequate for the vast majority of patients; increasing the dose beyond the dose range may only aggravate side effects without improving antipsychotic efficacy. IM and IV administration tends to require roughly half the dose. In the elderly, 0.5 mg to 2 mg of haloperidol at bedtime may be sufficient. If a patient has not previously received an antipsychotic, it is best to start with a low dose (e.g., haloperidol 2 to 5 mg orally) before increasing it to a standard therapeutic dose.

Extrapyramidal Side Effects and Tardive Dyskinesia

Younger patients (i.e., those younger than 40 years of age) started on high-potency first-generation antipsychotics are especially vulnerable to developing an acute dystonic reaction during the first week of treatment.[55] Dystonia, the sudden constriction of muscles, is a frightening and uncomfortable experience; when manifest as a laryngeal spasm, it can be life-threatening. The occurrence of dystonia early in treatment jeopardizes future compliance with antipsychotics; therefore it is important to anticipate and treat this side effect aggressively. Prophylaxis with an anticholinergic agent, such as benztropine 1 to 2 mg twice daily, substantially reduces the likelihood of a dystonic reaction even in a high-risk patient.[56] Dystonia is less common with the use of second-generation agents than with first-generation high-potency agents; moreover, it probably does not occur with either quetiapine or clozapine.

Akathisia is an extremely unpleasant sensation of motor restlessness that is primarily experienced in the lower extremities in patients who receive an antipsychotic medication. For the psychotic patient hospitalized on a medical service, akathisia can make bedrest unbearable. Akathisia

substantially increases the risk that a patient will leave the hospital against medical advice, and it has been associated with self-injurious behaviors as well as with a worsening of psychosis. Untrained staff frequently mistake akathisia for psychotic agitation, which leads to unfortunate escalations of antipsychotic doses. For patients in acute distress, diazepam 10 mg can provide immediate relief. For the long-term management, dose reduction may improve akathisia; if relief is not obtained, propranolol (10 to 20 mg two to four times daily) is often helpful. Even more effective is a switch to a second-generation antipsychotic, which usually resolves the problem.

Antipsychotic-induced parkinsonism can easily be mistaken for depression or for the negative symptoms of schizophrenia.[57] The presence of tremor and rigidity distinguishes this side effect in more severe cases; subtle cases can easily be missed. Parkinsonian side effects commonly improve with a reduction of the neuroleptic dosage or with addition of an antiparkinsonian agent (e.g., benztropine 1 to 2 mg twice daily or amantadine 100 mg two or three times daily). Because anticholinergic agents impair attention and memory and can produce a vast array of troublesome side effects in the elderly, long-term use of these agents should be avoided.[58] Second-generation antipsychotics as a class produce substantially fewer parkinsonian side effects; both clozapine and quetiapine are essentially free of EPS, which makes them the drugs of choice for patients with idiopathic Parkinson's disease complicated by psychosis.[59]

Tardive dyskinesia rarely appears after less than 6 months of treatment with an antipsychotic; once present, TD may be irreversible.[60] TD usually takes the form of involuntary, choreiform movements of the mouth, tongue, or upper extremities, although a dystonic form has also been described.[61] Studies suggest that the risk for developing TD with first-generation agents is approximately 5% per year of exposure, with a lifetime risk possibly as high as 50% to 60%.[62] The incidence of TD is much higher in the elderly, although a substantial proportion of these cases may represent spontaneously occurring dyskinesias.[63] As part of informed consent, patients requiring prolonged antipsychotic treatment with first-generation agents should be educated about the risk of developing TD after their acute psychosis has been treated and before 6 months has elapsed. Preliminary evidence that indicated α-tocopherol (vitamin E), at dosages of 400 to 1200 IU daily, improved symptoms of TD was not supported by a much larger controlled trial, and the best treatment for TD is prevention.[64] Clozapine has not been linked to TD; switching a patient from a conventional agent to clozapine increases the likelihood of improvement in TD.[65] Lowering the dose of a conventional antipsychotic or switching to an atypical agent can occasionally produce a "withdrawal dyskinesia," which typically resolves within 6 weeks, or may unmask an underlying dyskinesia that was previously suppressed by the antipsychotic.[66]

Second-Generation Antipsychotics

Second-generation antipsychotics as a class produce fewer neurologic side effects (e.g., dystonia, akathisia, and parkinsonism) than first-generation agents; they are also associated with less TD (about 0.8% per year).[67] In this class, risperidone is most likely to induce EPS, particularly at dosages higher than 6 mg/day. It is important to appreciate that second-generation antipsychotics differ substantially with regard to other side effects. Risperidone and its active and marketed metabolite, 9-hydroxyrisperidone (paliperidone) are unique among the second-generation agents because of their propensity to produce hyperprolactinemia.[43] Aripiprazole by contrast can lower prolactin levels.[68] Clozapine and olanzapine have been associated with substantial weight gain that can be a major obstacle to adherence. Risperidone and quetiapine are associated with intermediate weight gain, and ziprasidone and aripiprazole appear to produce little or no weight gain.[69] Considerable research over the past decade has focused on the effects of second-generation antipsychotics on glucose metabolism and lipids. The observed insulin-resistance and dyslipidemia are only in part explained by weight gain, and some antipsychotics seem to directly affect metabolism.[70] Despite differences in the propensity to cause metabolic side effects, it is recommended that all patients who receive second-generation antipsychotics be carefully monitored, with particularly close monitoring of patients at higher risk (e.g., family history of diabetes; clozapine or olanzapine treatment).[71]

Olanzapine and aripiprazole have few or no cardiac effects, and they can safely be initiated at a full therapeutic dose. Clozapine, risperidone, quetiapine, and ziprasidone have alpha-adrenergic effects that necessitate dose titration to avoid orthostatic hypotension; paliperidone can be given without titration. Clozapine produces the most hypotension and tachycardia. Ziprasidone appears to prolong the QT interval more than other atypical agents, but less than thioridazine.[72] Serious cardiac events have been rare in patients treated with ziprasidone (not differing from placebo in registration trials), and reported cases of overdose have been benign. However, ziprasidone's effect on cardiac repolarization may be problematic in the presence of underlying heart disease or when it is added to other agents with similar effects. Potential cardiac toxicity remains a clinical concern with all antipsychotics, however. A large retrospective cohort study did not find a difference between first- and second-generation antipsychotics in associated risk for sudden death.[73] Instead, both classes produced a dose-related increase in risk for sudden death.

Clozapine, although clearly possessing unique antipsychotic efficacy, can produce many bothersome and even potentially lethal side effects, including agranulocytosis (in approximately 1% of patients), sialorrhea, weight gain, hypotension, tachycardia, seizures, impairment of esophageal and bowel motility, and urinary incontinence.[43] Clozapine has also been linked to cardiomyopathy, pericarditis, and pulmonary embolism. Despite the list of potentially serious medical complications, clozapine was found in one study to decrease mortality; this net positive effect on mortality rates probably reflects the magnitude of its protective effect against suicide in contrast to its relatively low frequency of serious adverse effects.[74] However, any potential protection from death due to suicide has to be weighed against the possibility of a premature death from cardiovascular disease for the individual patient.[75,76]

If a patient is to be started or restarted on clozapine, a colleague with experience in the use of this agent should be

consulted to clarify the system for monitoring white blood cell counts and to outline strategies for the initiation and optimization of the dosage of this unique agent. Clozapine treatment should not be interrupted when patients are admitted to a medical or surgical service because abrupt discontinuation has been associated with acute worsening of psychosis and with cholinergic rebound. If clozapine has been discontinued for more than 4 days, clozapine should be reintroduced at a low dose and titrated upward toward the patient's previous optimal dose.

Treating Agitation

Usual therapeutic doses of antipsychotics do not always treat agitation associated with psychosis successfully. Benzodiazepines can effectively enhance the tranquilizing effect of antipsychotics or be used alone for the treatment of agitation.[77–79] Lorazepam can be combined (in the same syringe) with haloperidol for acute behavioral control—usually 1 mg of lorazepam is given with 5 mg of haloperidol intramuscularly. Once agitation is controlled, the patient can be started on a usually therapeutic dose of an antipsychotic, with a benzodiazepine (e.g., lorazepam 1 to 2 mg) given as needed or as a standing order two to three times daily for as long as is needed. Typically, as the psychotic symptoms improve with use of an antipsychotic, use of a benzodiazepine often becomes unnecessary. Alternatively, several second-generation antipsychotics (i.e., aripiprazole, olanzapine, and ziprasidone) are available for IM use for the control of agitation.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare, potentially lethal complication of neuroleptic treatment characterized by hyperthermia, rigidity, confusion, diaphoresis, autonomic instability, elevated creatine phosphokinase (CPK), and leukocytosis. Although the first symptoms of NMS may involve mental status changes, the syndrome may evolve gradually and culminate in fever and an elevated CPK. NMS probably occurs in fewer than 1% of patients who receive conventional antipsychotics, although subsyndromal cases may be much more common.[80,81] Parallels have been drawn between NMS and malignant hyperthermia (which results from general anesthesia), largely on the basis of common clinical characteristics. Patients with a history of either NMS or malignant hyperthermia, however, do not appear to be at increased risk for developing the other syndrome, and analysis of muscle biopsy specimens has not consistently demonstrated a physiological link between the two conditions. Lethal catatonia is a spontaneously occurring syndrome that may be indistinguishable from NMS and that has been described in the absence of neuroleptic treatment.[82] In addition, antipsychotic agents may impair temperature regulation and so may produce low-grade fever in the absence of other symptoms of NMS.[83] The clinician's immediate response to NMS should be to discontinue antipsychotic medications and hospitalize the patient to allow for IV fluids and cooling. Whether bromocriptine or dantrolene facilitates recovery remains the subject of debate. It is important that reinstitution of antipsychotics be delayed until at least 2 weeks after the episode of NMS has resolved.[84] NMS has been associated with use of clozapine and other second-generation antipsychotics.[85] It has been suggested that a variant of NMS without rigidity may result from use of second-generation antipsychotics; although if such a syndrome occurs, it is probably quite rare, and typical presentations (i.e., with muscular rigidity) are to be expected.

Drug Interactions with Antipsychotic Agents

Antipsychotic drugs interact with other medications as a result of alterations of hepatic metabolism and combined use of drugs with additive side effects (such as anticholinergic effects or impairments of cardiac conduction). Most conventional antipsychotics are extensively metabolized by the 2D6 isoenzyme of the hepatic P450 enzyme system, whereas atypical agents generally have more variable hepatic metabolism, typically involving isoenzymes 3A4, 1A2, and 2D6.[86] Fortunately, the therapeutic index (safety/risk ratio) of antipsychotic drugs is quite large, and interactions with agents that inhibit hepatic metabolism are unlikely to be life-threatening, but may increase side effects. Among the atypical antipsychotics, clozapine produces the most serious adverse effects when blood levels are dramatically elevated; obtundation and cardiovascular effects have been associated with inhibition of clozapine metabolism by fluvoxamine or erythromycin. Fluvoxamine, a selective serotonin reuptake inhibitor (SSRI), has been shown to quadruple clozapine plasma concentrations.[87] Some patients experience a doubling of clozapine blood levels when they quit smoking, along with sedation and worsening of other side effects. Addition of 2D6 inhibitors (e.g., SSRIs) to conventional antipsychotics would be expected to increase EPS, but in one placebo-controlled trial this was not clinically significant despite substantial increases in blood levels of haloperidol and fluphenazine.[88] Drugs that induce hepatic metabolism, such as certain anticonvulsants (e.g., carbamazepine, phenobarbital, and phenytoin), may lower blood concentrations of antipsychotics substantially and cause loss of therapeutic efficacy.[89]

Considerable inter-individual variability exists for the metabolism of antipsychotic drugs, even without the complication of drug interactions. Therapeutic plasma concentrations have been best established for haloperidol because it is the antipsychotic least complicated by active metabolites. Plasma concentrations between 5 and 15 ng/ml have been associated with an optimal therapeutic response.[90] Clozapine has been found to be effective at serum concentrations of between 200 and 300 ng/ml, although some patients might benefit from levels above 350 ng/ml.[91] The risk of toxicity, particularly seizures, is generally believed to be significant at levels above 1000 ng/ml.

Great care must be taken if low-potency agents (such as chlorpromazine or clozapine) are combined with other highly anticholinergic drugs because the additive anticholinergic activity may produce confusion, urinary retention, and constipation. In addition, low-potency antipsychotics can depress cardiac function and can significantly impair cardiac conduction when added to class I antiarrhythmic agents (such as quinidine and procainamide). Ziprasidone also significantly affects cardiac conduction and should not be combined with low-potency phenothiazines or with antiarrhythmic agents.

WORKING WITH THE PATIENT AND THE FAMILY

Patients with schizophrenia may be unable to directly express their fears or concerns; instead, they may exhibit anxiety or insomnia and may become increasingly delusional in the face of stress. Efforts to anticipate and answer a patient's unspoken fears about his or her medical status can greatly alleviate other symptoms, although this process may need to be repeated daily. Patients with schizophrenia may also lack the capacity to "filter out" extraneous stimuli in their environment and so may become easily overwhelmed or overly stimulated in a busy, chaotic environment.[92] Placing a patient with schizophrenia in as quiet and orderly a room as possible can help the patient retain a sense of control and foster reality testing. The patient's need for privacy should be respected, and nursing staff should be advised that some patients with schizophrenia do not respond to overly nurturing or seemingly intrusive attention.

Families of patients with schizophrenia can be an invaluable source of information in any setting; they can help establish the diagnosis and identify potential behavioral problems. Family members might have a clear idea if poor adherence or illicit drug use contribute to psychiatric problems. Patients are poor judges of cognitive problems and functional limitation, whereas family members can often provide an accurate picture of these domains.[93] Working with families is always important; it is arguably most important when the patient experiences or is recovering from his or her first psychotic episode. Education about the illness, a discussion about the use of medication, and identification of the early signs of relapse after remission can start in the hospital and help with the transition to outpatient care. Families need to know about the risk for suicide in schizophrenia because they could be the first ones to recognize that a patient is becoming hopeless or disillusioned after discharge. It has been well demonstrated that educating families about the illness and helping them develop reasonable expectations for their loved one with schizophrenia significantly improves the course of the illness and is time well spent.[94]

MORE PROBLEMS IN THE CARE OF PSYCHOTIC PATIENTS

Assessment of Dangerousness

The public has long associated mental illness with violence. However, any such link is complex, and having a mental illness per se does not predict violence.[95] Instead, clinicians need to assess well-established predictors of violence, particularly substance use and past violence, preferably not only by self-report which is unreliable.[96] Obviously, unmitigated psychosis can potentially result in acts of violence. Although assaultive behavior is probably more likely in disorganized patients as a result of impaired control of aggression, violent acts such as homicide, which involve planning or complex behaviors, are much more likely in patients with persecutory or religious delusions (when they are convinced that they have no alternative but to act violently—either to defend themselves or family or to obey God's command). Negative symptoms reduce the risk for violence because afflicted patients are less likely to initiate activity. Command hallucinations appear to increase the risk of violence only when the individual interprets the voices within a delusional system in such a way that the voices cannot be disobeyed.[97] For example, a patient may believe that it is God's voice giving orders to attack someone believed to be possessed by Satan. Although the potential for violence from disorganized or delusional patients is a cause for concern, homicide is actually committed by fewer than 1% of patients with schizophrenia.

Suicide is the main cause of premature death in patients with schizophrenia; 5% of patients with schizophrenia commit suicide and as many as 50% make an attempt.[98] In addition to delusions and hallucinations, depression and substance abuse are important risk factors for suicide. The consultant must explore carefully these risk factors as well as any history of violent or self-injurious behaviors. In patients at high risk for violence or suicide, the antipsychotic clozapine should be considered. Studies have shown a specific protective effect of clozapine on violence and suicide that may not be shared by other antipsychotics.[99,100]

Even in patients with schizophrenia and a history of violence, unusual diagnoses of concurrent illness like encephalitis need to be ruled out.[101] Regardless of its cause, in cases in which risk of violence or self-harm is ongoing in the hospital, patients must be monitored continuously. If safe, a sitter is preferred over use of restraints, but some situations require restraints for the safety of the patient, other hospital patients, and staff. However, the indication for restraint must be clear, and restraint has to be part of an overall treatment plan. Inappropriate restraint is not only unjust, but any restraint carries risks, such as deep vein thrombosis and death from pulmonary embolism.[102]

Pain Threshold in Schizophrenia

A large literature suggests that patients with schizophrenia may have dramatically elevated pain thresholds, which can obscure serious medical problems.[103] In one study, 21% of schizophrenic patients did not describe pain associated with a perforated peptic ulcer, and 37% felt no pain during acute appendicitis.[104] It has been estimated that more than 95% of the general public would experience excruciating pain with either condition. The mechanism underlying this often-dramatic analgesic effect remains unclear, but it does not appear to be the result of medication. It is important for the psychiatric consultant to make medical colleagues aware of this characteristic of patients with schizophrenia so that the existence of serious pathological processes is not dismissed because of an absence of typical manifestations of pain.

Polydipsia (Water Intoxication)

Polydipsia is defined as chronic or intermittent ingestion of large volumes of water; it is reported in 6% to 17% of chronically ill psychiatric patients. Polydipsia is most frequently diagnosed in patients with schizophrenia, in whom it generally appears 5 to 15 years after the onset of illness.[105] Polydipsia may lead to several complications, including bladder dilatation, enuresis, incontinence, hydronephrosis,

renal failure, and congestive heart failure. Approximately 25% to 50% of patients with polydipsia develop hyponatremia within the first 10 years of this condition. Often referred to as *water intoxication*, symptoms of polydipsia with hyponatremia include nausea, vomiting, blurred vision, tremors, cramps, ataxia, confusion, lethargy, seizures, coma, and death. Polydipsia with hyponatremia should be considered a serious complication of psychotic illness that requires careful evaluation and management. Acute care includes supportive treatment, fluid restriction, normal saline, and, in severe cases, use of hypertonic saline. Rapid correction of an abnormal serum sodium level is unwise, however, because it can lead to congestive heart failure and central pontine myelinolysis. A medical admission is often necessary until the serum sodium normalizes. Long-term management includes frequent monitoring of serum sodium concentrations and restriction of fluid intake when possible. Switching from conventional neuroleptics to clozapine may significantly improve polydipsia and hyponatremia in some patients.[106]

Medical Co-Morbidities

As a group, patients with schizophrenia carry a high burden of medical illnesses, including, among others, obesity, diabetes, cardiovascular disease, HIV infection, and hepatitis,[107] Cardiovascular disease has surpassed death from suicide as the primary contributor to an average reduction in life expectancy of two decades or more, a gap that seems to be worsening.[108] Unfortunately, part of the excess mortality is iatrogenic, because antipsychotics, regardless of class, can potentially contribute to cardiac deaths directly (i.e., from sudden death) and more indirectly via the development of cardiac disease (due to weight gain, diabetes, and dyslipidemia).[73,109] Appropriate attention to the medical care of patients with psychotic illnesses has emerged as an important mandate for psychiatrists.[110–112] A medical hospital admission provides an excellent opportunity to review the adequacy of medical treatment with emphasis on the highly prevalent metabolic syndrome (about 40% in one large sample), cardiovascular risk factors, and antipsychotic-related problems.[113–115] Patients who do not have a primary care doctor can be identified and linked with community providers.

Cigarette Smoking

Twenty years ago, approximately 85% of patients with schizophrenia smoked cigarettes, usually quite heavily.[116] However, more recent surveys show that patients with schizophrenia can successfully quit. In one cohort study, the rate of everyday smokers had dropped to below 50%.[117] For those patients who still smoke, quitting should be one of the most important health goals, particularly in the light of the aforementioned importance of cardiovascular disease. A hospital admission might provide a window of opportunity to motivate the patient for a quit attempt, particularly if the admission was predicated by smoking. During admission, nicotine dermal patches can provide some protection against nicotine withdrawal. Smoking reduces the drug levels of most antipsychotic drugs, particularly drugs that are metabolized by the 1A2 P450 enzyme system (e.g., olanzapine and clozapine). During lengthier hospital stays, the possible effects (e.g., an increase in EPS) of forced abstinence on drug metabolism should be considered[118]; this effect is not mediated by nicotine, but by tar products, and hence not reversed by nicotine patches.

Medication Adherence and Insight into Illness

One hallmark of schizophrenia is an often striking lack of insight into their mental illness: its symptoms, consequences, and need for treatment.[119] A psychotic patient who has just been involuntarily committed to a psychiatric hospital after fighting with police might report that the reason for the admission was that he came for coffee. Thankfully, this is an extreme example, and many patients have at least some understanding of the role of psychiatric treatment and can participate meaningfully in decisions regarding use of antipsychotics. Clinicians need to determine the specific reason for poor antipsychotic adherence so specific remedies can be sought.[120] In some patients, supervision is all that is required, whereas in others, one of the assisted treatment options (such as assertive community treatment [ACT]) will be required. There is little doubt that for the great majority of patients, maintenance antipsychotics must play a pivotal role in preventing psychotic relapse. This is true for patients who have been ill for many years, and for patients who are recovering from their first psychotic episode. In one study of first-episode psychosis patients who discontinued maintenance antipsychotics, 78% and 96% of patients experienced another psychotic episode within 1 and 2 years, respectively.[121] The prevention of further psychotic episodes is paramount because psychotic episodes come at a high cost to the patient: professional lives are interrupted; there is stigma and embarrassment associated with a psychiatric hospitalization; and there is always the danger of violence, accidental injury, and death.[122] On the other hand, medical hospital staff can be reassured that antipsychotics can usually be held for a brief medical hospital stay or procedure *if necessary* because relapse is measured in weeks or months, not days for remitted patients. For most patients with schizophrenia who require a medical admission these long-term adherence issues are not usually relevant, and house staff will merely need to continue the psychiatric outpatient regimen. However, an admission is a good decision point to review the adequacy of oversight of all medications.

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13

Anxious Patients

Mark H. Pollack, M.D.
Michael W. Otto, Ph.D.
Curtis W. Wittmann, M.D.
Jerrold F. Rosenbaum, M.D.

Clinical challenges in the diagnosis and treatment of anxiety are abundant in the general hospital setting: discerning normal from pathologic anxiety, differentiating medical from psychiatric causes, and choosing effective therapeutic approaches. In addition to a knowledge of medical and psychiatric differential diagnosis, the clinician may rely on a variety of strategies and interventions that involve pharmacologic, cognitive–behavioral, interpersonal, and psychodynamic skills. The ubiquity of anxiety and the nonspecific nature of anxiety symptoms can confound the care of the patient. Pathologic anxiety symptoms and behavior may be attributed to other physical causes or, when viewed as "only anxiety," may be prematurely dismissed as insignificant.

Anxiety is indistinguishable from fear except as to cause. The former is the same distressing experience of dread and foreboding as the latter, except that it derives from an unknown internal stimulus or is inappropriate to the reality of the current situation. Anxiety is manifested in the physical, affective, cognitive, and behavioral domains. The possible physical symptoms of anxiety reflect autonomic arousal and include an array of bodily perturbations (Table 13–1). The anxious state ranges from edginess and unease to terror and panic. Cognitively, the experience is one of worry, apprehension, and thoughts concerned with emotional or bodily danger. Behaviorally, anxiety triggers a multitude of responses concerned with diminishing or avoiding the distress.

The importance of recognizing and attending to the suffering of the anxious patient is not always readily apparent, given the universality of the experience of anxiety. Anxiety is expected and normal as a transient response to stress and may be a necessary cue for adaptation and coping. Excessive or pathologic anxiety, however, is no more a normal state than is the production of excess thyroid hormone.

Pathologic anxiety is distinguished from a normal emotional response by four criteria: autonomy, intensity, duration, and behavior. *Autonomy* refers to suffering that, to some extent, has a life of its own, with a minimal basis in recognizable environmental stimuli. *Intensity* refers to the level of distress; the severity of symptoms is such that the patient's level of anguish moves the physician to offer relief. The patient's capacity to bear discomfort has been exceeded. The *duration* of suffering also can define anxiety as pathologic. Symptoms that are persistent rather than transient, possibly adaptive, responses indicate disorder and are a call to evaluation and treatment. Finally, *behavior* is a critical criterion; if anxiety impairs coping, if normal function is disrupted, or if behavior such as avoidance or withdrawal results, the anxiety is of a pathologic nature.

Stereotyped syndromes of pathologic anxiety are described in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, under anxiety disorders (Table 13–2).[1] In epidemiologic studies, anxiety disorders were found to be among the most common psychiatric disorders in the general population.[2] This observation predicts that a significant percentage of the general hospital population would also suffer from anxiety symptoms. Some patients suffer from an anxiety disorder before admission to the hospital for medical care, but medical and surgical settings are also associated with the onset of anxiety symptoms as a consequence of hospitalization, medical illness, or treatment (e.g., adjustment disorder with anxious mood and organic anxiety disorder).[3]

THE NATURE AND ORIGIN OF ANXIETY

Despite the protean physiologic manifestations of anxiety, the experience of anxiety can be divided into two broad categories: (1) an acute, severe, and brief wave of intense anxiety with impressive cognitive, physiologic, and behavioral components, and (2) a lower-grade persistent distress, quantitatively distinct and with some qualitative differences as well. Pharmacologic and epidemiologic observations suggest a clinically relevant distinction between these two states.

In light of phenomenological similarities, fear and anxiety most likely reflect a common underlying neurophysiology. The first category of anxiety resembles acute fear or alarm in response to life-threatening danger: a cognitive state of terror, helplessness, or sense of impending disaster or doom, with autonomic but primarily sympathetic activation, and an urgency to flee or seek safety. The second type of anxiety corresponds to a state of alertness with a heightened sense of vigilance to possible threats and less intense levels of inhibition, physical distress, and behavioral impairment.

The two fear states resemble the clinical syndromes of panic attacks and generalized or anticipatory anxiety. As innate responses for protecting the organism and enhancing survival, panic and vigilance are normal when faced with threatening stimuli. As anxiety or psychopathologic symptoms, other factors besides actual physical threat must

TABLE 13–1 Physical Signs and Symptoms of Anxiety

Anorexia	Muscle tension
"Butterflies" in stomach	Nausea
Chest pain or tightness	Pallor
Diaphoresis	Palpitations
Diarrhea	Paresthesias
Dizziness	Sexual dysfunction
Dry mouth	Shortness of breath
Dyspnea	Stomach pain
Faintness	Tachycardia
Flushing	Tremulousness
Headache	Urinary frequency
Hyperventilation	Vomiting
Light-headedness	

TABLE 13–2 Anxiety Disorders

Panic disorder: Recurrent panic attacks ranging in severity from severe (experienced as terror, "going to die," or "losing control") to mild (only limited-symptom attacks or a rare panic attack); if complicated by fear of places with restricted or embarrassing escape or where help is unavailable, by travel restriction (or need for a companion), or by endurance of such situations despite intense anxiety, the diagnosis is panic disorder with (mild, moderate, or severe) agoraphobia.

Phobic disorders:

Simple phobia: Intense fear of and attempt to avoid specific objects or situations (e.g., heights)

Social phobia: Intense anxiety or discomfort in situations of scrutiny by others, with typical fear of embarrassment or humiliation (e.g., stage fright)

Agoraphobia: Fear of wide open spaces, crowds (without history of panic disorder)

Generalized anxiety disorder: A 6-month history of anxious symptoms but no panic attacks, with cognitive (worry) and autonomic symptoms

Posttraumatic stress disorder: A syndrome with onset following a traumatic, usually life-threatening, event. The course may resemble panic disorder with the herald attack a real-life threat rather than spontaneous panic. Recurrent images of the original event frequently occur.

Obsessive–compulsive disorder: Recurrent intrusive unwanted thoughts and images as well as compulsive behaviors, such as rituals, characterize this disorder; panic attacks and generalized anxiety also occur

Adapted from American Psychiatric Association: *Diagnostic and statistical manual of mental disorders*, ed 4, Washington, DC, 1994, American Psychiatric Association.

Note: The most common form of anxious suffering in a hospital population is most likely a transient situational reaction or an adjustment disorder with anxiety.

be implicated as triggers or cause. Of several explanatory models proposed, the biological model places emphasis on the nervous system, the psychodynamic on meanings and memories, and the behavioral on learning.

Animal and neuronal receptor studies suggest that a number of central systems are involved in fear and pathologic anxiety.[4,5] The alarm or panic mechanism is likely to have a critical component involving central noradrenergic mechanisms, with particular importance placed on a small retropontine nucleus, the primary source of the brain's norepinephrine, the locus ceruleus (LC). When this key to sympathetic activation is stimulated in monkeys, for example, an acute fear response can be elicited with distress vocalizations, fear behaviors, and flight. Furthermore, destruction of the LC leads to abnormal complacency in the face of threat.[6] Biochemical perturbations that increase LC firing similarly elicit anxious responses in animals and humans that are blocked by agents that decrease LC firing, some of which are in clinical practice as anti-panic agents (e.g., antidepressants, alprazolam).[7]

Another critical system involves limbic system structures, including the amygdala and septohippocampal areas. An important role of the limbic system is to scan the environment for life-supporting and life-threatening cues, as well as to monitor internal or bodily sensations, and to integrate these with memory and cognitive inputs in assessing the degree of threat and need for action to maintain safety.[8]

Vigilance, or its psychopathologic equivalent, generalized anxiety, most probably involves limbic system activity: limbic alert. Benzodiazepine receptors in high concentration in relevant limbic system structures may play a role in modulating limbic alert, arousal, and behavioral inhibition[9] by increased binding of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).[10] As one might expect, there are neuronal connections between the LC and the limbic system. An increased firing rate of LC neurons may serve as a rheostat to generate levels of arousal from vigilance to alarm.

A number of neurotransmitters are implicated as modulators of both the limbic alert and the central alarm systems. For example, LC firing is regulated by the α_2-noradrenergic autoreceptors as well as by 5-hydroxytryptamine (5-HT), serotonin receptors, GABA-benzodiazepine receptors, and opioid and other receptors. The limbic system also has important GABA-benzodiazepine receptor and serotonergic modulations. Peptides, such as cholecystokinin,[11] have also been implicated as potential activators of the alarm system, and an accruing body of work points to abnormalities in corticotropin-releasing factor and hypothalamic pituitary axis function as critical in the genesis and maintenance of pathologic affective states.[12] As a critical function, the central security system is endowed with redundancy of regulation.

When inappropriately activated, vigilance and alarm (the stereotyped functions of the security system) are manifested as psychopathology: anxiety states. The more sustained, variably intense, but distressing arousal state of vigilance (i.e., preparation for threat) becomes generalized anxiety. The sudden, stereotyped, and intense (but false) alarm response is a panic attack.

Cognitive–behavioral formulations of anxiety disorders, although attending to possible differences in biological reactivity, focus primary attention on the information processing and behavioral reactions that characterize an individual's anxiety experience. Although anxiety patterns may stem from a variety of experiences, including (mis)information, observational learning, and direct conditioning events with real or perceived trauma, the enduring consequences of such learning can be found in current patterns of behavior. In cognitive–behavioral formulations, emphasis

is placed on the role of thoughts and beliefs (cognitions) in activating anxiety, as well as on the role of avoidance or other escape responses in maintaining both fear and faulty thinking patterns. Faulty cognitions are frequently marked by the overprediction of the likelihood or degree of catastrophe of negative events and may focus on external experiences (e.g., "my colleagues will laugh at me if I ask this question") or internal experiences (e.g., "I am going to lose control if this anxiety gets worse"). Intolerance and catastrophic misinterpretations of the anxiety experience itself play a role in a variety of anxiety conditions and can help propel mild anxiety into a full, intense panic attack. Attempts to neutralize anxious feelings, with avoidance or compulsive behavior, can serve to lock in anxiety reactions and help develop the chronic arousal and anticipatory anxiety that marks many anxiety disorders.

Recent evidence has offered a bridge between neurobiological and cognitive–behavioral understandings of anxiety. Increased attention has been paid to the consolidation of memories after traumatic experiences and potential therapeutic interventions (e.g., blocking of the noradrenergic or glucocorticoid systems to decrease the potential for developing posttraumatic stress disorder [PTSD] after trauma). Knowledge of the *N*-methyl-D-aspartate (NMDA) system's involvement in the extinction of learned behaviors has offered the possibility of pharmacologic enhancement of cognitive behavior therapy (CBT) techniques. D-Cycloserine, a partial NMDA agonist, has facilitated treatment of specific phobias, obsessive–compulsive disorder (OCD), panic disorder, and social anxiety disorders when combined with CBT.[13]

Developmental experiences receive particular emphasis in psychodynamic approaches to anxiety. Although Freud's early writing implied a more physiologic basis for anxiety attacks in terms of undischarged libido, later emphasis was on anxiety as a signal of threat to the ego, signals elicited because of events and situations with similarities (symbolic or actual) to early developmental experiences that were threatening to the vulnerable child (traumatic anxiety), such as separations, losses, certain constellations of relationships, and symbolic objects or events (e.g., snakes, successes). More recently, psychodynamic thinking has emphasized object relations and the use of internalized objects to maintain affective stability under stress.

Phobic disorders, associated with the experience of panic, anticipatory anxiety, or no anxiety symptoms at all (depending on the success of avoidance behavior), serve to illustrate the different models of understanding anxiety. The biological view recognizes the stereotyped nature of phobias. Most of the objects and situations in everyday life that truly threaten us are rarely selected as phobic stimuli; children, who proceed normally through a variety of developmental phobias (e.g., strangers, separation, darkness), rarely become phobic of objects and situations that parents attempt to associate with danger (e.g., electric outlets and roads), and most phobic stimuli have meaning in the context of biological preparedness and were presumably selected through evolution.[14] Most human phobias are of objects and situations that make sense in the context of enhancing survival before the dawn of civilization: places of restricted escape, groups of strangers, heights, and snakes, for example. Social phobias—for example, fear of scrutiny by others—resemble the intense discomfort elicited in primates introduced into a new colony or in any animal simply being stared at. A glare is a threat. When panic attacks and anticipatory anxiety heighten the general sense of danger and insecurity, a variety of phobias may be manifested as part of the patient's increased concern with security and safety.

The principal explanatory models in psychiatry of how a normal protective system might become the source of distress and dysfunction include the biological (with its emphasis on constitutional vulnerability), the cognitive–behavioral (with its emphasis on self-perpetuating patterns of cognitions and behaviors), and the psychodynamic (with its emphasis on meanings, memories, and internal representations derived from developmental experience). The pragmatic and pluralistic modern clinician should not regard these models as mutually exclusive. Potential biological vulnerabilities, for example, may never become manifest without specific developmental experiences, sustained adversity, or trauma. Accumulating evidence indicates that for anxiety disorders, as with affective and psychotic disorders, biological systems are responsive to, and perturbable by, environmental influences. Potentially dysregulated (i.e., anxiety-prone) neurobiologic systems may remain homeostatic until developmental experience, life events, or other stressors disturb them. An integrated model predicts risk for manifested anxiety disorders as a consequence of constitutional vulnerability shaped by developmental experience (whether harmful or protective) and, in later (adult) life, either activated or influenced by environmental factors and maintained by ongoing chains of maladaptive cognitions and avoidance responses.

ANXIETY IN THE MEDICAL SETTING

Although some distress from anxiety is expected as a routine consequence of hospitalization, anxiety may also be a significant clinical issue in the treatment of patients in a medical setting. The hospitalized patient encounters a world of both internal and external dangers: assaults on bodily integrity in the form of uncomfortable procedures and forced intimacy with strangers; the atmosphere of illness, pain, and death; and separation from loved ones and familiar surroundings. The patient typically experiences uncertainty about his or her illness and its implications for the patient's capacity to work and maintain social and family relationships. Just as depression has been described as a "psychobiologic final common pathway" of a number of interacting determinants,[15] it is likely that anxiety too represents a multiply determined expression of the variety of psychological, biological, and social factors having impact on the patient.

The anxious patient can be a diagnostic challenge. The presence of anxiety may represent the patient's reaction to the meaning and implications of medical illness or to the medical setting, a manifestation of the physical disorder itself, or the expression of an underlying psychiatric disorder. The distinction between anxiety as a symptom and anxiety as a syndrome may be difficult to make in the medical setting, where there may be an overlap between normal situational anxiety or fear, anxiety-like symptoms resulting from a variety of organic disease states and their treatments, and the characteristic presentation of anxiety disorders.

Methodological obstacles surface in attempts to identify the nature and prevalence of anxiety in medical patients.[16]

Studies of anxiety in the medical setting are often difficult to interpret because of a lack of clarity of case definition and assessment measures, heterogeneity of the study populations, absence of appropriate control groups, and the nonspecific and often transitory nature of the anxiety symptoms themselves.

Approximately 60% of patients with psychiatric conditions are treated by primary practitioners; the most common disorders are depression and anxiety.[17,18] In a study of patients who presented to a group of primary care physicians, anxiety was the fifth most common diagnosis overall; others suggest this may be an underestimate.[19,20] Anxiety is the chief complaint of 11% of patients presenting in primary care settings.[21] This prevalence is mirrored by the high rate of prescribing benzodiazepines by primary care physicians.[22] Panic disorder has a reported prevalence of 1% to 2% in the general population,[23] as compared with 6% to 10% of patients in a primary care setting[24] and 10% to 14% of patients in a cardiology practice.[25] Patients with anxiety disorders, furthermore, are but a subgroup of those for whom anxiety is a complicating factor in their diagnosis and treatment in the hospital.

In view of the likely frequency of normal anxiety in this setting, there must be special circumstances surrounding those patients identified by primary caregivers as deserving psychiatric attention. Although some overly anxious patients go unrecognized, those who generate concern have impressed their caregivers in some way by the autonomy, intensity, duration, or behavior associated with their distress. Several typical scenarios of anxiety in the general hospital can be recognized.

Anxiety from the Failure to Cope

For most patients, potentially overwhelming stressors of hospitalization are mitigated by a variety of coping mechanisms. The sources of threat and the flood of perceptions signaling potential danger are managed by common strategies: rationalization and self-reassurance ("I've come this far," "the doctors know what they're doing," "safest place in the world"), denial and minimization ("the chest pain is just heartburn," "these machines will protect me"), religious faith, support from family and friends, and other strategies determined by the patient's personality style.

Even for those without a pre-illness anxiety disorder, coping strategies may fail and yield to a sense of fear and vulnerability. A host of factors may be implicated in this failure: personality features with brittleness or a tendency to regress in the face of threat (or paradoxically in a setting that evokes passivity and offers access to nurturance), the suddenness of the onset of threat (acute, life-threatening medical or surgical disease), unavailability of familial or other social support, feelings of aloneness or abandonment, or the unconscious meaning of the particular illness or injury. The patient becomes frightened, trembles, cannot sleep, repeatedly seeks attention and reassurance, registers excessive pain complaints and other physical symptoms, and becomes disruptive and unable to manage the fear. For many, especially the young or those with organic brain syndromes (e.g., mental retardation or dementia), catastrophic emotional responses are more readily triggered.

CASE 1

A psychiatric consultation request was received for a 17-year-old high school junior following above-the-knee amputation for osteogenic sarcoma without evidence of metastasis at the time of surgery. He had returned to school with a prosthesis and had done well. Some months later, a pulmonary metastasis was discovered, and he was rehospitalized for surgery and chemotherapy. Although anticipating a favorable outcome at this point, his behavior was unlike that of his prior hospitalization. He raged at caregivers, acted panicky, and withdrew from contact. Consultation was sought for treatment of his anxiety.

He was a tall, handsome, athletic young man admired by his peers, a leader who managed his life with braggadocio and pseudo-independence. For the first time in his illness, he was overwhelmed and frightened. Two critical issues emerged from the interview. In the past, he had had a great deal of support from his peers, but lately he had refused their visits. He was embarrassed by hair loss from chemotherapy. Second, during this hospitalization, his father, feeling overwhelmed by this turn of events, had decreased the frequency of visits to his son, claiming increased work demands.

Two interventions calmed the acute anxiety. First, an effort was made to find a well-suited wig; second, a psychotherapeutic contact with the father helped him to manage his grief adequately to increase the frequency of visits and thereby relieve his son's separation anxiety.

Although the oncologist's request was for an anxiolytic prescription, recognition of the failure of coping ability yielded the appropriate therapy for the acute anxiety.

This case serves to underscore two points: (1) Previously well-adapted individuals can become anxious in the face of serious or life-threatening illness, and (2) despite the appropriateness of anxiety in the face of serious illness, other factors, potentially remediable, may be involved in triggering anxious symptoms or behavior. In this case, troublesome behavior was evident; for others, only more subtle physical symptoms may have occurred.

Anxiety That Results from Traumatic Procedures

In recent years, increasing attention has been paid to the role of serious medical illness and invasive procedures in producing marked anxiety reactions that approach or meet criteria for PTSD. For example, symptoms of PTSD have been documented in patients after myocardial infarction (MI), coronary artery bypass graft surgery,[26] and treatment for breast cancer,[27] and in those who require intensive care (a setting associated with increased morbidity and mortality).[28] Estimates of rates of PTSD in these samples of patients range from 5% to 10%,[27] with rates of PTSD in patients hospitalized after traumatic physical injuries as high as 30% to 40%.[29] The emergence of PTSD is considered most likely when a traumatic event is perceived as both uncontrollable and life-threatening[30]; as such, any attempts to help patients regain or maintain a sense of control over their experiences may prevent or reduce emergent distress.

CASE 2

A 52-year-old woman with a prior history of depression, anxiety, chronic back pain, and severe peripheral vascular disease was admitted to the hospital as preparation for a femoral artery–popliteal artery bypass. Consultation was requested for management of anxiety because surgery had previously been attempted but was aborted when the patient became acutely anxious after propofol had been administered and the staff was beginning to disrobe her.

During the course of the consultation, the patient revealed that she had been the victim of a sexual assault at age 24. In the past, she had not needed treatment for symptoms related to this event. However, during the initiation of the prior surgery, she began to suffer from reexperiencing phenomenon while she was being disrobed.

Education was provided to the patient regarding the sequence of events that would take place leading up to and during the operation. The surgical staff was educated about the effects of past trauma and the need for special consideration regarding this patient. An agreement was made to allow the patient to disrobe herself prior to the initiation of the surgery. This increased her sense of control and she was able to tolerate the surgery, which went very well.

This case demonstrates the importance not only of the events that take place during a hospitalization, but also a patient's previous experiences with trauma. By talking with the patient and identifying the historical factors as well as the present conditions that made this experience difficult for her, a plan was devised to alleviate as much of her anxiety as possible. Under these conditions, she was able to take a more active role and complete the necessary medical procedure.

Attention is also being paid to the PTSD that may follow surgery performed under inadequate anesthesia.[31] Memory for events during anesthesia has been documented in controlled trials,[32,33] leading to recommendations that the surgical staff provide reassurance to patients during surgery and monitor their own verbalizations in the presence of anesthetized patients. In a series of 30 patients who underwent coronary artery bypass graft surgery, postoperative anxiety was a significant predictor of those who reported recall, with the proportion of patients recalling intraoperative events ranging between 10% and 23%,[32] although other reports suggested that rates of recall may be far less.[34] Sources of this variability may be that some patients do not readily discuss their memories and that memories may emerge some time after discharge.[35] Routine postoperative inquiry about possible awareness has been recommended to ensure that patients have an opportunity to discuss their memories, if present, and to allow assessment of the need for treatment if traumatic reactions are evident.[36]

Reactions to awareness during surgery include generalized anxiety and irritability, repetitive nightmares, and preoccupation with death, as well as reluctance to discuss the memory or associated symptoms.[35] More severe reactions have also been documented, including the full emergence of PTSD after experiences of awareness during surgery. Patients who are aware during surgery may face the terrifying experience of pain occurring in conjunction with anesthesia-induced paralysis (ensuring that no overt coping or escape responses are available) and the fear of death. As memories of the trauma emerge, patients may face the full spectrum of PTSD symptoms, including reexperiencing symptoms (intrusive memories, nightmares, and overresponsivity to cues of the surgery), avoidance of reminders of the experience (e.g., avoidance of strong emotions, prone bodily positions or sleep, medical television shows, colors similar to those of surgical scrub suits), and symptoms of pervasive autonomic arousal (e.g., exaggerated startle, sleep difficulties, hypervigilance, and irritability). Timely identification of this syndrome can aid in rapid referral for full psychiatric evaluation and treatment, which may include both cognitive–behavioral and pharmacologic interventions.

Anxiety That Interferes with Evaluation or Treatment

A request for consultation may be a consequence of anxiety that interferes with a patient's evaluation or treatment: refusal of work-up or treatment because of fear of pain or discomfort, catastrophic interpretation of physical symptoms or of the planned work-up ("they're looking for cancer") with an excessively fearful response, or the need to minimize or deny a potentially serious condition and its implications, limiting cooperation with evaluation.

CASE 3

Examination of a 38-year-old woman revealed a large breast lump. Although initially reluctant, she eventually agreed to a mammogram. In the waiting room, she became increasingly anxious and, when her name was called, refused to come in for the test. A psychiatric consultation was called to provide management of the patient's anxiety to permit the mammogram.

An attractive woman, she had stopped working as a teacher 12 years earlier after marrying a successful business executive and having the first of her two children. On interview she spoke of a favorite aunt who had died of breast cancer after disfiguring surgeries, and of her own fear of a similar lesion. She was plagued by the thought that the loss of a breast would cause her husband to lose interest and abandon her. She had not informed her husband of her current medical situation.

Meeting subsequently with both husband and wife, the psychiatrist gave explicit information about the possibility of malignancy and treatment options. The husband's manifest interest, support, and affection were reassuring; after the mammogram, a benign lump was removed.

Discovery of the meaning to the patient of the illness and the procedure permitted an intervention that sufficiently reduced her anxiety to allow evaluation and treatment. As with any situational anxiety, the fear of serious or fatal illness can be managed with education, support, cognitive and behavioral strategies, and at times the short-term use of benzodiazepines.

Review of a patient's conceptualization of his or her medical condition, the procedures the patient faces, and the patient's interpretation of symptoms offers the physician the opportunity to correct quickly cognitive distortions

that may needlessly engender anxiety. Care should be taken in discussing symptoms and procedures, with sensitivity to an individual's coping style. The clinician should elicit the patient's conceptualization of his or her condition (or upcoming procedure) and provide corrective information when distortions are encountered.

Additional strategies may be helpful when phobias about select medical procedures are encountered. For example, the enclosed chamber of the magnetic resonance imaging (MRI) scanner presents a phobic challenge to some individuals, engendering fears of overwhelming anxiety because of the inability to "escape" the MRI scanner quickly. For individuals with a history of claustrophobia, panic disorder, or PTSD, pretreatment with medications (e.g., benzodiazepines) or CBT may be required. In less severe cases, anxiety may be managed with simple procedures designed to maximize the patient's sense of safety and control. For example, compliance and comfort during the MRI scan may be aided by explaining to the patient the periods when he or she can shift positions or rub his or her hands together, the patient's ability to communicate with the nurse or technician, the patient's understanding of sounds and sensations to be experienced during the procedure, and the patient's ability to terminate the procedure, if need be. Initial practice of being moved into and out of the scanning chamber before the actual experience, as well as discussion of normal sensations of heat and anxiety experienced by patients while being scanned, can help normalize the experience and prevent catastrophic interpretations. There is evidence from analogue studies that information about the somatic sensations to be experienced during a procedure can help reduce anxiety and panic reactions.[37] Instruction in comforting imagining may also aid the patient in tolerating the procedure.

Anxiety that occurs in patients with a known and potentially fatal illness is more accurately termed *fear* because there is a known danger. Such fear, however, can adversely affect the course of illness and treatment. A study of survivors of MI, for example, indicated that 95% had increased tension and anxiety, and of one group of post-MI patients discharged from the hospital, 40% did not return to work; in 80%, psychological impairment, including anxiety, was the cause.[38] Worry that activity will cause further heart damage or death interferes with rehabilitation and the return to autonomous function. Most effective therapeutic approaches for these patients center on education, group discussion, and support and stress management techniques.[39] Anxious patients with a diagnosed serious or fatal illness require treatment that includes education in addition to the possible use of supportive, cognitive–behavioral, or insight-oriented psychotherapy and anxiolytic or antidepressant medications.

Among patients with medical disorders, such as gastrointestinal (GI) disorders or allergies, the course and symptoms of the illness may be exacerbated by anxiety.[39,40] Anxiety, like other emotional responses, may adversely affect normal physiologic function; asthma symptoms are exacerbated by emotional arousal or stress, and the increased symptoms generate further anxiety.[41] Psychological and emotional responses and behavior possibly affect the survival of patients with cancer through effects on the immune system.[42]

Medical Illness That Mimics Anxiety Disorder

Anxiety symptoms may be the principal manifestation of an underlying medical illness.[43] Of patients referred for psychiatric treatment, 5% to 42% have been reported as having an underlying medical illness responsible for their distress, with depression and anxiety as frequent complaints.[44,45] Of reported cases of medical illnesses causing anxiety symptoms, 25% have been secondary to neurologic problems; 25% to endocrinologic causes; 12% to circulatory, rheumatoid, or collagen vascular disorders and chronic infection; and 14% to miscellaneous other illnesses.[43] A most common organic cause of anxiety may be alcohol and drug use; the anxiety results from either intoxication or, more typically, withdrawal states.[46]

The clinical presentation of anxiety in the medical setting takes many forms. The bewildering array and variable nature of the physical and psychic symptoms reported by anxious patients may lead the physician to overlook symptoms related to another disorder.[47] The relative contribution of situational, psychiatric, and physiologic factors to the presentation of anxiety-like symptoms in a medical patient is often murky. The number of medical illnesses, furthermore, that may generate or exacerbate anxiety symptoms (Table 13–3) clearly renders an exhaustive evaluation for each of them impractical. A thorough yet efficient evaluation of the differential diagnostic possibilities, however, includes the following considerations[43,48]:

1. In a patient with a known medical illness, the condition and its associated complications and treatment may be the cause of anxiety. For example, in the asthmatic patient, hypoxia, respiratory distress, and sympathomimetic bronchodilators may all contribute to the experience of anxiety. In some patients, risk factors or predisposition, such as a family history of medical illness capable of causing anxiety-like symptoms (e.g., thyroid disease), may be clues to diagnosis.
2. In medical illnesses considered mimics of anxiety, the quality of anxiety symptoms when closely examined may be different from that seen in primary anxiety disorders. For example, Starkman and associates[49] studied 17 patients with pheochromocytoma and compared their anxiety symptoms with those of a group of 52 patients with anxiety disorders. Most patients with pheochromocytoma did not meet the criteria for panic disorder or generalized anxiety disorder (GAD); none developed agoraphobic symptoms, and their overall severity of symptoms was lower. There was a significant lack of psychological as opposed to physical symptoms of anxiety in most of these patients.
3. Similarly, patients with primary anxiety disorders are more likely to have emotional trauma related to the onset of anxiety, daily symptoms, neurotic features, and gradual resolution of symptoms after an attack and are less likely to have a loss of speech or consciousness during an episode of anxiety than are patients with anxiety associated with temporal lobe epilepsy.[50] Thus, the lack of a significant emotional experience of anxiety or the occurrence of anxiety only coincidental with particular physical events (e.g., a run of ventricular tachycardia on a cardiac monitor or spike activity on an electroencephalogram) may suggest the presence of an organic anxiety syndrome. Evaluation directed toward the somatic

TABLE 13–3 Selected Medical Causes of Anxiety

Endocrine
Adrenal cortical hyperplasia (Cushing's disease)
Adrenal cortical insufficiency (Addison's disease)
Adrenal tumors
Carcinoid syndrome
Cushing's syndrome
Diabetes mellitus
Hyperparathyroidism
Hyperthyroidism
Hypoglycemia
Hypothyroidism
Insulinoma
Menopause
Ovarian dysfunction
Pancreatic carcinoma
Pheochromocytoma
Pituitary disorders
Premenstrual syndrome
Testicular deficiency

Drug-Related
Intoxication
Analgesics
Antibiotics
Anticholinergics
Anticonvulsants
Antidepressants
Antihistamines
Antihypertensives
Antiinflammatory agents
Antiparkinsonian agents
Aspirin
Caffeine
Chemotherapy agents
Cocaine
Digitalis
Hallucinogens
Neuroleptics
Steroids
Sympathomimetics
Thyroid supplements
Tobacco

Withdrawal
Ethanol
Narcotics
Sedative-hypnotics

Cardiovascular and Circulatory
Anemia
Cerebral anoxia
Cerebral insufficiency
Congestive heart failure
Coronary insufficiency
Dysrhythmias
Hyperdynamic β-adrenergic state
Hypovolemia
Mitral valve prolapse
Myocardial infarction
Type A behavior

Respiratory
Asthma
Hyperventilation
Hypoxia
Pneumonia
Pneumothorax
Pulmonary edema
Pulmonary embolus

Immunologic-Collagen Vascular
Anaphylaxis
Polyarteritis nodosa
Rheumatoid arthritis
Systemic lupus erythematosus
Temporal arteritis

Metabolic
Acidosis
Acute intermittent porphyria
Electrolyte abnormalities
Hyperthermia
Pernicious anemia
Wilson's disease

Neurologic
Brain tumors (especially in the third ventricle)
Cerebral syphilis
Cerebrovascular disorders
Combined systemic disease
Encephalopathies (toxic, metabolic, infectious)
Epilepsy (especially temporal lobe epilepsy)
Essential tremor
Huntington's disease
Intracranial mass lesion
Migraine headaches
Multiple sclerosis
Myasthenia gravis
Organic brain syndrome
Pain
Polyneuritis
Postconcussive syndrome
Postencephalitic disorders
Posterolateral sclerosis
Vertigo (including Ménière's disease and other vestibular dysfunction)

Gastrointestinal
Colitis
Esophageal dysmotility
Peptic ulcer

Infectious Disease
Acquired immunodeficiency syndrome
Atypical viral pneumonia
Brucellosis
Malaria
Mononucleosis
Tuberculosis
Viral hepatitis

Miscellaneous
Nephritis
Nutritional disorders
Other malignancies (e.g., oat cell carcinoma)

system (e.g., GI or cardiac) most prominently affected by anxiety symptoms may provide the greatest yield from further diagnostic investigations.

4. In patients with an onset of anxiety symptoms after the age of 35 years, a lack of personal or family history of anxiety disorders, a negative childhood history of anxiety symptoms, an absence of significant life events heralding or exacerbating anxiety symptoms, a lack of avoidance behavior, and a poor response to standard antianxiety agents, the presence of an organically based anxiety syndrome should be considered.[40]
5. Even for the apparently healthy patient, particular scrutiny should be directed at more common conditions associated with anxiety: arrhythmias, thyroid abnormalities, excessive caffeine intake, and other drug use. Anxiety-like symptoms may be the first clue to a withdrawal syndrome in a patient with unreported regular sedative–hypnotic (e.g., ethchlorvynol, glutethimide, or a benzodiazepine) or alcohol use before admission to the hospital. Intoxication or withdrawal from prescription or over-the-counter medication or substances of abuse should also be suspected. Up to 3% of individuals have been reported to develop psychiatric symptoms after using prescribed or over-the-counter medication.[51]

CASE 4

A psychiatric consultation was requested from the medical service for a 31-year-old female clerk who developed anxiety attacks shortly after learning that she had contracted syphilis from her boyfriend. She had previously experienced spontaneous anxiety attacks in her mid 20s that had remitted early in a 6-month course of imipramine hydrochloride, and she had been symptom free since. During the interview with the psychiatrist, she manifested anger and sadness about her boyfriend's infidelity and her own victimization, as well as anxiety about the future of their relationship. Her anxiety attacks, however, were different from those she had previously experienced. They consisted of blurred vision; dull biparietal headaches, primarily left-sided; numbness in her extremities; and feelings of dizziness. She reported feeling anxious after the onset of these symptoms. On further questioning, the patient described a history of menstrual irregularities over the past 2 to 3 years, and galactorrhea. Her prolactin level was found to be elevated, and a computed tomography scan revealed a pituitary adenoma. Surgical resection of the adenoma resulted in resolution of her anxiety attacks, although she elected to pursue psychotherapy to consider issues raised by the difficulties in her relationship.

This case serves to illustrate the following points. The presence of a history of an anxiety disorder or a recent stressor does not eliminate the need to consider medical illness in the differential diagnosis of a new or different presentation of anxiety. The patient's experience of anxiety attacks was primarily somatic, and it was fortuitous that she had a history of more typical anxiety attacks for comparison; the nature of her symptoms led to a careful exploration for neurologic disease and allowed an appropriate and timely intervention.

Anxiety That Mimics Medical Illness

The autonomic arousal associated with anxiety states allows anxiety to present as a great imitator of medical illness. Patients with anxiety disorders repeatedly visit their primary care physicians or make the rounds of a variety of medical practitioners to seek a medical diagnosis to explain their symptoms. Along the way, they may be considered hypochondriacs, crocks, or just nervous, and they may receive benzodiazepines or reassurance but fail to be offered adequate or definitive treatment. Patients with untreated panic disorder, for example, have increased rates of alcoholism and sedative–hypnotic abuse, presumably in an attempt to self-medicate.[20,52] Sheehan and associates[53] noted that 70% of patients with panic disorder in their series had been to at least 10 medical practitioners without receiving a diagnosis or adequate treatment. They had high somatization scores on the Symptom Checklist-90, which decreased with the treatment of the panic disorder. The majority of these patients met the criteria for somatization disorder and tended to focus on the somatic symptoms of the untreated panic disorder. The nature of a patient's complaints may contribute to missed diagnosis and misdiagnosis. Greater than 90% of patients with panic present primarily with somatic complaints.[54] Although 95% of patients with mood or anxiety disorders are correctly diagnosed if the affective symptoms are their presenting complaint, only 48% are accurately assessed if they present with somatic complaints.[55] Individuals with somatization disorder are nearly 100 times more likely than those in the general population to suffer from a co-morbid panic disorder.[56] Of 55 patients with panic disorder referred by primary care physicians in one study, 49 (89%) initially presented with one or two somatic complaints and were misdiagnosed for from months to years.[20] The three most common somatic loci of symptoms were cardiac, GI, and neurologic, with 45 (81%) of the 55 patients presenting with a pain complaint. These patients may focus on specific physical symptoms, such as chest pain or diarrhea, thereby obscuring other anxiety symptoms, or they may deny affective or cognitive responses to avoid the stigmatization of psychiatric illness. As noted, anxiety may also exacerbate preexisting physical conditions, such as asthma, which then become the focus of the attention of both the patient and the physician.

The cost of unrecognized and untreated anxiety disorders in patients is high in terms of continued suffering, inefficient use of medical personnel, and costly repetitive diagnostic procedures. In one study of "high utilizers" of medical services, 58% had a mood or anxiety disorder, including 22% with panic disorder.[57] Clancy and Noyes[58] have documented the high rate of medical specialty consultations and procedures (most commonly cardiologic, neurologic, and GI) requested by patients with panic disorder. In one series of patients with chest pain who were undergoing coronary arteriography, Bass and co-workers[59] noted that 61% of the patients with insignificant coronary disease had psychiatric morbidity on a standardized interview, as opposed to only 23% of those with significant coronary disease. In those with normal coronary arteries, the most common psychiatric diagnosis was anxiety neurosis. Recognition and treatment of the anxiety disorder, in some cases, may have eliminated the necessity for arteriograms.

In another study, 30% of patients admitted to a cardiac care unit were determined to have no coronary disease but were subsequently diagnosed with panic disorder.[60] Wulsin and colleagues[61] noted that 43% of patients who presented to the emergency department (ED) with chest pain had panic attacks, and 16% had panic disorder; patients with panic disorder who presented to the ED with chest pain made more subsequent medical and ED visits than those without panic disorder.[62] Richter and associates[63] estimated that the average patient with noncardiac chest pain spends $3500 per year on ED, physician, and hospital visits and medications. In one series,[21] panic disorder exacerbated the symptoms of patients with preexisting medical disease and led to multiple hospitalizations—a trend that was reversed with treatment of the panic disorder. Dirks and associates[64] reported that patients with chronic asthma and high levels of anxiety had more hospitalizations than asthmatic patients with physiologic illness of comparable severity but normal degrees of anxiety.

Anxiety may play an especially important role in the intensification of hypochondriacal concerns. Once a fear of disease is activated, that fear provides a context for organizing subsequent experiences, including the experience of anxiety symptoms. The fear of disease helps direct attention to somatic symptoms, including anxiety-related symptoms, and can help engender a self-perpetuating cycle of vigilance, worry, and disease concern.[65,66]

Although consideration of the medical differential diagnosis for anxiety is crucial, recognition and treatment of anxiety disorders is essential in preventing inefficient use of medical resources and patient exposure to costly and occasionally dangerous diagnostic and therapeutic procedures. Failure to make the pertinent psychiatric diagnosis may result in a patient continuing to "doctor shop" in the search to discover "what's really wrong with me," with repeated diagnostic procedures resonating with the patient's hypochondriacal concerns. Untreated anxiety can exacerbate symptoms of existing medical pathologic conditions and drive a cycle of escalating help-seeking behavior and hospitalization.

CASE 5

An ED psychiatric consultation was requested for a 35-year-old man seen acutely by cardiology staff six times in the past month for chest pain and tachycardia. He had been admitted to the cardiac care unit twice, where MIs were ruled out. An extensive negative work-up at another hospital had included a cardiac angiogram. After being told "there's nothing wrong with your heart, you're just nervous" and being given a prescription for diazepam, he sought emergency treatment at our institution in the hope that "they'll find out what's wrong." He had refused previous consultations with psychiatry in the fear that he would be dismissed as "a head case," but he finally agreed to evaluation at the insistence of the medical team.

He was an athletic-looking salesman in his 30s, a self-described "take-charge kind of guy" without any previous psychiatric or medical history. He had a family history of hypertension and was concerned about potential "inherited heart problems." His electrocardiogram recorded a sinus tachycardia of 120 beats per minute and ST-T wave changes deemed secondary to the elevated rate. The episodic periods of anxiety, chest pain, tachycardia, diaphoresis, and hyperventilation had begun approximately a year earlier without clear precipitants during highway driving and had caused him to pull off the road and to seek emergency medical treatment. He reported anticipating long trips with trepidation lest the episodes of chest pain be repeated.

His diagnosis was panic disorder with mild agoraphobia, and treatment was initiated with alprazolam. He felt reassured that he was not crazy and had a definable condition for which treatment was available. The panic attacks remitted shortly thereafter, as did the patient's use of emergency medical services.

Treatment with a number of agents can dramatically relieve the spells and secondary complications of panic disorders, thus underscoring the importance of early diagnosis. Further, because of the physical nature of the symptoms, general medical and ED evaluators need to be alert to the clinical phenomena of a panic attack. Patients who describe their symptoms as anxiety or who evolve a major depression may be more likely to be identified as having a psychiatric disorder. Given the dramatic physical complaints in a variety of bodily systems, however, as with depression, in which somatic symptoms may dominate the presentation and mask diagnosis, an analogy may be made with missed or masked panic disorder.

The absent report of the affective, behavioral, or cognitive components of a panic attack can obscure the diagnosis in the face of paroxysmal physical symptoms. One case report[67] described a patient with a symptom picture that suggested a panic attack but the patient failed to describe the emotional experience of anxiety or panic; alexithymia, or the inability to describe one's emotions, was offered as a possible mechanism for the clinical picture. The predominance of physical symptoms or the absence of cognitive or behavioral responses, however, may not reflect alexithymia or a cognitive impairment, but rather variability in symptom expression. Some patients suffer panic attacks without experiencing a need to flee; others experience panic attacks without a sense of terror or dread, but do not necessarily lack the ability to describe their own emotions.

Most patients with clinically significant panic attacks also suffer limited-symptom attacks that feature only one or two physical symptoms. These may be interspersed with major attacks and may be either situational or unexpected, consisting, for example, of runs of tachycardia or bouts of flushing, hyperventilation, or dizziness. Panic disorder, in its early stages, may be manifested exclusively by such minor attacks. Similarly, as anti-panic therapy is effective, both unexpected and situational limited-symptom attacks may be the last vestige of the disorder or continue to represent a residual disorder.

As stated, patients vary in the primary somatic locus of anxiety distress.[48] For example, predominant panic attack symptoms may appear as cardiovascular symptoms (tachycardia or palpitations), neurologic symptoms (dizziness or paresthesias), respiratory symptoms (dyspnea), GI symptoms (diarrhea), and so forth. Recurrent limited-symptom attacks may therefore be initially indistinguishable from

symptoms of a number of disorders in these systems (see Table 13–3). Limited-symptom attacks also may be a harbinger of progression to the full syndrome, but in some cases they may also be disabling themselves and progress to such panic disorder complications as persistent anxiety, phobic avoidance, and depression.

CASE 6

A 32-year-old married factory supervisor had been out of work for 2 years because of stomach pain, nausea, and vomiting. He described his discomfort as "gnawing pains" that would occur paroxysmally, followed by vomiting with little warning. In the previous 5 years, he had had extensive GI work-ups and medical management, vagotomy and pyloroplasty, and ultimately hemigastrectomy without relief of symptoms. He was totally disabled and was referred for psychiatric evaluation. The following features were noted: (1) His severe pain was paroxysmal with lower-grade persistent symptoms; (2) diazepam helped diminish, but did not eradicate, his symptoms; (3) he was homebound and described attacks of stomach pain and vomiting only when he left his apartment—for example, to go shopping; (4) the onset had followed the break-up of a relationship; (5) a major depression had evolved.

On treatment with sertraline (co-administered with diazepam), he experienced complete symptomatic relief in 6 weeks and with maintenance treatment remained symptom free for 5 years. He sought and found a new job after treatment and has been continuously employed for the past 5 years. He recalled frequently needing to leave school as a child because of a nervous stomach.

This case reflects a missed or masked diagnosis of panic disorder because of the predominance of a limited-symptom attack resembling a GI syndrome. Clues to a diagnosis of panic disorder were evident, and appropriate treatment led to dramatic improvement in this disabled patient. Features reminiscent of more typical patients with panic disorder were identified before definitive treatment, including severe paroxysmal and lower-grade persistent symptoms, onset with a major life event, agoraphobic features, a childhood history suggesting separation anxiety, partial relief with benzodiazepines, and secondary depression. No family history of panic attacks or agoraphobia was reported in this case.

Panic Disorder Associated with Medical Illness

An association between panic disorder and other medical illnesses has been described. More than a third of patients with chronic obstructive pulmonary disease have an anxiety disorder, including 8% to 25% with panic disorder.[68–70] Pollack and associates[71] found an elevated prevalence of panic disorder (11%) among patients referred to a general hospital for pulmonary function testing, including two thirds of those with chronic obstructive pulmonary disease. Almost half of all patients evaluated reported substantial symptoms of anxiety.

Katon[20] and Noyes and co-workers[72] reported an increased incidence of peptic ulcers and hypertension in patients with panic disorder. Close to a third of patients with irritable bowel syndrome have panic disorder, and 44% of panic patients have irritable bowel syndrome; symptoms of both conditions improve with treatment of the panic disorder.[73]

Retrospective studies by Coryell and colleagues[74] suggest an increased risk of premature mortality from cardiac disease in men with panic disorder. A relationship also exists between mitral valve prolapse (MVP) and panic disorder. MVP, usually asymptomatic, may predispose to arrhythmias and occurs in roughly 5% to 10% of the population. Although diagnosed much more frequently in patients with panic disorder (30% to 50%) than in normal subjects or in those with generalized anxiety,[75,76] the nature of the association between the disorders remains unclear. A proposed genetic linkage remains controversial.[77] Patients with panic attacks and MVP do not differ from those with panic alone in their family history of panic disorder or their response to treatment.[78]

PRIMARY ANXIETY DISORDERS

Patients with a number of primary psychiatric disorders may present with anxiety in the medical setting. A history of psychiatric illness may precede the patient's entry into the medical setting and then be exacerbated by the medical condition. For some, however, the onset of symptoms associated with a psychiatric disorder is provoked by the stress of medical illness. Anxiety disorders include panic disorder with and without agoraphobia, GAD, simple phobia, social phobia, PTSD, and OCD.[1]

Panic Disorder

A panic attack usually lasts minutes with fairly stereotypical physical, cognitive, and behavioral components. Patients with panic disorder may experience these attacks intermittently over time or in clusters and, as stated, may develop a number of complications, including persistent anxiety, phobic avoidance, depression, alcoholism, or other drug overuse.

Physical symptoms (e.g., cardiac, respiratory, neurologic, and GI symptoms) are experienced as if there is a sudden surge of autonomic, primarily sympathetic, arousal. Cognitively, the patient feels a sense of terror or fear of losing control, dying, or going crazy and behaviorally often feels driven to flee from the setting in which the attack is experienced to a safe, secure, or familiar place or person.

The initial attack that appears to "turn on" the disorder, the herald attack, is particularly well remembered by the patient. Subsequent attacks may be a mixture of spontaneous, unexpected attacks and those preceded by a buildup of anticipatory anxiety; the latter, called situational attacks, occur in settings in which the patient might sense being at risk for panic, such as crowded places. Attacks may be major, with four or more symptoms, or limited-symptom attacks with fewer symptoms.

Panic disorder has its typical onset in early adult life and afflicts women two to three times as commonly as men. More than half of patients with panic disorder have a history of anxiety disorders beginning in childhood.[79] The disorder is clearly familial and very likely has a genetic basis,

given a higher concordance in monozygotic as compared with dizygotic twins,[80] but it is not clear whether a genetic influence is specific to panic disorder or whether it represents a general anxiety-proneness that may be expressed variably as any of a number of anxiety disorders.

The onset of the disorder in a clinical population typically follows either a major life event, such as a loss, threat of loss, other upheavals in work or home situations, or some physiologic event, such as medical illness (e.g., hyperthyroidism, vertigo) or drug use (marijuana, cocaine). For example, some patients whose first or herald attack appears to be triggered by a physiologic perturbation, such as follows marijuana use, may continue thereafter with persistent or recurrent symptoms without further drug use.

A panic attack, like an endogenous false alarm, appears to turn on a state of vigilance or postpanic anxiety that resembles GAD. Between attacks, patients may remain symptomatic with low-level constant anxiousness and anticipatory anxiety that may crescendo into panic in certain situations or be punctuated by panic unexpectedly.

In this state of vigilance, phobic avoidance may occur as a complication. The patient may develop mild or extensive phobic avoidance, usually of travel or places of restricted escape, immediately after the onset of attacks, after a number of attacks, or never at all. In some cases, the phobic avoidance evolves as a progressive constriction with the cumulative avoidances of settings where attacks have occurred.

Major depressive episodes may also complicate the course of the patient with panic disorder and occur in up to two thirds of cases.[81] For some, the demoralization attending the sustained distress and progressive disability of panic disorder extends to a typical depression with characteristic signs and symptoms. As noted, the relationship between panic and depression is a complicated one, however. Some patients manifest no depressive symptoms; for others, it is unclear which disorder is primary because symptoms arise concurrently. Alcohol use can temporarily tame the distress of panic disorder but soon yields to rebound symptoms, thereby setting the stage for alcohol overuse.

Generalized Anxiety Disorder

Patients with GAD suffer from chronic worry about a number of life circumstances (e.g., finances or danger to loved ones) that is difficult to control and is present on more days than not for longer than 6 months.[1] These patients are often called "nervous" or "worriers" by family or friends. Their anxiety is accompanied by a number of somatic and cognitive symptoms associated with motor tension and autonomic hyperactivity (e.g., muscle tension, restlessness, difficulties concentrating, and sleep disturbances). Although the disorder may be differentiated from panic disorder by the persistent rather than episodic nature of the symptoms, careful questioning often reveals that patients with GAD may experience panic attacks as well.[82,83] Many patients with GAD in the medical setting manifest anxiety in addition to the symptoms of other psychiatric disorders (e.g., panic disorder, depression, or alcohol abuse).[84]

Specific Phobias

Patients with specific phobias are afraid of circumscribed situations or objects (e.g., heights, closed spaces, animals, or the sight of blood).[1] Exposure to the feared stimulus results in intense anxiety and avoidance that interferes with the patient's life. Some patients are so afraid of needles or blood that compliance with procedures in the medical setting is nearly impossible. Acute treatment with benzodiazepines may decrease the patient's anxiety to the point where he or she agrees to treatment. The only consistently effective treatment for specific phobias, however, is behavioral therapy, a technique that involves exposure and desensitization to the feared object or situation.[85]

Social Phobia (Social Anxiety Disorder)

Social phobia, also referred to as social anxiety disorder, is diagnosed when the patient perceives that he or she will be the object of public scrutiny and fears that he or she will behave in a way that will be humiliating or embarrassing.[1] This perception leads to persistent fear and avoidance, or to endurance with intense distress. Circumscribed situations may be feared (e.g., speaking before a group, performance anxiety, writing or eating in the presence of others, or urinating in public lavatories); many patients experience more global difficulties in which most social interactions are difficult. Again, depression and alcoholism can frequently occur with social phobia.[86,87] Patients with a social phobia may have intense anxiety in the hospital because they are under intense scrutiny by others. Long-term treatments include antidepressants with selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram), serotonin–norepinephrine reuptake inhibitors (SNRIs) (venlafaxine), and monoamine oxidase inhibitors (MAOIs) (phenelzine, tranylcypromine) generally being more effective than tricyclic antidepressants (TCAs) (e.g., imipramine, desipramine, nortriptyline), β-blockers (for performance anxiety rather than generalized social phobia), or CBT. Some reports support the clinical efficacy of high-potency benzodiazepines (HPBs) (e.g., clonazepam,[88] alprazolam[89]) for the treatment of social phobia; when immediate intervention is necessary, the use of these agents is appropriate.

Posttraumatic Stress Disorder

Patients with PTSD have experienced or witnessed a traumatic event involving death or serious injury to themselves or others and responded with feelings of intense fear, horror, or helplessness.[1] Afflicted patients frequently reexperience the traumatic event. They have recurrent dreams or suddenly act or feel as though the event is recurring (i.e., a flashback). Individuals with PTSD frequently avoid situations that remind them of the event and may become numb, irritable, or hypervigilant and experience difficulty with sleep or concentration. Although much attention has been directed toward PTSD in combat veterans, PTSD can occur in civilians who suffer life-threatening accidents or assaults or who have survived natural disasters. PTSD is unfortunately common and often unrecognized in the medical setting, with reported rates of PTSD in over

a third of patients hospitalized after traumatic injury, such as occurring in motor vehicle accidents, assaults, or fires.[90,91] Injured patients who develop PTSD have increased functional impairment and problem-drinking when followed up a year after surgery.[92]

Acute stress disorder involves the development of dissociation and reexperiencing symptoms along with avoidance, anxiety, increased arousal, and significant distress or impairment lasting up to 4 weeks after a trauma.[1] The presence of acute stress disorder is associated with the development of PTSD.[93]

There is growing interest in whether early intervention for trauma victims can prevent the development of PTSD. Emerging data suggest that whereas single-session debriefing after a traumatic event is likely to have no benefit and may in fact interfere with the natural recovery process,[94,95] more extensive, multiple–session cognitive–behavioral interventions incorporating information, cognitive restructuring, and exposure elements appear effective.[96,97] Pharmacologic interventions have also demonstrated potential benefit in reducing the morbid sequelae of trauma. One small double-blind randomized trial in a cohort of burned children demonstrated significant reduction in symptoms of acute stress disorder with imipramine as compared with chloral hydrate treatment.[98] A small placebo-controlled trial demonstrated that a 10-day course of propranolol (40 mg four times daily) initiated within 6 hours of a traumatic event resulted in reduction of PTSD symptoms and physiologic arousal at 3-month follow-up.[99] In addition to agents that inhibit the adrenergic system, there has been increasing investigation of glucocorticoids as a means of preventing PTSD, as well as of decreasing symptoms related to recall of traumatic memories.[100] Although further research in this area is warranted and ongoing, the work to date suggests a potential benefit of pharmacologic intervention strategies that address memory systems in reducing the morbid consequences of trauma exposure.

Both CBT[101] and SSRI pharmacotherapy have become first-line interventions for the treatment of PTSD.[102] They are frequently co-administered to improve outcome. Although far from definitive, there is evidence suggesting that benzodiazepine administration may impede the recovery process in traumatized individuals,[103,104] and that other agents, including atypical neuroleptics (e.g., risperidone, olanzapine) and anticonvulsants (e.g., lamotrigine, topiramate, gabapentin) may be useful alternatives as well as having a role in management of the refractory patient.

Obsessive–Compulsive Disorder

Patients with OCD suffer from recurrent, intrusive, unwanted thoughts (i.e., obsessions, such as the fear of hurting a loved one or the fear of contamination) or compulsive behaviors or rituals (such as repetitive handwashing or checking a door multiple times to make sure it is locked).[1] The obsessions and compulsions are distressing and time consuming (i.e., they may take more than 1 hour per day) and interfere with the patient's normal function. In the medical setting, the patient with OCD may suffer a marked increase in anxiety if physical disability or hospital routine makes it impossible for him or her to perform compulsive rituals. CBT aimed at reducing the patient's obsessive thoughts and compulsive behavior has demonstrated clear efficacy for OCD. Benzodiazepine therapy may be necessary to control overwhelming anxiety, particularly in acute treatment. Effective long-term treatments include use of serotonergic antidepressants (e.g., SSRIs, clomipramine) as well as behavioral therapy.

Other Psychiatric Disorders

Anxiety symptoms may be associated with a number of psychiatric disorders (such as schizophrenia, depression, and bipolar disorder) other than primary anxiety disorders. Vague uneasiness extending to severe anxiety may either precede or accompany the symptoms of schizophrenia. Patients with significant degrees of anxiety may have a reduced level of function and manifest withdrawal that superficially resembles schizophrenia. The presence of hallucinations, delusions, and bizarre and disordered thinking, a marked degree of social withdrawal, and a characteristic premorbid personal and family history usually allows an uncomplicated differentiation of schizophrenia from anxiety disorders.

The relationship between anxiety and depression is complex. Weissman and co-workers[105] reported an increased prevalence of both panic disorder and depression in the families of probands with both disorders. One estimate holds that one third of patients with panic disorder, with or without agoraphobia, develop a secondary major depression, and 22% have had a major depressive disorder before developing panic disorder.[106] The incidence of a major depressive episode in patients with panic disorder has been reported as ranging between 28% and 90%, depending on the diagnostic criteria used.[107] Leckman and associates[108] found that 58% of a group of depressed patients had anxiety symptoms meeting *Diagnostic and Statistical Manual for Mental Disorders*, 3rd edition, criteria for agoraphobia, panic disorder, or GAD.

Although this overlap between syndromes can make the distinction between anxiety and depression difficult, a number of clinical considerations may be useful. Psychomotor retardation, persistent dysphoria, early morning awakening, diurnal variation, a sense of hopelessness, and suicidal thoughts are more indicative of depression. Patients with an anxiety disorder have often not lost interest in their usual activities but rather have lost the ability to negotiate them comfortably. They are more likely to report autonomic hyperactivity, derealization, perceptual distortions, and anxious impatience than hopelessness.[46] Advances in neurobiology at this time offer few diagnostic markers for differentiating anxiety and depressive disorders. The sleep of patients with panic disorders differs from the sleep of depressives during all-night polysomnograms.[109] There are also differences in physiologic parameters and platelet receptor–binding patterns between anxious and depressed patients.[110,111]

The principal concern in differentiating depression from anxiety is to not overlook treatment with an antidepressant and, in particular, to avoid the common scenario of prescribing only a benzodiazepine for the anxiety component of a depression, thereby leaving the depression untreated. Fortunately, the frequent overlap in clinical presentations

between primary depressive and primary anxiety disorders is mirrored by an overlap in therapeutic considerations. One important consideration, however, is the possibility that depressed symptoms may reflect an underlying bipolar (manic–depressive) disorder. Anxiety disorders are a common co-morbidity among bipolar individuals.[112] However, the use of antidepressants in bipolar patients may precipitate mania and provoke greater mood cycling. Bipolar disorder should be considered in the differential diagnosis of depression, particularly in those patients with a history of marked mood instability or a family history of manic–depressive illness, as well as in individuals who become more agitated or dysphoric after antidepressant administration. For bipolar patients, use of an anticonvulsant may treat both the mood and the anxiety disorder, with use of benzodiazepines, in preference to antidepressants, considered for persistent anxiety in individuals without a substance abuse diathesis. Although cognitive–behavioral interventions for anxiety and depression differ in both their focus and procedures, it is not unusual for treatment of one condition to extend benefit to the associated disorder. For example, the CBT of panic disorder is associated with improvement in co-morbid depression. Nonetheless, co-morbidity generally serves as a predictor of worse overall treatment response to CBT, just as it does for pharmacologic approaches.[113]

TREATMENT

The nature of the medical setting favors expedient interventions, such as drug treatment to ease acute distress, because of the time-limited nature of medical and surgical stays (Table 13–4). Nonetheless, as illustrated by the case examples, comprehensive assessments, including systematic scrutiny of cognitive and psychosocial factors, may lead to practical interventions short of formal psychotherapy, including CBT. In addition, disrupted relations with family members may be provocative, and family interventions may prove therapeutically expedient.

Pharmacologic Treatment of Panic Disorder

The drug treatment of anxiety essentially involves selecting agents for panic, GAD, or both. As with recognizing the primacy of depression in some anxious patients, if the presence of panic attacks is overlooked, treatment for generalized anxiety alone is likely to be inadequate, and patient suffering will continue. Familiarity with panic disorder, its complications, and its treatments is a necessary resource in evaluating and caring for anxious patients.

Although early intervention offers the likelihood of preventing complications, many patients come for treatment

TABLE 13–4 Selected Pharmacologic Treatments for Anxiety Disorders

AGENT	USUAL INITIAL DOSAGE (mg)	DOSAGE RANGE (mg)	CHIEF DOSAGE LIMITATIONS	DISORDERS
Tricyclic Antidepressants (TCAs)				
Imipramine	10-25	150-300	Jitteriness, TCA side effects	PD, AG, GAD, PTSD, OCD
Clomipramine	25	25-250	Sedation, weight gain, TCA side effects	PD, AG, GAD, PTSD
Monoamine Oxidase Inhibitors (MAOIs)				
Phenelzine	15-30	45-90	Diet, MAOI side effects	PD, AG, SP, ?GAD, OCD, PTSD
Selective Serotonin Reuptake Inhibitors (SSRIs)				
Fluoxetine	10	10-80	SSRI side effects	PD, AG, SP, OCD, PTSD
Sertraline	25	25-200	SSRI side effects	PD, AG, SP, OCD, PTSD
Paroxetine	10	10-50	SSRI side effects	PD, AG, SP, OCD, PTSD
Paroxetine-CR	12.5	12.5-62.5	SSRI side effects	PD, AG, SP, OCD, PTSD
Fluvoxamine	50	50-300	SSRI side effects	PD, AG, SP OCD, PTSD
Citalopram	10	20-60	SSRI side effects	PD, AG, SP, OCD, PTSD
Escitalopram	5	10-20	SSRI side effects	PD, AG, SP, OCD, PTSD
Serotonin–Norepinephrine Reuptake Inhibitor (SNRI)				
Venlafaxine	37.5	75-225	SSRI side effects, hypertension	PD, AG, SP, OCD, PTSD
Benzodiazepines				
Alprazolam	0.25 qid	2-10/day	Sedation, discontinuation syndrome	PD, AG, GAD, SP, ?SpP
Clonazepam	0.25 hs	1-5/day	Abuse, psychomotor and memory impairment	PD, AG, GAD, SP, ?SpP
Diazepam	2.5	5-30/day	—	GAD, SpP, PD, SP
Other anxiolytics				
Buspirone	5 tid	15-60/day	Dysphoria	GAD
Propranolol	10-20	10-160/day (maintenance use)	Depression	SP, ?PD, ?GAD

AG, Agoraphobia; *d*, day; *GAD*, generalized anxiety disorder; *OCD*, obsessive-compulsive disorder; *PD*, panic disorder; *PTSD*, posttraumatic stress disorder; *SP*, social phobia; *SpP*, specific phobia.

after years of symptoms and disability. Even in the face of chronicity, however, most patients achieve substantial if not dramatic benefit with available treatments, which include anti-panic pharmacotherapy and CBT. Given the apparent primacy of the panic attack in the distress and evolution of complications of the disorder, our usual approach is to initiate anti-panic medications for patients who continue to experience panic attacks, with the expectation of regression and remission of complications once the attacks have ceased. For patients with residual phobic avoidance despite the prevention of panic attacks, behavioral and cognitive strategies are employed. For some patients, behavioral and cognitive strategies are employed initially, especially when the frequency and intensity of unexpected panic are minimal, with pharmacotherapy subsequently applied if emergence or exacerbation of panic attends the behavioral program.

Antidepressants

The SSRIs (including fluoxetine, sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine) have become first-line agents for the treatment of panic disorder as well as other anxiety disorders[114,115] because of their broad spectrum of efficacy, favorable side-effect profile, and lack of cardiotoxicity. Although effective, these agents may worsen anxiety for some patients at the initiation of treatment. Thus, treatment of panic patients or the anxious depressed should be initiated at half or less of the usual starting dosage (e.g., fluoxetine 5 to 10 mg/day, sertraline 25 mg/day, paroxetine 10 mg/day [or 12.5 mg/day of the controlled-release formulation], citalopram 10 mg/day, escitalopram 5 mg/day, and fluvoxamine 50 mg/day) to minimize the early anxiogenic effect. Dosages can usually be raised, after about a week of acclimation, to typical therapeutic levels. Typical target dosages for this indication are fluoxetine 20 to 40 mg/day, paroxetine 20 to 60 mg/day (25 to 72.5 mg/day of the controlled-release formulation), sertraline 100 to 150 mg/day, citalopram 20 to 60 mg/day, escitalopram 10 to 20 mg/day, and fluvoxamine 150 to 250 mg/day, although some patients may respond at lower levels. Patients with OCD and PTSD may require higher dosages (e.g., fluoxetine 60 to 80 mg/day) to receive maximal benefit.

Onset of benefit with the SSRIs and other antidepressants usually occurs after 2 to 3 weeks of treatment. Although generally better tolerated for acute and long-term treatment than older available classes of antidepressants, SSRIs may be associated with transient or persistent adverse effects, including nausea and other GI symptoms, headaches, sexual dysfunction, and apathy. Despite their reputation as stimulating agents, sleep disturbance is generally not a persistent or significant problem during SSRI therapy. The SSRIs are usually administered in the morning; emergent sleep disruption can usually be managed by the addition of hypnotic agents.

The extended release SNRI venlafaxine has also demonstrated efficacy for the treatment of panic disorder and the other anxiety disorders. Like other antidepressants, it may cause uncomfortable stimulation early in the treatment of anxious patients, so dosing should be initiated with low dosages (i.e., venlafaxine 37.5 mg/day). Other antidepressants, such as mirtazapine, are also probably effective for the treatment of anxiety disorders, but the systematic data supporting their use for these indications are limited. Trazodone appears to be less effective for panic disorder than other agents; studies assessing the effectiveness of bupropion for panic disorder are small and have shown mixed results.

The TCA imipramine hydrochloride has well-established efficacy in panic disorder.[116] Although other TCAs are probably also effective (e.g., desipramine is frequently employed because of its lower anticholinergic burden), this class of agents has several drawbacks, including a delayed onset of benefit and treatment-emergent adverse effects. In addition to the usual TCA side effects (such as dry mouth, constipation, and orthostatic hypotension), panic patients are particularly prone to a sudden worsening of their disorder with the first doses. To minimize the effect of this adverse response, treatment can be initiated with small test doses (e.g., 10 mg of imipramine hydrochloride). If this is well tolerated, standard antidepressant dosing can be pursued; for others, the adverse response typically fades over a few days, thus allowing an upward titration of dosage. For a small percentage of patients, this apparent worsening of the disorder does not subside. Mavissakalian and Perel[117] reported that a reasonable target dosage of imipramine for treatment of panic disorder and agoraphobia in most patients is approximately 2.25 mg/kg per day (usually between 100 and 200 mg/day for most patients), with a total plasma level of 75 to 150 ng/mL for imipramine and its metabolite, desipramine.

The MAOI phenelzine has stood up well in clinical use and controlled trials,[116] and many clinicians believe that MAOIs may be the most comprehensively effective agents for treating panic disorder, blocking panic attacks, relieving depression, and offering a confidence-enhancing effect of considerable value to the patient needing to recover from vigilance and phobic avoidance. Except for postural hypotension, MAOIs are free of most of the early TCA and SSRI side effects, including the anxiogenic response. Unfortunately, as treatment proceeds, a variety of challenging problems emerge, including insomnia, weight gain, edema, sexual dysfunction, nocturnal myoclonus, and other unusual symptoms. Further, many anxious patients are most circumspect about the dietary precautions and instructions about hypertensive crises. Because the SSRIs and the MAOIs offer similar spectra of efficacy in terms of treating panic disorder, social phobia, and atypical depressive symptoms, along with a superior safety and side-effect profile, they are generally used first in most patients. MAOIs, however, may be effective in patients failing to respond to other interventions; thus, although this has not been systematically studied, many clinicians believe that no patient should be considered truly treatment refractory to pharmacotherapy until the patient has had an MAOI trial.

Benzodiazepines

When treatment refusal, treatment discomfort from side effects, and treatment failure are considered, the need for a better-tolerated and effective anti-panic treatment is apparent. In some respects, benzodiazepines, such as alprazolam and clonazepam, fit this need. They have demonstrated anti-panic efficacy as well as patient acceptability and a reasonable record of safety. In addition, they provide the speed of action that is desirable in a medical setting.

Although it was once believed that higher-potency agents, such as alprazolam and clonazepam, were more effective than lower-potency agents, such as diazepam, for the treatment of panic, it appears that all benzodiazepines may be effective at equivalent dosages (i.e., 4 mg/day of alprazolam and 40 mg/day of diazepam).[118]

The usual dosage range for most panic disorder patients receiving alprazolam is 2 to 8 mg/day, with most achieving a benefit from around 4 to 6 mg/day. Clinical response is evident early, but lower dosages are necessary to initiate treatment so that the patient can accommodate to sedation. Most patients adapt within a few days to the sedating effects, and this allows a stepwise increase in panic-blocking doses. Adaptation to sedation usually occurs without a loss of therapeutic benefit, but some upward adjustment may be required after the first 2 weeks. A small percentage of patients appear particularly sensitive to the drug and experience persisting sedation despite time and careful titration. Alprazolam must be given in divided doses, usually three to four times a day, because of its relatively short duration of action; a recently introduced extended-release formulation permits once-a-day dosing. It does not change the elimination half-life or need for a gradual taper with discontinuation.

Despite the ease of administration of alprazolam and frequently dramatic results even in the first days of treatment, clinical drawbacks include concerns about abuse and dependency, rebound symptoms between doses, withdrawal, and early relapse. The abuse potential of alprazolam, like that of other benzodiazepines, varies widely among clinical populations; patients with a history of alcohol or other substance abuse are most at risk for abusing benzodiazepines. Numerous studies are reassuring that panic patients treated with benzodiazepines do not experience therapeutic tolerance or dosage escalation; in fact, dosages of benzodiazepines generally decrease over the maintenance period, often despite the presence or persistence of untreated anxiety symptoms.[119] Most well-informed panic and phobic patients who have endured severe distress over time treat their medication with respect and understand the wisdom of maintaining the lowest effective dose; thus, unless there is evidence that a particular patient is at risk, the use of this agent appears generally safe for the disorder under consideration. As with any benzodiazepine, without controlled prescribing for targeted symptoms, inappropriate use may occur. As seen with a benzodiazepine with a relatively short half-life, the discontinuation of alprazolam therapy, especially after long-term treatment, without a gradual taper tailored to the individual patient's sensitivity to decreasing dosages, may be followed by rebound symptoms (worsened anxiety) or a withdrawal syndrome.

With the pharmacokinetic drawbacks associated with a short half-life agent in mind, the longer-acting high potency benzodiazepine (HPB) clonazepam, has been effective for those patients who require an HPB. Because of its long half-life (15 to 50 hours), clonazepam is generally administered on a twice-a-day dosage schedule, with patients less likely to experience interdose rebound and withdrawal symptoms than on shorter-acting agents.

With a milligram-for-milligram potency approximately twice that of alprazolam, clonazepam's effective dosage range for panic patients is between 1 and 5 mg/day when given in morning and bedtime doses. Sedation is the limiting factor in dosage titration and is managed by initiating treatment with a low bedtime dosage and titrating upward if symptoms persist and sedation resolves. An initial dosage as low as 0.25 mg may be used in drug-naive patients or those particularly sensitive to benzodiazepines. Greater dosages may be given at bedtime than in the morning if the patient is not readily accommodating to sedation, but many patients function without sedation on equal morning and bedtime dosages, as with alprazolam.

The effect of a daily dose on panic attacks and generalized anxiety is apparent within a few days. Some patients, for unclear reasons, develop depressive symptoms as a treatment-emergent adverse effect when taking alprazolam or clonazepam. Resolution of depressive symptoms typically occurs with the introduction of an antidepressant; benzodiazepine treatment can then be withheld with the expectation of a comprehensive response to the antidepressant. Combined treatment can again be used if anxiety symptoms break through the antidepressant treatment.

Some clinicians initiate combined treatment with an antidepressant and an HPB to obtain the rapid anxiolysis associated with HPB treatment, decrease the activation associated with initiation of antidepressant therapy, and provide antidepressant coverage of co-morbid or benzodiazepine-induced depression. For many patients, the HPB can be tapered after a few weeks when the antidepressant begins to exert therapeutic effects; however, some patients remain on combined treatment with benefit and without adverse consequences.

Pharmacologic Treatment of Generalized Anxiety

As noted previously, the SSRIs and the SNRIs have become first-line pharmacologic agents for the treatment of anxiety disorders, including GAD. They are better tolerated than the older classes of antidepressants and have a broad spectrum of efficacy, which is a critical clinical concern given the high rates of co-morbidity, particularly depression affecting the generally anxious individual. In addition, SSRIs and SNRIs do not have significant abuse potential, which is an important consideration for generally anxious individuals with a predisposition to substance abuse. However, use of these agents may be associated with side effects, including sexual dysfunction and GI distress, that may adversely affect compliance. The delay in the onset of therapeutic benefit is a relative disadvantage for antidepressants as well as for buspirone; the call to intervene with medication for the anxious patient in the hospital typically requires a response with a more immediate-acting agent. Thus, benzodiazepines are usually used for acute management of anxiety, with antidepressant addition or substitution considered in patients requiring maintenance pharmacotherapy, particularly those with a depressive or substance abuse diathesis.

Benzodiazepines, by dint of their efficacy, tolerability, and rapid onset of effect, have long been the mainstay of anxiolytic pharmacotherapy, although the clinical decision to prescribe these agents for symptom relief is a difficult one. The attitudes of individual physicians toward prescribing may be characterized as falling along a spectrum between pharmacologic Calvinism and psychotropic hedonism,

reflecting a personal and moral stance toward prescribing medication for the relief of psychic distress. The abundant literature on antianxiety agents falls short of providing reliable measures for diagnosis and prescribing. Given the ubiquity of anxiety in hospital settings, the physician must frequently confront the question of whether to prescribe. The use of a benzodiazepine for the distressed, anxious patient is often a therapeutic act analogous to the provision of pain relief.

When compared with barbiturates and nonbarbiturate sedative and hypnotic agents (meprobamate, ethchlorvynol, glutethimide, methaqualone, and others), the benzodiazepines are more selectively anxiolytic, with less sedation and less morbidity and mortality in overdose and acute withdrawal. Because using a benzodiazepine represents a clinical decision to offer symptomatic relief, the critical clinical assessment is to evaluate the patient's response. The patient's coping should be enhanced in addition to, and as a consequence, of relief from suffering.

Choice of Benzodiazepine

All available benzodiazepines are effective in treating generalized anxiety. Drug selection is based on pharmacokinetic properties, which determine the rapidity of onset of effect, the degree of accumulation with multidosing, the rapidity of offset of clinical effect, and the risk of drug discontinuation syndrome.

For single or acute dosing, the onset of effect is determined by the rate of absorption from the stomach, and the offset by distribution from plasma into lipid stores. The half-life of a drug predicts the amount of accumulation of drug in plasma with multidosing and the speed of washout on drug discontinuation (and thus the quickness of return of symptoms or the risk of rebound and withdrawal). For example, a rapidly absorbed, lipophilic agent, such as diazepam, given acutely, has a rapid but relatively short-lived effect; with repeated dosing, however, plasma levels are higher than for a short half-life drug at steady state. The long half-life offers some tapering effect to help protect against rebound or withdrawal on discontinuation.

The clinician can choose a drug to have a fast onset for greater clinical effect, a slow onset to minimize sedation or confusion, short action to allow rapid clearing, or long action to minimize interdose or posttreatment rebound symptoms (Table 13–5). Treatment begins with low doses (e.g., diazepam 5 to 10 mg/day or its equivalent) and upward titration. Dosages vary, but for usual situational anxiety, 30 to 40 mg of diazepam a day or its equivalent are not usually exceeded.

Patients in whom benzodiazepine therapy is being prescribed to manage acute situational reactions should expect that treatment will be of limited duration. For specific phobic anxiety (e.g., fear of flying), occasional use is indicated. For generalized anxiety, using anxiolytics for periods of exacerbation may be effective, although increasing recognition of the distress and chronicity associated with persistent anxiety has underscored the observation that many patients often report sustained improvement and improved quality of life with maintenance treatment.

Precautions in Prescribing

A withdrawal syndrome, usually mild but potentially severe depending on the dose and the duration of treatment, may follow abrupt cessation of therapy. For patients receiving usual doses for less than 3 to 4 weeks—during hospitalization, for example—without prior use of sedatives, the risk of an abstinence syndrome is less. In general, however, treatment is discontinued by tapering doses, gradually adjusting decrements according to patient response.

Overuse of medication and drug-seeking from multiple sources is a concern for outpatient prescribing, but with the controlled use of drugs in the hospital, particular vigilance is appropriate primarily for the patient with a history of drug or alcohol abuse.

The sedative effects of benzodiazepines are additive with those of other CNS depressants, and plasma levels are higher with the use of certain drugs, such as cimetidine. A few patients, particularly with use of HPBs, are prone to increased hostility, aggressivity, and rage eruptions.

Pharmacologic Alternatives to Benzodiazepines

Anticonvulsants (including valproate, gabapentin, topiramate, and lamotrigine) are increasingly being studied

TABLE 13–5 Characteristics of Commonly Used Benzodiazepines

DRUG	HALF-LIFE (hr)	DOSAGE EQUIVALENT (mg)	ONSET	SIGNIFICANT METABOLITES	TYPICAL ROUTE OF ADMINISTRATION
Midazolam (Versed)	1-12	2.0	Fast	No	IV, IM
Oxazepam (Serax)	5-15	15	Slow	No	PO
Lorazepam (Ativan)	10-20	1.0	Intermediate	No	IV, IM, PO
Alprazolam (Xanax)*	12-15	0.5	Intermediate-fast	No	PO
Chlordiazepoxide (Librium)	5-30	10	Intermediate	Yes	PO, IV
Clonazepam (Klonopin)*	15-50	0.25	Intermediate	No	PO
Diazepam (Valium)	20-100	5.0	Fast	Yes	PO, IV
Flurazepam (Dalmane)	40	15.0	Fast	Yes	PO
Clorazepate (Tranxene)	30-200	7.5	Fast	Yes	PO

*Commonly used to treat panic disorder.

and used for a range of anxiety disorders, with some (e.g., gabapentin) administered as an alternative to benzodiazepines because of their sedating properties and tolerability.[120] Although typical neuroleptics (e.g., trifluoperazine) have long been used in clinical practice for the treatment of anxiety, concerns about extrapyramidal effects and tardive dyskinesia have limited this practice. Based on accruing open-label reports and controlled studies, the atypical neuroleptics also appear to have anxiolytic effects across a variety of conditions.[121]

However, although less likely to be associated with neurologic side effects (e.g., extrapyramidal symptoms, tardive dyskinesia) than older-generation agents,[122] the severity of potential metabolic consequences (e.g., weight gain, diabetes, increased triglycerides) associated with these agents suggests that caution must be taken when prescribing them.

β-blocking drugs, such as propranolol hydrochloride, have proved useful in alleviating some of the peripheral autonomic symptoms of anxiety (such as tremor and tachycardia). Although of second-line or third-line importance in treating panic attacks or more cognitively experienced symptoms (e.g., worry), β-blockers are often impressively useful in the performance-anxiety subtype of social phobia and when persistent peripheral symptoms (somatic anxiety) predominate. Agents, such as atenolol, that are less able to cross the blood–brain barrier than propranolol may have advantages for patients who experience fatigue or dysphoria when taking propranolol. Effective doses vary, and treatment requires upward titration from low initial doses.

Buspirone is a nonbenzodiazepine anxiolytic without sedative and anticonvulsant properties or abuse potential. It interacts with postsynaptic 5-HT (serotonin) receptors as a partial agonist and with dopamine receptors but apparently not with the benzodiazepine-GABA receptor.[123] Buspirone is ineffective in panic disorder, and although clinical trials suggest that it is effective for the treatment of GAD, many clinicians and patients have found it disappointing for this indication as well. For some patients, this may in part result from a latency of therapeutic response of weeks, similar to the antidepressants, and the presence of a critical beneficial dose threshold. The dosage range is 5 to 20 mg three times a day.

Cognitive-Behavioral Therapy

For patients with persisting anxiety symptoms, cognitive–behavioral strategies similar to those used for ambulatory patients with anxiety disorders may be adapted to the hospitalized medical patient. CBT for anxiety disorders brings to bear an array of cognitive restructuring, exposure, and symptom management techniques that target the core fears and behavioral pattern characterizing each anxiety disorder. Cognitive interventions include a variety of procedures to challenge and restructure the inaccurate and maladaptive cognitions that increase anxiety and help maintain anxiety disorders. Procedures range from informational discussions, self-monitoring, and socratic questioning to the construction of behavioral experiments in which patients can directly examine the veracity of anxiogenic expectations. A reliance on corrective experiences also lies at the heart of exposure interventions that provide patients with opportunities to extinguish learned fears, by directly confronting (in a hierarchical fashion) feared events and sensations. Symptom management techniques typically include relaxation and breathing retraining procedures to help eliminate anxiogenic bodily reactions. In addition, training in problem-solving or social skills may be necessary to eliminate behavioral deficits that help maintain anxiety disorders. Likewise, couple's sessions may be required to change family patterns that help maintain avoidant or other anxiety-related behaviors.

Cognitive–behavioral treatment centers on the elimination of core features of each disorder, with treatment for panic disorder targeting fears of arousal, anxiety, and panic symptoms; treatment for social phobia targeting fears of negative evaluations by others; and treatment for PTSD targeting fears of cues of the traumatic event, including fears of the memory and anxiety symptoms accompanying the memory of the trauma. Treatment for GAD focuses on the aberrant worry process itself but also includes symptom management procedures, and treatment for OCD focuses on breaking the link between intrusive thoughts, anxiety, and compulsive behaviors using exposure techniques combined with compulsion-response prevention.

The success of these strategies has made them among the most promising in the treatment literature, with the efficacy of CBT equaling or surpassing that of alternative treatments.[101,124–128] Nonetheless, referral for CBT may be limited by the availability of clinicians specializing in these methods. In addition, the hospital setting may not allow timely initiation of treatment or the completion of basic treatment packages. Basic treatment interventions are commonly delivered in a series of 12 to 16 sessions, although patients may respond much earlier. For patients unresponsive, uninterested, or unwilling to make the initial time investment required for CBT, pharmacotherapy offers the most efficacious alternative.

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14 Alcoholic Patients: Acute and Chronic

Julie D. Ross, M.D., Ph.D.
David R. Gastfriend, M.D.
John A. Renner, Jr., M.D.

From cases of simple intoxication, when the diagnosis can be made on the basis of breath odor and slurred speech, to the more complicated mental status of withdrawal states, alcohol is responsible for more psychiatric and neuropsychiatric problems in general hospitals than are all other substances combined. One study found that nearly 25% of patients who were hospitalized for injuries were intoxicated at the time of their trauma,[1] and estimates of the prevalence of alcohol-related problems in general hospitals range from 12.5% to 30%.[2] Even when problem drinking is not in the immediate picture, a history of alcoholism or of heavy social drinking predisposes a patient to delirium in conjunction with surgery, fever, head trauma, or massive burns. This vulnerability may be related to the neuropathologic changes that have been found in the brains of heavy drinkers and alcoholics. Yet, the Centers for Disease Control and Prevention (CDC) reports that millions of Americans with drinking problems are still not given advice about how to restrict and control their use of alcohol.[3]

Failure to diagnose alcoholism and other substance abuse in hospitalized patients is exceedingly costly in terms of morbidity and expense. At a major East Coast teaching hospital, when investigators reviewed more than 1000 consecutive admissions during a 23-day period, the actual number of substance abusers admitted was 160, as assessed by an independent evaluator; however, in no cases did physicians document that substance abuse was addressed. Hospital costs for these 160 substance abusers totaled $4.3 million over the 23-day period.[4] When substance abusers were identified by hospital-based physicians and offered referrals, nearly two thirds accepted.[5] Months after referral, these patients reported improved outcomes with respect to alcohol problems (e.g., abstinence, duration since last drink, job performance, and personal happiness).[5–7]

Controlled studies have confirmed that even a single, brief, detailed discussion by the physician yields measurable reductions in the consequences of alcoholism.[8,9] Therefore, the Institute of Medicine[10] called for the screening of hospitalized patients for alcohol problems. A simple, inexpensive screening interview, the CAGE questionnaire (Table 14–1)[11] offers brevity, as well as low cost, and better sensitivity and specificity for alcohol problems than currently available blood markers (such as serum γ-glutamyl transpeptidase, serum transaminases, and mean corpuscular volume).[12] Laboratory markers, particularly the serum level of carbohydrate-deficient transferrin, can be helpful, however, in tracking decrements in patients' drinking following intervention.[11]

DRUNKENNESS

Inebriation is a potentially disruptive and dangerous state. Few sights are more frightening than that of a young and powerful patient, mindlessly angry, anesthetized to pain, yet in full possession of coordination and muscular power.

Management

The actions of ethanol on neuronal systems are complex; initially, use of ethanol at low doses produces electrical excitability, whereas at higher doses it depresses it. Behavioral disinhibition is mediated by alcohol's action as a gamma-aminobutyric acid (GABA) agonist, and its interactions with the serotonin system might account for its association with violent behavior.[13] Blood alcohol concentrations (BACs) as low as 40 mg/dL can impair memory, leading to an alcoholic blackout; argumentativeness or assaultiveness can arise at 150 to 250 mg/dL, and coma or death can occur at 400 to 500 mg/dL. Yet, chronic alcoholics, owing to tolerance, may be fully alert with blood alcohol concentrations of more than 800 mg/dL.[14] Because these interactions are unpredictable, the first principle of management is to *alert the hospital police or security force* before starting an interview with a boisterous drunk. Although such support is seldom required, it is reassuring to have police assistance at the ready, especially if the patient is armed or has a history of violence.

The second principle is for staff to *be tolerant and nonthreatening*. People who possess a skill for disarming an abusive intoxicated individual seem to have little or no need to express their authority or toughness, even though they may possess both qualities in abundance. They tolerate insults, threats, and oaths because they do not take them personally. Conversely, we have observed that persons who galvanize the alcoholic's anger and mobilize his or her aggression are often autocratic and rigid; their flimsy sense of security is easily punctured by an inebriate's invective. The successful interviewer temporarily accepts the intoxicated person as he or she is; the unsuccessful interviewer rapidly attempts to make the drunk act civil. This latter effort usually backfires.

When approaching an alcohol abuser, a handshake of introduction should be extended. Unless the patient

TABLE 14–1 CAGE Questionnaire for Alcohol Problems Screening*

C	Have you felt the need to **C**ut down on your drinking?
A	Have people **A**nnoyed you by criticizing your drinking?
G	Have you ever felt bad or **G**uilty about your drinking?
E	Have you had a drink first thing in the morning to steady your nerves or to get rid of a hangover (i.e., an "**E**ye opener")?

*A score of two positive items indicates the need for detailed assessment.[11]

CASE 1

A psychiatrist was called to the emergency department (ED) to see a patient who had leapt from the examining table while a scalp laceration was being repaired. The patient accused the intern of deliberately trying to hurt him. The patient was a large man with a deep and penetrating voice and a menacing manner. The psychiatrist, a small woman, asked the others to leave, which they did reluctantly. They heard the patient thunder accusations for 3 to 4 minutes. Then quiet reigned. The psychiatrist emerged 5 minutes later, and the patient was lying peaceably on the examining table after having consented to an intramuscular (IM) injection of a sedative. The psychiatric technique was simple. During a pause for breath in his ranting, she told him that she was frightened. He stared at her for a moment. Then he muttered, "Don't want to scare you," and accepted the sedative.

is well known, the patient should be addressed by his or her proper name, for example, "Mr. Smith" or "Ms. Smith." For the time being, no attempt should be made to change the patient's behavior; instead, it is better to listen to their tirade and to make sense of it, rather than to demand that the patient lower his or her voice and to talk temperately. This approach has occasionally uncovered a legitimate grievance or misunderstanding that, once corrected, quickly alleviated the patient's bellicosity.

It is advisable to avoid direct eye contact that lasts for more than a few seconds at a time. More than momentary eye contact is often taken as a challenge; it becomes the prelude to combat (as it can be for animals). The interviewer should listen intently to what the patient has to say and appear puzzled or perplexed rather than angry or amused if the accusation or complaint is absurd. Above all, it is important to avoid a belligerent posture. A colleague once observed that he patterned his behavior with hostile drunks after the humble-submissive posture assumed by a wolf when bested in battle. Transposed to the human habitus, this physician keeps his eyes downcast, fists unclenched, and shoulders stooped. Once the patient sees that the interviewer is not going to attack, his outburst may quiet and his anger slacken.

The third principle is to *offer food*. Some of the most antagonistic alcoholics have been soothed by an offer of coffee. If the person is willing to leave the scene with the inducement of coffee, food, and quiet, he or she should be escorted to a lobby or foyer where people are within easy calling distance. Many alcoholic persons are claustrophobic and feel trapped in small rooms. Furthermore, it is discomforting for most physicians to be in an enclosed area with a potentially violent person. The value of offering food, cigarettes, or drink in this case can be justified by empirical evidence only. With food, the patient often loses his or her belligerence. The next step is to persuade the patient to take a sedative (if alert and agitated) or an antipsychotic (if still ataxic and dysarthric) and to go to bed.

As in handling other conditions of psychotic excitement, it often helps to let the patient know that his or her behavior is frightening. Resolution of intoxication follows steady-state kinetics, so that a 70-kg man metabolizes approximately 10 mL of absolute ethanol or 1.5 to 2 drink equivalents (1½ oz whiskey = 5 oz wine = 12 oz beer) per hour.[15]

To sedate an intoxicated patient, one must begin with a smaller dose than usual to avoid confusion secondary to the cumulative effects of alcohol and the agent used. Once the patient's tolerance has been established, a specific dose can be safely determined. In the patient who is excessively agitated without ataxia or dysarthria, lorazepam (Ativan) 1 to 2 mg offers effective absorption via all routes—orally, intramuscularly, or intravenously; diazepam (Valium) and chlordiazepoxide (Librium) are erratically and slowly absorbed after IM administration unless they are given in large, well-perfused sites. When incoordination suggests that the additive effect of a benzodiazepine has produced excessive sedation, it may be advantageous to use haloperidol (5 to 10 mg). The initial dose should be followed by a wait of 30 minutes to 1 hour before augmenting it.

Just being acutely intoxicated does not require hospitalization. If there is no risk of withdrawal, the patient can safely be referred to an alcohol detoxification program. Inpatient detoxification is preferable to outpatient care if the patient is not well known to the team; is psychosocially unstable; has serious medical, neurologic, or psychiatric co-morbidity; has previously suffered withdrawal complications; or is undergoing his or her first episode of treatment.[16] Repeatedly undertreated withdrawal can put the patient at subsequent risk for withdrawal seizures and for other neurologic sequelae. This increasing risk is believed to occur through "kindling," a type of electrophysiologic effect,[17] and it may be mediated, similar to other neurodegenerative effects of ethanol, via the glutamate excitatory neurotransmitter system.[18]

ALCOHOLIC COMA

Alcoholic coma, although rare, is a medical emergency. It occurs when extraordinary amounts of alcohol are consumed, often in conjunction with another drug. The main goals of treatment are to prevent aspiration by taking appropriate precautions, to monitor closely for respiratory depression (because of the potential need for admission to the intensive care unit), and to be prepared for respiratory arrest with a need for mechanical ventilation (realizing that the GABA antagonist flumazenil might not reverse ethanol's respiratory depression).[19]

PATHOLOGIC INTOXICATION AND ALCOHOLIC PARANOIA

In pathologic intoxication, the patient becomes intoxicated on small amounts (as little as 4 oz) of alcohol. There may be subsequent automatic behavior that is violent and for which the patient is totally amnestic. The alcoholic person with a known history of pathologic intoxication should be sedated heavily and confined until sobriety is ensured to avoid possible danger to others.

Pathologic intoxication might last for an hour or for days, and it usually ends after prolonged sleep. During the episode, the patient is agitated, impulsive, and often aggressive. Delusions and visual hallucinations can occur. Generally the disorder is marked by hyperactivity, anxiety, or depression. Suicide risk is increased during these episodes. It may be more likely in patients with borderline personality disorder or epilepsy or in persons who tend toward emotional instability and whose pattern of defense is easily disorganized. Haloperidol 5 to 10 mg PO or IM decreases agitated or violent behavior with a minimum of sedation and with little likelihood of potentiating seizures. Doses may be repeated in 30 minutes, if necessary.[20]

Alcoholic paranoia is somewhat similar to pathologic intoxication. It is a state of cognitive disorganization brought about by use of alcohol that may manifest as strong feelings of jealousy, antagonism, or suspicion.

The prognosis is poor for patients with pathologic intoxication or alcoholic paranoia. Such patients often have a history of violence and aggression with repeated incarcerations. The consultation psychiatrist should be on the watch for emergence of amnesia or for the return of the premorbid behavior after the intoxication has been slept off. Although the premorbid personality of the paranoid alcoholic patient is apt to be somewhat suspicious, it is not nearly as intense or threatening as when the patient is under the influence of alcohol.

ALCOHOL WITHDRAWAL SYNDROME

The syndrome of alcohol withdrawal can range from mild discomfort that requires no medication to multiorgan failure that requires intensive care. Uncomplicated withdrawal is surprisingly common and often missed. Although more than 90% of alcoholics in withdrawal need nothing more than supportive treatment, those with co-morbid illness in the general hospital undoubtedly have a higher rate of complications.[21] The most common features of uncomplicated alcohol withdrawal emerge within hours and resolve after 3 to 5 days as the blood alcohol concentration decreases. Symptoms of uncomplicated withdrawal are predictable: Loss of appetite, irritability, and tremulousness are early features. A hallmark of the abstinence syndrome is generalized tremor (fast in frequency and more pronounced when the patient is under stress). This tremor can involve the tongue to such an extent that the patient cannot talk. The lower extremities can tremble so that the patient cannot walk. The hands and arms can shake so violently that a drinking glass cannot be held without spilling the contents. The patient is hypervigilant, has a pronounced startle response, and complains of insomnia.

Less commonly, a patient experiences hallucinations (without delirium) or seizures associated with alcohol withdrawal. Illusions and hallucinations of a mild variety can appear and produce vague uneasiness. These symptoms can persist for as long as 2 weeks and then clear without the patient developing delirium. Grand mal seizures ("rum fits") can occur, usually within the first 2 days. More than one out of every three patients who suffer seizures develop subsequent delirium tremens (DTs).[22]

Treatment

Rigid adherence to only one protocol for all alcohol withdrawal is unrealistic. Moreover, the failure to individualize treatment can increase costs—an undesirable result in the era of managed and capitated care. Symptom-triggered dosing, in which dosages are individualized and only administered upon the appearance of early symptoms, can reduce medication doses and shorten symptom duration,[23,24] although benefits may be less dramatic in the medically ill.[25]

Chlordiazepoxide (50 to 100 mg orally) may be given initially, and may be followed by 50 to 100 mg every 1 to 2 hours until the patient is sedated and the vital signs are within normal limits. Alternatively, diazepam 10 to 20 mg may be given initially, and then repeated every 1 to 2 hours until sedation is achieved.

Often a first day's dose of a long-acting benzodiazepine is sufficient for the entire detoxification process because of the self-tapering effect and slow elimination.[26] Patients with impaired liver function are better managed with drugs that avoid oxidative metabolism and rely on glucouronidation (such as oxazepam or lorazepam); after control is achieved, doses may be tapered by 25% per day over the subsequent 3 to 6 days. Other protocols involve use of standing doses for prophylaxis and treatment of withdrawal; these can also reduce length of stay and hospital costs.[27]

ALCOHOLIC HALLUCINOSIS

Diagnosis

Much less common than delirium from alcohol withdrawal, but more bizarre, is alcoholic hallucinosis. The onset is usually within 48 hours after alcohol cessation, but it can occur during active drinking or weeks later. The patient experiences vivid auditory illusions and hallucinations that occur in an otherwise clear sensorium. These hallucinations can become accusatory and threatening. The patient reacts with fear but is fully oriented and realizes that the voices are hallucinations. As the accusations persist, however, the patient develops ideas of persecution. Although hallucinosis is more apt to occur in the setting of alcohol withdrawal, it is by no means uncommon in persons who continue to drink. Some authors believe that hallucinosis is programmed by a disturbance of the auditory pathways. Olfactory hallucinations can occur with alcoholic hallucinosis, but visual hallucinations seldom occur.

The clinical picture is one in which auditory hallucinations occur in the absence of tremor, disorientation, and agitation. Soon after the voices begin, a frightening systematized delusional system develops that can incite the patient to call the police or to arm himself or herself. Then

the patient is particularly dangerous. The patient is capable of acting with an otherwise clear mind. Suicide is a distinct danger in this condition and it can occur, as in delirium, without appreciable warning.

CASE 2

A 27-year-old merchant seaman had begun listening to a local disc jockey while at a bar the previous evening. His attention was suddenly caught when he heard his name announced as a third-prize winner. He had won 14 sheep, 5 head of cattle, and a strawberry farm in Kansas. A taxi driver who had listened to him for 3 hours and had driven him to multiple radio stations finally insisted on taking him to a hospital. Because this was the early 1950s, the era of the colossal giveaways, the story sounded plausible, especially because the patient told it in a straightforward and reasonable manner. The cab driver was asked by hospital personnel whether he had heard the announcement on the car radio. The driver exclaimed, "Oh, no! Not you too! " The seaman clearly believed these voices to be real. He readily agreed, however, to enter the hospital and seemed certain that the truth of his statement would be quickly discovered if he were hospitalized. A week later, he no longer heard voices and had substantially minimized the experience, just as he forgot that alcohol had caused it.

Other psychotic conditions, such as paranoid schizophrenia, may be confused with alcoholic hallucinosis. Creation of a differential diagnosis is apt to be difficult. The predominance of the auditory component of the disorder and a history of alcoholism can aid in the diagnosis of this condition.

Treatment

There is no specific treatment for alcoholic hallucinosis. Generally the condition clears within 30 days, but it can last another month. There are reported instances in which the hallucinosis continued for years. If the person continues to drink, recurrences are the rule.

The most important aspect of treatment is to determine whether the patient should be in a protected environment. Behavior destructive to the self or to others is common, and it can require commitment to a psychiatric hospital. Sedation with benzodiazepines can be given as needed. Because patients in general feel quite normal after the disappearance of auditory hallucinations, they often insist on being discharged as soon as the voices desist. As in DTs, the course can be intermittent, and the patient should be kept in a hospital until 1 to 2 days have passed without hallucinations. The patient should also be vigorously warned against drinking because the hallucinations are apt to return with a relapse.

ALCOHOL WITHDRAWAL SEIZURES

Withdrawal seizures are estimated to occur in only 1% of unmedicated alcoholics undergoing withdrawal, although the prevalence is increased in persons with prior alcohol withdrawal seizures, seizure disorders, and previous brain injury.[22] Although brain imaging may not be necessary in first-episode patients,[28] seizures during alcohol withdrawal require careful examination for other causes. Indications for imaging studies include neurologic and other physical findings suggesting focal lesions, meningitis, and subarachnoid hemorrhage—all of which can occur in patients with prior alcohol withdrawal seizures. Multiple prior detoxifications predispose to withdrawal seizures more than the quantity or duration of a drinking history; this implies kindling.[29] Seizures can occur during relative withdrawal or during the 6 to 24 hours after the cessation of drinking. Generalized seizures typically occur (i.e., in 75% of cases) in the absence of focal findings and in persons with otherwise unremarkable electroencephalogram (EEG) findings. Repeated seizures can occur over a 24-hour period; however, status epilepticus occurs in less than 10% of those who seize.[30]

Treatment

In patients without a prior seizure disorder, diphenylhydantoin offers no benefit over placebo, and given the potential for side effects, diphenylhydantoin is therefore not indicated.[29] Also, given that loading with carbamazepine or valproate might not address the rapid time course of withdrawal seizures, the most parsimonious approach remains effective treatment with benzodiazepines. In cases where there is a known seizure disorder, however, conventional management with anticonvulsants is in order.

DELIRIUM ASSOCIATED WITH ALCOHOL WITHDRAWAL

The major acute complication of alcohol withdrawal, DTs, has been renamed *alcohol withdrawal delirium* in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).[31] Until open heart procedures spawned new postoperative deliria, DTs were by far the most commonly encountered delirium in a general hospital, reportedly occurring in 5% of hospitalized alcoholics.[32] Because deaths have occurred in 10% of patients with untreated alcohol withdrawal delirium and in 25% of those patients with medical or concomitant surgical complications,[33] it is imperative to be on the alert for this life-threatening condition.

Prediction

It is difficult to predict who will develop DTs. Until a decade ago, DTs rarely developed in patients younger than 30 years. This is no longer true. Today the condition is often observed in young patients who may have had a decade or more of chronic heavy alcohol consumption. The mechanisms might involve *N*-methyl-D-aspartate (NMDA)-glutamate receptor supersensitivity.[17] Although DTs are regarded as a withdrawal syndrome, some heavy drinkers fail to develop delirium after sudden withdrawal of ethanol. Infection, head trauma, and poor nutrition probably contribute to delirium. A history of DTs is an obvious predictor of future DTs.

CASE 3

A 64-year-old longshoreman entered the hospital with recurrent gout (16 episodes during a 3-year period). During each hospital admission he became tremulous and disoriented on the second night and went on to develop mild visual and vestibular hallucinations that cleared over 3 days. Large ships would issue though the walls or windows, and the whole room would rock and sway like a wharf in a storm. The pattern was identical, including his insistence that the only alcohol he ever swallowed was a drop or two from his mouthwash.

Diagnosis

The incidence of DTs is approximately 5% among hospitalized alcoholics and about 33% in patients with alcohol withdrawal seizures.[34] If DTs are to occur, they generally do so within 72 hours after abstinence begins. There have been reports, however, of cases in which the clinical picture of DTs did not emerge until 7 days after the last drink.[34] The principal features are disorientation (to time, place, or person), tremor, hyperactivity, marked wakefulness, fever, increased autonomic tone, and hallucinations. Hallucinations are generally visual but they may be tactile, olfactory, or auditory. Vestibular disturbances are common and often hallucinatory. The patient might complain of the floor moving beneath his or her feet or believe that he or she is on an elevator. The hallucinatory experience is always frightening. Animals, typically snakes, are seen in threatening poses. Mice or lice are felt and seen crawling on the skin.

Once the condition manifests itself, DTs usually last 2 to 3 days,[34] often resolving suddenly after a night of sound sleep. Should it persist for a longer time, one must suspect an underlying disorder, such as an infection or subdural hematoma. There are a few patients whose course is characterized by relapses with intervals of complete lucidity. These patients offer the consultant the most challenging diagnostic opportunities. As a rule of thumb, it is always wise to include DTs in the list of diagnoses considered whenever delirium appears.

A psychiatric consultant is apt to miss the diagnosis of DTs when the patient's manner, social position, or reputation belies the possibility of alcoholism. For example, the following problem arose after emergency surgery.

CASE 4

A 54-year-old woman was admitted to the hospital for a cholecystectomy. On her third postoperative day (her fifth day without alcohol), the nurses reported that they could not keep her in bed. She got up and walked about her room in a restless, agitated fashion, constantly gazing back over her shoulders as though she feared she was being followed. She wandered into other patients' rooms as well as down the hospital's corridor. She vigorously resisted every attempt to keep her confined to her quarters. The surgeon, when called, described her as "fearful, overactive, stubborn, but polite." Although she would not give any reason for her distress, she readily swallowed a 25-mg capsule of chlordiazepoxide hydrochloride. This produced no change in her behavior after 2 hours. She talked to herself while she paced, but she was able to maintain a shaky semblance of poise when approached by others. Although her physician opposed psychiatric consultation, the nurses prevailed because they feared she might inadvertently hurt herself. When a house officer suggested the possibility of a small stroke because of the patient's long history of hypertension, the physician agreed to request psychiatric advice.

After reviewing the history and noting a bilateral hand tremor while observing the patient, the psychiatrist diagnosed DTs. Although the patient refused to speak with him after he identified himself, the psychiatrist maintained his diagnosis because it was the most likely possibility in the absence of other signs. Her personal physician refused to accept the diagnosis but did follow the recommended regimen of medication (100 mg of chlordiazepoxide each hour) until the patient was able to stay in bed. The medication was then reduced to a maintenance level and supplemented by 50 mg of thiamine daily. Round-the-clock special nurses were also employed. In the morning, following a night's sleep, the patient was her normal self.

The patient subsequently admitted to drinking four to seven very dry martinis (each about 4 oz) daily. She had been doing so for the last 30 years and had delivered all her children without having developed DTs. She was so frightened by her experience, however, that she agreed to enter treatment for alcohol dependence.

The consultant can be easily misled when the delirium is intermittent and the patient is examined during a lucid period.

CASE 5

A 52-year-old architect was admitted to the hospital because of hematemesis. He readily admitted to heavy alcohol intake but had no difficulty until the fourth hospital day when he began to gaze fixedly at a point on the ceiling and to talk in low, menacing tones to an imaginary companion. He sweated, trembled, and thrashed about so wildly that he had to be restrained. He readily described auditory hallucinations of a persecutory nature; these became alarmingly vivid in the evening. The following morning when a psychiatrist was called to see him he was fully oriented, lucid, perfectly capable of discussing his hallucinations of the previous evening, and willing to accept the diagnosis of DTs. Restraints were removed. However, a few hours later the patient leapt out of bed, ran through the corridors, upset tables, and screamed that someone was chasing him. Once again he was placed in bed, forcibly restrained,, and given 8 mL of paraldehyde orally and 50 mg of chlorpromazine intramuscularly. When the psychiatrist returned a few hours later, the patient's mental status was entirely normal, and he could recall the violent episode. He was, in fact, so clear-thinking that the psychiatrist again suggested that the restraints be removed. Within 20 minutes, the patient sprang out of bed, left the unit, and almost left the hospital. After this second unexpected episode, the consultant sent him to a psychiatric hospital where he remained for the next 2 weeks with intermittent episodes of delirium.

Although a course marked by intermittent episodes is highly atypical for DTs, it does occur. Consultants should be wary of relinquishing restraints or discontinuing intensive observation until the patient has been lucid for 24 hours.

Differential Diagnosis

The differential diagnosis must include the many causes of delirium in a general hospital. Hypoglycemia and alcoholic and diabetic ketoacidosis can co-occur with alcohol withdrawal; these are readily distinguished by their attendant electrolyte and blood glucose abnormalities and by their differential response to emergency treatment. Delirium occurs after surgery and after concussion, as well as with other metabolic disorders. Two examples of the latter are impending hepatic coma and acute pancreatitis. A patient with impending hepatic coma may well be disoriented and confused but tends to manifest decreased activity rather than agitation.[35] Speech is slow and monotonous, and the face is masklike. Physical signs, such as jaundice, hepatomegaly, and *fetor hepaticus* from elevation of blood ammonia levels, help determine this diagnosis. A delirium sometimes occurs in acute pancreatitis. In this condition, however, there is generally severe abdominal pain and an elevated serum amylase concentration.[35]

Prognosis

The prognosis for DTs is reasonably good if the patient is aggressively medicated; however, death can occur as the syndrome progresses through convulsions to coma and death. Death can also result from heart failure, an infection (chiefly pneumonia), or injuries sustained during an agitated period. In a small percentage of patients the delirium can co-exist with Korsakoff's psychosis, in which case the patient might not regain full mentation.

Treatment

Prevention is the key. Symptom-triggered dosing for alcohol withdrawal has been shown to reduce DTs compared to standing orders for benzodiazepines in medically ill inpatients, and fixed-dose, round-the-clock protocols have also been beneficial.[25,27] As in the treatment of any delirium, the prime concern must be round-the-clock surveillance so that the patient cannot harm himself or herself or others. This monitoring is essential. Although not necessarily suicidal, delirious patients take terrible unpremeditated risks. Falling from windows, slipping down stairs, and walking through glass doors are examples of such unintended lethal behavior. Restraints should be used for as short a period as is needed. As required by law, when four-point restraints are used, the patient must be closely observed, and relief must be provided hourly. Usually, physical restraint can be avoided with aggressive pharmacotherapy.

The patient can require careful rehydration (up to several liters of saline per day), correction of electrolyte imbalance (particularly magnesium), prevention of hypoglycemia, or correction of hyperthermia (with a cooling blanket), as well as nutritional supplementation. Concurrent aggravating conditions (e.g., sepsis, meningitis, subdural hematoma, hepatic failure, and pancreatitis) must be considered.

The delayed onset of this state of hyperarousal might reflect alcohol's broad effects across multiple neurotransmitter systems, chief among which may be the NMDA-glutamate system.[18] Adrenergic hyperarousal alone appears to be an insufficient explanation; therefore, α-adrenergic agonists (e.g., clonidine and lofexidine) alone are not sufficient. Benzodiazepines might not suffice either; in rare cases, we have seen doses in excess of diazepam 2000 mg/day prove insufficient. Haloperidol (5 to 10 mg PO or IV) may be added and repeated after 1 to 2 hours when psychosis or agitation is present.

Because the B vitamins are known to help prevent peripheral neuropathy and the Wernicke–Korsakoff syndrome, their use is vital. Thiamine 100 mg should be given intravenously immediately, and 100 mg should be given intravenously for at least 3 days until a normal diet is resumed. Folic acid (1 to 5 mg per day PO or IM) should be included for megaloblastic anemia and peripheral neuropathy. A high-carbohydrate soft diet containing 3000 to 4000 calories a day should be given with multivitamins.

WERNICKE–KORSAKOFF SYNDROME

Victor and associates,[32] in their classic monograph *The Wernicke–Korsakoff Syndrome*, stated that "Wernicke's encephalopathy and Korsakoff's syndrome in the alcoholic, nutritionally deprived patient may be regarded as two facets of the same disease." Although perhaps 5% of alcoholics have this disorder, in 80% of these, the diagnosis is missed. In all of the cases reported by Victor and associates, alcoholism was a serious problem and was almost invariably accompanied by malnutrition. Malnutrition, particularly in the absence of thiamine, has been shown to be the essential factor.

Korsakoff's Psychosis

Korsakoff's psychosis, also referred to as *confabulatory psychosis* and *alcohol-induced persisting amnestic disorder* in DSM-IV,[31] is characterized by impaired memory in an otherwise alert and responsive person. This condition is slow to start and may be the end stage of a lengthy alcohol-dependence process. Hallucinations and delusions are rarely encountered. Curiously, confabulation, long regarded as the hallmark of Korsakoff's psychosis, was exhibited in only a limited number of cases in the large series collected and studied by Victor and associates.[32] Most of these patients had diminished spontaneous verbal output, no insight into the nature of their illness, and a limited understanding of the extent of their memory loss.

The memory loss is bipartite. The retrograde component involves the inability to recall the past, and the anterograde component is the lack of capacity for retention of new information. In the acute stage of Korsakoff's psychosis, the memory gap is so blatant that the patient cannot recall simple items (such as the examiner's first name, the day, or the time) after a few minutes, even though the patient is given this information several times. As memory improves, usually within weeks to months, simple problems can be solved, limited always by the patient's span of recall.

Patients with Korsakoff's psychosis tend to improve with time. In the series of Victor and associates,[32] 21% of the patients recovered more or less completely, 26% showed no recovery, and the rest recovered partially.[31] During the acute stage, there is, however, no way of predicting who will improve and who will not. The EEG may be unremarkable or might show diffuse slowing, and magnetic resonance imaging (MRI) might show changes in the periaqueductal area and medial thalamus.[14] The specific memory structures that are affected in Korsakoff's psychosis are the medial dorsal nucleus of the thalamus and the hippocampal formations.

Wernicke's Encephalopathy

Wernicke's encephalopathy appears suddenly and is characterized by ophthalmoplegia and ataxia followed by mental disturbance.[32] The ocular disturbance, which is necessary for the diagnosis, consists of paresis or paralysis of the lateral rectus muscles, nystagmus, and a disturbance in conjugate gaze. A global confusional state consists of disorientation, unresponsiveness, and derangement of perception and memory. Exhaustion, apathy, dehydration, and profound lethargy are also part of the picture. The patient is apt to be somnolent, confused, and slow to reply and can fall asleep in midsentence.

Once treatment with thiamine is started for Wernicke's encephalopathy, improvement in the ocular palsies is often evident within hours. Recovery from ocular muscle paralysis is complete within days or weeks. In cases reported by Victor and asssociates,[32] approximately one third recovered from the state of global confusion within 6 days of treatment, another third within 1 month, and the remainder within 2 months. The global confusional state is almost always reversible, in marked contrast to the memory impairment of Korsakoff's psychosis.

Treatment

Administration of the B vitamin thiamine (IM or IV) should be routine for all suspected intoxicated and dependence patients, directly in the ED or immediately on admission, whichever comes earlier.[36] The treatment for Wernicke's encephalopathy and Korsakoff's psychosis is identical, and both are medical emergencies. Because subclinical cognitive impairments can occur even in apparently well-nourished patients, routine orders should include thiamine, folic acid, and multivitamins with minerals, particularly zinc. Prompt use of vitamins, particularly thiamine, prevents advancement of the disease and reverses at least a portion of the lesions where permanent damage has not yet been done.[32] The response to treatment is therefore an important diagnostic aid. In patients who show only ocular and ataxic signs, the prompt administration of thiamine is crucial in preventing the development of an irreversible and incapacitating amnestic disorder.

Treatment consists of 100 mg of thiamine and 1 mg of folic acid given intravenously immediately and 100 mg of intravenous thiamine each day until a normal diet is resumed, followed by oral doses for 30 days. Parenteral feedings and the administration of B-complex vitamins become necessary if the patient cannot eat. Because these patients have impaired mental function, nursing personnel should be alerted to the patient's possible tendency to wander, to be forgetful, and to become psychotic. If the last should occur, benzodiazepines can be given.

MEMORY AND ALCOHOL

Cranial computed tomography (CT) and MRI scans, and neuropsychological tests have demonstrated a loss of brain tissue and cognitive impairments in persons who are alcoholics or heavy drinkers, findings that largely escaped notice until the advent of these modern techniques. Abnormalities on the CT scan have been reported in 50% or more of chronic alcoholic subjects.[37] These abnormalities can occur in subjects in whom there is neither clinical nor neuropsychological test evidence of cognitive defects. In chronic alcoholics, MRI has demonstrated accelerating gray matter loss with age, which is to some extent reversible with abstinence, suggesting that some of these changes are secondary to changes in brain tissue hydration.[38]

Short-term memory, performance on complex memory tasks, visual motor coordination, visual spatial performance, abstract reasoning, and psychomotor dexterity are the areas most seriously damaged. Intelligence scores often do not change, and there is a sparing of verbal skills and long-term memory. As a consequence of this sparing, it is possible for patients to appear quite intact unless they are administered neuropsychological tests. According to Rinn and coworkers,[39] subtle impairment of executive function might underlie fixed denial, which inhibits self-awareness of alcohol's damaging effects, impairs learning from counseling, simulates resistance, frustrates caregivers, and generates anger toward the patient. These defects, particularly memory disturbances, can be reversed at least in part with abstinence.

For both the cognitive reasons described and emotional reasons, the principal problem encountered in all therapeutic modalities is denial. Many alcoholic patients in the general hospital who have problems secondary to drinking have difficulty admitting their addiction to alcohol. Research on substance abuse cessation has demonstrated that most patients do not suddenly leap from denial into active recovery, but rather proceed over time through five *stages of change* (Table 14–2).[40] Each patient must be assessed for his or her current stage regarding cessation of substance abuse and assisted to make the transition from the current to the next desired stage in a linear progression. The alternative (e.g., asking a patient in denial to enter intensive treatment immediately) is unrealistic and likely to disappoint both patient and provider. Intervention with the help of a significant other or family members can often make the pivotal difference. Family members often need education about the disease's potential effects on them as well, including the tendency to feel frustrated and hopeless about recovery. A brief meeting that covers the potential benefits of Al-Anon support can have lasting benefits for both family and patient.

REFERRAL AFTER HOSPITALIZATION

Brief intervention in general medical practice is a well-developed, effective technique.[9] Even brief contact with a specialist addiction consultant has been shown to yield

TABLE 14–2 Stages of Change and Treatment Objectives

STAGE OF CHANGE	TREATMENT OBJECTIVE
Precontemplation (i.e., denial)	Cultivate rapport through repeated contact to promote patient's self-examination
Contemplation (awareness of problem)	Review substance use losses and potential risks, such as detailed teaching about hematologic and liver abnormalities and prognostic implications with continued drinking
Preparation (intends behavioral change, seeks treatment)	Anticipate treatment benefits, promote sense of self-efficacy and optimism for recovery
Action (cessation and treatment or self-help participation)	Facilitate entry to treatment and contingency plan in the event of dropout
Maintenance (ongoing avoidance of relapse cues)	Plan for relapse prevention via longitudinal treatment and recovery treatment and recovery activity (i.e., self-help group participation)
Relapse (resumption of substance use)	Support rapid reconnection with treatment system

improvement rates in 30% to 50% of patients months after hospitalization, and this is more effective with those who have no prior psychiatric illness and addiction treatments and good social function and resources.[6] Compared with general consultation psychiatrists, specialist addiction nurse consultants were found to double the rate of patient follow-through and completion in rehabilitation (40% versus 88%, $P < .001$).[7] Addiction psychiatry consultation to hospital physicians should assist with diagnosis, intervention, pharmacologic management, and post–acute care referral. At the Massachusetts General Hospital (MGH), a centralized intake procedure has been available to conduct objective, multidimensional assessment and protocol-driven referral. Consultants tell each alcoholic patient about the types of treatment programs available in the community.

Alcohol dependence causes diverse disruptions in people's self-awareness, communication skills, capacity for relationships, sense of purpose in life, and spirituality. Alcoholics Anonymous (AA) and similar approaches that examine the broader character, lifestyle, and spiritual issues have a record of successful accomplishments and accessibility. Visits on the inpatient unit from AA volunteers may be particularly helpful when patients are ambivalent about accepting their physician's recommendation for alcoholism treatment. Such personal contact increases the likelihood that the patient will attend the AA program. Once the community resources have been identified and their differences described, the patient is advised of the optimal choice.

Despite the severity of their drinking problem, some alcoholics reject intensive approaches as too restrictive or stigmatizing. In this event, a *contingency contract* in which the patient may begin a less-intensive treatment is helpful, but if improvement does not follow within 4 to 6 weeks, the patient agrees to enter the recommended treatment (e.g., inpatient rehabilitation or a halfway house). When this plan is supported by family members, patients often follow through to a successful treatment episode.

Two decades ago, it was common policy at the MGH to insist that the patient make the first contact with the treating agency; however, only approximately one in five patients actually made contact with treatment. After the introduction of a *central intake model*, referral completion rates increased to 58%. Key features of central intake include directly assisting patients with access to treatment, helping patients to call programs, subsidizing transportation to treatment program interviews, obtaining concrete services to diminish treatment obstacles (such as homelessness or lack of child care), and motivational interviewing. Motivational interviewing is a directive, patient-centered counseling for eliciting behavioral change by helping to explore and resolve ambivalence to change.[41] With this brief technique, the provider assesses the patient's losses and risks in detail, helps the patient recognize the underlying cause as substance abuse, and uncovers ambivalence about the potential value of treatment. By avoiding a threatening style of confrontation about denial, motivational interviewing has been found to enhance motivation for recovery.[41]

Studies of treatment outcome show that up to two thirds of patients who enroll in therapeutic programs improve[42] in terms of abstinence or reduced amount of drinking. Pressures to shorten lengths of stay, while improving patient follow-through, are stimulating creative strategies. Examples include intensive case management, home nursing, counseling visitation, and predischarge initiation of pharmacotherapies (such as disulfiram, naltrexone, or selective serotonin reuptake inhibitors [SSRIs]).

Disulfiram (125 to 250 mg orally daily), an aversive agent when combined with alcohol, has reduced subsequent drinking days in chronic alcoholics by approximately 50%.[43] If a patient drinks alcohol after taking disulfiram, the disulfiram–ethanol reaction produces flushing, hypotension, headache, nausea, and vomiting. Naltrexone (50 mg orally daily), an opiate antagonist, has no adverse reaction with alcohol and has produced similar reductions in drinking days presumably through diminished reward from alcohol.[44,45] Because both agents have slight hepatotoxic risk themselves in addition to the risks from chronic ethanol use, liver function studies are helpful at baseline and then at 1, 3, and every 6 months thereafter.

Selective serotonin reuptake inhibitors have produced only modest drinking reductions—independent of antidepressant effects—at typical antidepressant doses, presumably through an anticraving effect, which may be more effective in patients with depression and early-onset type alcoholism.[46,47] These agents are gaining renewed interest as adjuncts to a comprehensive psychosocial recovery plan. If corroborated data indicate the existence of a comorbid psychiatric syndrome, and a treatment plan with expected good prognosis for abstinence can be put into place, studies support initiation of an SSRI antidepressant for co-occurring major depression, mood stabilizers for bipolar illness, buspirone for generalized anxiety, and third-generation antipsychotics for schizophreniform disease.[48]

The disposition of patients with an acute or chronic alcohol syndrome is clinically complicated and increasingly subject to economic pressures because of managed care. This requires multidimensional assessment to optimize the use of treatment resources.[49] The key dimensions of assessment are specified by the Patient Placement Criteria of the American Society of Addiction Medicine.[50] They include:

- Acute intoxication or withdrawal potential
- Biomedical conditions and complications
- Emotional and behavioral conditions or complications
- Treatment acceptance or resistance
- Relapse potential
- Recovery environment

These dimensions help determine both acute treatment needs and prognosis, and their use can inform the managed care review process as well.[51] All active problem areas among these dimensions must be addressed in the treatment plan to achieve a good likelihood of success.[52]

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15 Drug-Addicted Patients

John A. Renner, Jr., M.D.
Julie D. Ross, M.D., Ph.D.
David R. Gastfriend, M.D.

The number of patients treated for substance abuse–related problems in the United States has grown steadily in the last decade. In fact, between 1997 and 2002, the number of emergency department (ED) visits for drug-related events increased by more than 24%.[1] Clinical presentations in this domain are also becoming more complex. More than 55% of the drug-related problems seen in EDs in the first half of 2002 involved use of multiple drugs. In 37% of these cases, drug dependence was identified as the primary problem; 20% of the cases involved individuals seeking drug-induced psychic effects, and 20% involved suicide attempts. Successful treatment of this expanding group of patients requires that clinicians improve their skills in the management of substance-related problems. Although most physicians feel comfortable treating the symptoms of substance abuse, it has been our experience that they are historically reluctant to deal with the core disease process, and little effort is made to refer patients for substance abuse treatment. The chronic, relapsing nature of substance abuse inspires cynicism and resignation and is inappropriately thought to imply that substance abuse treatment is not helpful. Because most clinicians fail to appreciate that the relapse rate for other common chronic medical disorders (e.g., diabetes, hypertension, asthma) exceeds that for substance abuse disorders, they do not treat substance abuse patients with comparable therapeutic diligence.[2] The policy at the Massachusetts General Hospital (MGH) is to ensure that problems related to substance abuse are addressed with the same degree of compassion and persistence that is directed to other common relapsing medical disorders. This chapter contains material to aid clinicians in the prompt recognition and effective management of patients with drug-related problems. The treatment of concurrent medical and surgical problems should always be seen as an opportunity for intervention regarding the underlying substance abuse problem.

STIMULANTS

Cocaine Abuse

After alcohol, cocaine continues to be the leading drug of abuse in terms of the frequency of ED contacts, general hospital admissions, family violence, and other social problems. The Drug Abuse Warning Network ED data for 2006 reported 548,608 visits related to cocaine, compared with 577,521 alcohol-related visits.[3] Acute users experience intense euphoria that is often associated with heightened sexual desire and improved sexual function. These rewards are often followed by a moderate to severe post-cocaine depression that sets the stage for further cocaine use.

The signs and the symptoms of acute cocaine intoxication are similar to those of amphetamine abuse. Typical complaints associated with intoxication include anorexia, insomnia, anxiety, hyperactivity, and rapid speech and thought processes ("speeding"). Signs of adrenergic hyperactivity (e.g., hyperreflexia, tachycardia, diaphoresis, and dilated pupils responsive to light) may also be seen. More severe symptoms (e.g., hyperpyrexia, hypertension, and cocaine-induced vasospastic events such as stroke or myocardial infarction) are relatively rare among users but are fairly common in the ED. Patients may also manifest stereotyped movements of the mouth, face, or extremities. Snorting cocaine may produce rhinitis or sinusitis and, rarely, perforations of the nasal septum. "Crack" is a highly-addictive freebase form of cocaine that is sold in crystals; it can be smoked, and freebasing (i.e., inhaling cocaine alkaloid vapors) may produce bronchitis. Grand mal seizures are another infrequent complication of cocaine use. Patients also describe "snowlights" (i.e., flashes of light usually seen at the periphery of the visual field).

The most serious psychiatric sequelae associated with chronic cocaine use is a cocaine-induced psychosis (frequently manifested by visual and auditory hallucinations, paranoid delusions, and violent behavior). Tactile hallucinations, called "coke bugs," involve the perception that something is crawling under the skin. Cocaine-induced psychosis may be indistinguishable from amphetamine psychosis, but it is usually shorter in duration.

Management

Cocaine abusers can be seen in any medical or surgical setting. Cocaine abuse became common among affluent young people in the early to mid-1980s; however, with the availability of packaged, smokable cocaine, or crack, in low-cost doses, all classes and racial groups have become potential users. Occasional cocaine use does not require specific acute treatment, unless a life-threatening overdose has occurred. Most large doses are metabolized within 1 hour by enzymes in the blood and liver. While the patient is awaiting metabolism, intubation and assisted breathing with oxygen may be necessary. Stroke has been reported, and death can be caused by ventricular fibrillation or myocardial infarction. The cardiac status of a cocaine user should therefore be monitored closely. IV diazepam should be used to control convulsions.

Chronic cocaine use produces tolerance, severe psychological dependency, and physiologic dependence marked by irritability, anhedonia, low mood, and anxiety.[4] Many cocaine-dependent individuals follow a cyclical pattern of 2 or 3 days of heavy binge use, followed by a withdrawal "crash." Use is resumed in 3 or 4 days, depending on the availability of cash and the drug. A gradual reduction in use of cocaine is almost never possible. Detoxification is accomplished by the abrupt cessation of all cocaine use, usually through restricted access (e.g., incarceration, the loss of funds or contacts). Withdrawal symptoms begin to resolve within 7 days; specific medical treatments are rarely indicated. The value of medication for withdrawal symptoms has yet to be confirmed. Drugs that enhance central nervous system (CNS) catecholamine function may reduce craving, although they are of limited benefit clinically and have not been proven efficacious in double-blind, placebo-controlled trials. The major complication of withdrawal is a severe depression with suicidal ideation. If this occurs, the patient usually requires psychiatric hospitalization.

For the cocaine addict, the compulsion to use is overwhelming. We have seen some patients who continued dealing drugs from their hospital rooms after near-fatal injuries, and others who injected cocaine through a region of intensely painful cellulitis that occasioned the admission. For this reason, an actively using cocaine-dependent patient who has been hospitalized should have a drug screen performed after any behavioral change, particularly after receiving visitors or leaving the floor. The patient's urine should be examined for cocaine metabolites or, preferably, all drugs of abuse.

All cocaine abusers should also be referred for individual or group counseling; participation in twelve-step self-help programs should also be strongly recommended. Similarly, family members or significant others should be referred separately to Al-Anon because they may gain insights that may help them eliminate systemic support for the patient's further drug use. Manual-guided cognitive-behavioral therapy has been shown as efficacious in the treatment of cocaine dependence.[5] Once compulsive cocaine use has begun, it is almost impossible for the user to return to a pattern of occasional, controlled use. Such individuals are also likely to develop problems with alcohol and other drugs. For that reason the goal of treatment should be total abstinence from cocaine and all other drugs.

Amphetamine Abuse

Stricter federal controls on the production and distribution of amphetamines have greatly reduced the number of amphetamine abusers. Routine medical evaluation may uncover the most common type of amphetamine abuse seen in the inpatient setting. Historically, this involves a patient who began using amphetamines to control obesity and later became a chronic amphetamine abuser. The patient quickly develops tolerance and may use 100 mg or more daily in an unsuccessful effort to control weight. This amphetamine abuse can be treated by abruptly discontinuing use of the drug or by gradually tapering the dose, whichever is more acceptable to the patient. In either case, the patient should be shown a more appropriate program for weight control.

A more serious problem involves the patient who develops a severe psychological dependence on amphetamines and who may present the same symptoms that are seen in younger street-drug abusers. Amphetamine and methamphetamine (speed) accounted for 16,215 ED visits in the first half of 2002.[1] Among amphetamine users, the signs and symptoms of acute amphetamine intoxication are similar to those described in the section on cocaine abuse.

The other classic syndrome, seen in either acute or chronic amphetamine intoxication, is a paranoid psychosis without delirium. Although typically seen in youth who use IV methamphetamine hydrochloride, it can also occur in individuals who use dextroamphetamine or other amphetamines orally on a chronic basis. The paranoid psychosis may occur with or without other manifestations of amphetamine intoxication. The absence of disorientation distinguishes this condition from most other toxic psychoses. This syndrome is clinically indistinguishable from an acute schizophrenic episode of the paranoid type, and the correct diagnosis is often made only in retrospect, based on a history of amphetamine use and a urine test positive for amphetamines. Intramuscular (IM) haloperidol is effective in the acute management of this type of substance-induced psychosis.

Treatment

Amphetamines can be withdrawn abruptly. If the intoxication is mild, the patient's agitation should be handled by reassurance alone. The patient should be "talked down," much as one would handle an adverse reaction to D-lysergic acid diethylamide. If sedation is necessary, benzodiazepines are the drugs of choice. Phenothiazines should not be used because they may heighten dysphoria and increase the patient's agitation. Hypertension will usually respond to sedation with benzodiazepines. For severe hypertension, we recommend vasodilation through the use of phentolamine; β- or mixed α- and β-adrenergic blockers (e.g., propranolol, labetalol) should be avoided because they may exacerbate stimulant-induced cardiovascular toxicity.

Most signs of intoxication clear in 2 to 4 days. The major problem is appropriate psychiatric management of post-amphetamine depression. In mild cases this depression is manifested by lethargy and the temptation to use amphetamines to increase energy. In more serious cases the patient may become suicidal and require inpatient psychiatric treatment. The efficacy of antidepressants in such cases has not been adequately documented. Even with support and psychotherapy, most patients experience symptoms of depression for 3 to 6 months after the cessation of chronic amphetamine abuse.

CLUB DRUGS

In the 1980s and 1990s, there was a significant increase in the abuse of so-called club drugs, primarily 3,4-methylenedioxy-methamphetamine (MDMA; Ecstasy), γ-hydroxybutyrate (GHB), and ketamine. MDMA has both amphetamine-like and hallucinogenic effects. It was initially used experimentally to facilitate psychotherapy, but its use was banned after it was found to be neurotoxic in animals. At higher doses, it produces distorted perceptions, confusion, hypertension, hyperactivity, and potentially fatal hyperthermia. GHB (sodium oxybate) is a

CNS depressant that has been approved by the Food and Drug Administration (FDA) for the treatment of narcolepsy (Xyrem). In overdose it can produce coma and death; it has also been identified as a "date-rape" drug. Another agent, ketamine, has been used as an anesthetic; it can produce delirium, amnesia, and respiratory depression when abused. The treatment for overdoses of all these drugs is primarily symptomatic.

NARCOTICS

Heroin-related ED visits have steadily increased in the last decade. The abuse of narcotic analgesics, primarily oxycodone (OxyContin), almost doubled between 1997 and 2002.[1] In addition, more than 31% of acquired immunodeficiency syndrome (AIDS) cases in the United States are related to the use of injection drugs.[6] As a result, the treatment of opiate dependence is becoming commonplace on medical and surgical units. Proper management of such patients necessitates knowledge of FDA regulations, appropriate techniques for using opiate substitution therapy, and community treatment resources.

The classic signs of opiate withdrawal are easily recognized and usually begin 8 to 12 hours after the last dose. The patient generally admits the need for drugs and shows sweating, yawning, lacrimation, tremor, rhinorrhea, marked irritability, dilated pupils, and an increased respiratory rate. More severe signs of withdrawal (e.g., tachycardia, hypertension, nausea, vomiting, insomnia, abdominal cramps) occur 24 to 36 hours after the last dose. Untreated, the syndrome subsides in 5 to 10 days. Similar withdrawal symptoms are seen in patients addicted to methadone, but they may not appear until 24 to 30 hours after the last dose, and they abate over 2 to 4 weeks, owing to its longer half-life. Patients addicted to oxycodone may experience a particularly severe and prolonged withdrawal syndrome and may require high doses of opiates to achieve adequate control.

FDA regulations define opiate substitution therapy (either methadone or buprenorphine maintenance) as any treatment with an approved opiate that extends beyond 30 days. Methadone maintenance clinics may extend detoxification treatment from 30 to 180 days if the briefer detoxification program is not successful. Addicts cannot be placed in methadone maintenance programs unless they show physiologic evidence of current addiction (i.e., withdrawal signs) and can document a 1-year history of addiction. The only exceptions to this rule are pregnant addicts; addicts who are hospitalized for the treatment of a medical, surgical, or obstetrical condition; and formerly addicted individuals who have just been released from prison. Under these regulations, the physician has the option of providing opiate substitution therapy to any addict for the duration of the pregnancy or the period of hospitalization required to treat the primary illness. At MGH, we strongly recommend that such treatment be continued until the addict has fully recovered from the presenting illness and that the addict then be referred to a maintenance clinic or a program for detoxification treatment.

In addition to methadone, other options for opiate substitution therapy include buprenorphine, a long-acting partial opiate agonist. Buprenorphine attenuates withdrawal symptoms by partial activation of the opioid receptor, and it can be used in the treatment of addicts who meet *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition, criteria for opiate dependence. When dispensed in a sublingual tablet in combination with naloxone, it has minimal potential for IV abuse and has been demonstrated effective for maintenance treatment.[7] It has been approved for use in the office-based treatment of opiate dependence and provides an attractive alternative to methadone treatment for higher-functioning addicts and individuals with short-term histories of opiate dependence. L-a acetylmethadol (LAAM), a synthetic opiate with a duration of action of 48 to 72 hours, was once used for maintenance treatment of opiate dependence and was withdrawn from the U.S. market in 2003 after the FDA required a black box warning because of cardiac-related adverse events related to prolongation of the QTc interval. LAAM is no longer available as a treatment in the United States.

If a patient is actively participating in an opiate substitution program on admission to the hospital, the methadone or buprenorphine dose should be confirmed by inpatient staff and should not be changed without consultation with the outpatient physician responsible for the patient's treatment. Under no circumstances should such a patient be withdrawn from drugs unless there is full agreement among the patient, the hospital physician, and the outpatient clinic staff on this course of action. Such detoxification is rarely successful, particularly if the patient is under stress from a concurrent medical or surgical condition. Withdrawal from drugs may complicate the management of the primary illness. The option of detoxification should not be considered until the patient has fully recovered from the condition that necessitated hospitalization.

Patients on long-term opiate substitution therapy should continue daily oral methadone treatment while hospitalized. If parenteral medication is necessary, methadone can be given in IM doses of 5 or 10 mg every 8 hours. This regimen should keep the patient comfortable regardless of the previous oral dose. An alternative method is to give one third of the daily oral dose as an IM injection every 12 hours. As soon as oral medication can be tolerated, the original oral dose should be reinstated.[8]

Establishing the appropriate dose of methadone for a street addict is a trial-and-error process. Because the quality of street heroin is never certain, the addict's description of the size of the current habit is of minimal value. The safest guide to dosage is to monitor the patient's pulse, respiration, and pupil size ("The eyes never lie"). After the presence of withdrawal is documented, the patient should receive methadone 20 mg orally. Only if the patient is known to be a heavy user should the starting dose be as high as 30 mg. A relatively young patient or a patient who reports a small habit can begin treatment with 10 mg orally. If vital signs have not stabilized or if withdrawal signs reappear after 2 hours, an additional 5 or 10 mg can be given orally. It is rare to give more than 60 mg during the first 24 hours. Successful long-term outpatient maintenance treatment generally requires doses in the range of 60 to 120 mg, although lower doses may be adequate to control withdrawal symptoms in the hospital. Prolongation of the QTc interval has been shown to occur in patients treated with methadone either for opioid substitution therapy or

pain management. Torsades de pointes has been reported in patients treated with more than 300 mg of methadone per day. The risk for a cardiac arrhythmia is thought to be higher in patients with preexisting cardiac disease and in those taking multiple medications that may affect cardiac conduction. Such patients should be monitored with an electrocardiogram (ECG) before starting methadone or before any significant dose increase.[9]

CASE 1

A 17-year-old woman was admitted for an evaluation of fever of undetermined origin and associated epigastric distress. She requested large doses of methadone and claimed to have a heroin habit costing $200 per day. Further history revealed that she and her husband had been addicted for less than 3 months, and both were relatively naïve heroin users. After she began to show signs of opiate withdrawal, she was given methadone 10 mg orally; an additional 5 mg was given 10 hours later, when her respiratory rate was again noted to be more than 18 breaths per minute. The following day she remained comfortable after a single dose of 15 mg. Later it was discovered that she had regional enteritis. Given the short history of opiate abuse in this patient, she would likely be an appropriate candidate for office-based detoxification treatment with buprenorphine once her medical problems were stabilized.

Addicts should be maintained on a single daily oral dose that keeps them comfortable and keeps their heart rate and respiratory rate within the normal range. The dose should be reduced by 5 or 10 mg if the patient appears lethargic. If the street-drug addict is to be withdrawn from drugs immediately, the methadone dose can be reduced by 10% to 20% a day. If the drug habit has been maintained in the hospital for 2 or more weeks or if the patient has been using methadone before admission, detoxification should proceed more slowly. The dose can be reduced by 5 mg per day until 20 mg per day is reached. Further dosage reduction should occur more slowly if the patient is unable to tolerate the withdrawal symptoms. Clonidine, an α_2-adrenergic agonist, suppresses the autonomic symptoms of withdrawal and can be used as an alternative withdrawal medication. Clonidine should not be substituted for methadone until the methadone dose has been reduced to 20 mg per day. After an initial oral dose of 0.2 mg, patients usually require doses in the range of 0.1 to 0.2 mg every 4 hours. The total daily dose should not exceed 1.2 mg. Patients on clonidine should be monitored closely for side effects, particularly hypotension and sedation. In an inpatient setting, the clonidine dose can be reduced and discontinued over 3 to 4 days.[10,11] A transdermal clonidine patch is often applied on the third day. Supplemental doses of lorazepam can also be used to moderate withdrawal-related anxiety. Use of clonidine does not adequately suppress the subjective symptoms of withdrawal as does use of methadone and buprenorphine, and rates for successful completion of opiate detoxification with clonidine are almost 65% lower than those reported for buprenorphine.[12]

Buprenorphine has been efficacious for the short-term inpatient detoxification of opiate addicts. Patients can be stabilized using sublingual doses of 2 to 4 mg, and these doses can usually be tapered and discontinued over 2 to 4 days. An alternative protocol uses 0.3 to 0.6 mg of IM buprenorphine for 3 to 5 days, with a transdermal clonidine patch applied on the second day.[13] Addicts typically report that a buprenorphine detoxification is more comfortable than detoxification with either methadone or clonidine. Long-term buprenorphine treatment and maintenance, similar to the methadone model, has been more effective for long-term sobriety than have short-course detoxification protocols (as might be standard on inpatient dual-diagnosis units).[14]

Chances for successful withdrawal treatment are enhanced if the patient is aware of the dose and is able to choose the withdrawal schedule within limits established by the physician. By involving the patient in the treatment process and using a flexible withdrawal schedule, the physician can keep withdrawal symptoms to a tolerable level. Rigid adherence to a fixed dosing schedule is less likely to achieve success, and it may lead to premature termination of treatment.

Other less frequently used techniques permit rapid inpatient detoxification from opiates but require more intensive medical management. The addict is first stabilized on clonidine, as described previously. On the second treatment day, naltrexone 12.5 mg is added and then increased later that day and the following days up to a single dose of 150 mg by the fourth day. A supplemental benzodiazepine is also given for agitation and insomnia. At the end of 5 days, there are no further withdrawal symptoms and the patient can be discharged directly to an outpatient naltrexone program.[11,15] A more rapid experimental protocol using high doses of opiate antagonists given under general anesthesia permits completion of detoxification in 24 to 48 hours.[16] This approach has not been adequately evaluated in randomized clinical trials, and it cannot be recommended at this time.

Although techniques that permit a safe, rapid, and medically effective detoxification from opiates seem highly attractive in an era of managed care, clinicians must understand that detoxification alone is rarely successful as a treatment for any addiction. Unless opiate addicts are transferred to a long-term treatment program, relapse rates following detoxification are extremely high. The resulting costs to the patient, to society, and to the health care system far outweigh any savings realized from a rapid and supposedly cost-effective detoxification protocol.

Another common problem in the management of opiate-dependent patients is determining the appropriate dosage of an analgesic for patients receiving opiate substitution therapy.

CASE 2

A 28-year-old woman was hospitalized for the treatment of acute renal colic. Approximately 4 years earlier, she had been hospitalized for similar symptoms that subsided after she passed a kidney stone. During the year before her second hospitalization, the patient was in a maintenance program in which she received methadone 60 mg per day. She was doing well in treatment, and for the last 6 months was working regularly as a secretary. A psychiatrist was asked to see the patient because she was threatening to sign out of the

hospital. She claimed that she was not obtaining relief from her pain and that she wanted heroin to treat herself. The nurses described her as constantly complaining, demanding, and attempting to get additional doses of narcotics. A review of her chart revealed that she was receiving doses of morphine 5 mg, approximately half the usual analgesic dose in such situations, with strict orders not to repeat the dose sooner than every 4 hours because of her history of drug abuse. Her physician assumed that she would require lower doses of morphine because she was taking methadone.

After the consultation the physician accepted the psychiatrist's recommendation that the usual dose of morphine 10 mg be given every 2 hours as circumstances required because the patient would probably metabolize any narcotic more rapidly than normal. This regimen effectively controlled the patient's pain, and she suddenly became more cooperative. There was no recurrence of behavior that had been interpreted as manipulative or any other management problems. She passed several renal stones 2 days later and was discharged. Her physician had not realized that her so-called demands and manipulations were legitimate requests for effective analgesia.

The analgesic effect of methadone is minimal in maintenance patients, and, at best, it lasts only 6 to 8 hours. If pain control is required, addicts should be given standard doses of other narcotics in addition to methadone. Because of cross-tolerance, a patient on maintenance narcotic therapy metabolizes other narcotics more rapidly and may require more frequent administration of analgesics than might a nonaddicted patient. Pentazocine, buprenorphine, and other partial opiate agonists–antagonists are contraindicated for such patients. Because of their action at the opioid receptor, these analgesics produce withdrawal symptoms in regular users. If a patient on the buprenorphine–naloxone combination tablet requires additional narcotic analgesia treatment, he or she can be given supplemental opioids. However, higher-than-usual narcotic doses will be required to overcome the partial antagonist action of buprenorphine. Alternatively, such a patient can be switched to methadone and managed as described previously.

Opiate overdoses are treated with 0.4 mg/ml of IV or IM naloxone. Naloxone doses can be repeated every 2 minutes, as needed, up to a total dose of 1 to 2 mg. Patients who do not respond after 20 minutes should be treated for a combined drug overdose. Because of the long duration of action of methadone, overdoses of this drug often require an IV naloxone drip.

Discharge planning should be initiated as quickly as possible after admission. For patients who are not already in treatment, several weeks may be required to arrange admission to a drug-free residential program or an opiate substitution therapy program. Because a serious illness usually causes an addict to reexamine his or her behavior and possibly choose rehabilitation, the physician in the general hospital should emphasize the need for long-term treatment while the hospitalization is still fresh in the patient's mind. No patient should be discharged while still receiving methadone unless he or she is returning to a maintenance program or specifically refuses detoxification. Even when a physician discharges a patient for disciplinary reasons, medical ethics necessitate that the patient be withdrawn from methadone before discharge. Hospital physicians cannot legally prescribe methadone to maintain a habit or to withdraw from a habit on an outpatient basis.

BENZODIAZEPINES

Patterns of Chronic Use Versus Abuse

Benzodiazepines can produce dependence, especially when used in high doses for prolonged periods. Up to 45% of patients who receive stable, long-term doses show evidence of physiologic withdrawal. Withdrawal symptoms, which are usually the same in both high-dose and low-dose patients, include anxiety, insomnia, irritability, depression, tremor, nausea or vomiting, and anorexia. Seizures and psychotic reactions have also been reported in a few cases. The more common symptoms are similar to those seen during withdrawal from all the sedative–hypnotic drugs, and they may often be difficult to distinguish from the symptoms for which the benzodiazepine was originally prescribed. In general, withdrawal symptoms abate within 2 weeks.

Benzodiazepines with a rapid onset of action (e.g., diazepam, alprazolam) seem to be sought out by drug abusers and are generally presumed to have a greater potential for abuse than benzodiazepines with a slower onset of action (e.g., oxazepam). Nonetheless, there is relatively little evidence for the abuse of benzodiazepines when they are prescribed for legitimate medical conditions. Ciraulo and colleagues[17] found that the use of benzodiazepines, even among former alcoholics, was similar to that of other psychiatric patients. A study of alcoholics conducted at the Addiction Research Foundation of Ontario found that 40% were recent users of benzodiazepines and that there was a 20% lifetime incidence of anxiolytic abuse or dependence.[18] Although these studies suggest that concerns about the abuse of benzodiazepines by alcoholics may be exaggerated, the problem is real. Because some evidence suggests that benzodiazepine administration may increase the motivation of chronic alcoholics to drink, patients must be monitored carefully, and benzodiazepines should never be a first-line treatment in chronic alcoholics.[19]

It is important to distinguish between a drug abuser who uses benzodiazepines primarily to get high, often deliberately mixing them with alcohol and other drugs of abuse, and an individual who takes benzodiazepines appropriately under medical supervision. In both cases, the user may develop physiologic and psychological dependence. Such dependence, in and of itself, is not evidence of drug abuse. Unless there is evidence of dose escalation, deliberate use to produce a high, or a dangerous state of intoxication, there is no reason to assume that chronic benzodiazepine users are abusers. Even though clonazepam is the only benzodiazepine with an indication for long-term use, common medical practice supports the merit of the continued use of benzodiazepines in some individuals with chronic medical and psychiatric conditions.

CASE 3

A 68-year-old retired teacher was admitted for evaluation of severe gouty arthritis. His internist requested a psychiatric consultation regarding the management of long-term chlordiazepoxide use. The patient had been a heavy drinker before retirement, but he had been sober for the last 5 years. Approximately 2 years after becoming sober, he developed complaints of severe anxiety and was started on a regimen of chlordiazepoxide 25 mg three times per day. Two attempts had been made to reduce or eliminate the medication, but the anxiety symptoms returned. The patient expressed a strong desire for continued medication, and he became fearful that he might resume drinking. The symptoms were well controlled when regular treatment with chlordiazepoxide was resumed. After reviewing the case, the psychiatrist determined that the patient was dependent on the chlordiazepoxide but that there had been no escalation of dose or other signs of abuse. The medication continued to be effective in controlling his anxiety. The consultant recommended that he be continued on his current dose of chlordiazepoxide.

Overdose

Flumazenil, a specific benzodiazepine antagonist, reverses the life-threatening effects of a benzodiazepine overdose. An initial IV dose of 0.2 mg should be given over 30 seconds, followed by a second 0.2 mg IV dose if there is no response after 45 seconds. This procedure can be repeated at 1-minute intervals up to a cumulative dose of 5 mg. This treatment is contraindicated in individuals dependent on benzodiazepines (after long-term use) or those taking tricyclic antidepressants because flumazenil may precipitate seizures in these patients.[20,21] When flumazenil is contraindicated, benzodiazepine overdoses should be handled similarly to other sedative–hypnotic overdoses (see next section).

Withdrawal

When clear evidence of benzodiazepine abuse exists or when the patient desires to stop use of these medications, it is important that detoxification occur under medical supervision. During the withdrawal process, patients should be warned to expect a temporary increase in anxiety symptoms. The simplest approach to detoxification is a gradual reduction in dose that may be extended over several weeks or months. When a more rapid inpatient detoxification is desired, dosage reduction can be completed within 2 weeks. For some patients, this rapid withdrawal process produces an unacceptable level of subjective distress. An alternate approach is to switch to a high-potency, long-acting benzodiazepine such as clonazepam. Most patients seem to tolerate detoxification on clonazepam quite well. Because of the prolonged self-taper during detoxification, patients experience a smoother course of withdrawal with a minimum of rebound anxiety.[22,23]

Withdrawal from high-potency, short-acting benzodiazepines (e.g., alprazolam) has been particularly problematic. A rapid tapering of these drugs is often poorly tolerated by patients, and a switch to equivalent doses of a long-acting benzodiazepine may mitigate acute withdrawal symptoms. We recommend that clonazepam be substituted for alprazolam, at a dose ratio of 0.5 mg of clonazepam for each 1 mg of alprazolam. Clonazepam should then be continued for 1 to 3 weeks. A drug taper is not always required, although abrupt discontinuation of even a long-acting agent, such as clonazepam, can be associated with a withdrawal syndrome that includes seizures. Adverse events tend to occur several days after discontinuation, and a 2- to 3-week taper is usually adequate.

Supplemental medication is of little use during benzodiazepine withdrawal; β-adrenergic blockers (propranolol) and α-adrenergic agonists (clonidine) offer no advantage over detoxification using benzodiazepines alone. Although they tend to moderate the severity of physiologic symptoms, they are ineffective in controlling the subjective sense of anxiety, and they do not prevent withdrawal seizures. Buspirone has no cross-tolerance for the benzodiazepines and does not control withdrawal symptoms from this class of drugs.

SEDATIVE–HYPNOTICS

Abuse

Use of CNS depressants accounts for high rates of ED visits related to suicide attempts and accidental overdoses (consequent to recreational use and self-medication). Although benzodiazepines have become the most commonly abused sedative–hypnotic in the United States, there are still areas where the nonmedical use of barbiturates, such as butalbital (Fiorinal and Esgic), and carisoprodol (Soma), and other sedative–hypnotics (e.g., methaqualone, glutethimide) causes serious clinical problems.

A person intoxicated by other CNS depressants typically presents with many of the same diagnostic problems that are associated with alcohol intoxication. Slurred speech, unsteady gait, and sustained vertical or horizontal nystagmus, or both, that occur in the absence of the odor of alcohol on the breath suggest the diagnosis. Unfortunately, drug abusers frequently combine alcohol with other sedative–hypnotic drugs. The clinician may be misled by the odor of alcohol. The diagnosis of mixed alcohol–barbiturate intoxication can be missed unless a careful history is taken and blood and urine samples are analyzed for toxic drugs. The behavioral effects of barbiturate intoxication can vary widely, even in the same person, and may change significantly depending on the surroundings and on the expectations of the user. Individuals using barbiturates primarily to control anxiety or stress may appear sleepy or mildly confused as a result of an overdose. In those seeking to get high, however, a similar dose may produce excitement, loud and boisterous behavior, and loss of inhibitions. The aggressive and even violent behavior commonly associated with alcohol intoxication may follow. The prescribed regimen for managing an angry alcoholic can also be used for the disinhibited sedative–hypnotic abuser.

As tolerance to barbiturates develops, there is not a concomitant increase in the lethal dose, as occurs in opiate dependence. Although the opiate addict may be able to double the regular dose and still avoid fatal respiratory depression, as little as a 10% to 25% increase over the usual daily dosage may be fatal to the barbiturate addict whose

tolerance has narrowed the therapeutic window. Thus a barbiturate overdose should always be considered potentially life-threatening, especially for a drug abuser.

In overdose a variety of signs and symptoms may be observed, depending on the drug or the combination of the drugs used; the amount of time since ingestion; and the presence of complicating medical conditions (e.g., pneumonia, hepatitis, diabetes, heart disease, renal failure, head injury). Initially the patient appears lethargic or semicomatose. The pulse rate is slow, but other vital functions are normal. As the level of intoxication increases, the patient becomes unresponsive to painful stimuli, reflexes disappear, and there is a gradual depression of the rate of respiration; eventually, cardiovascular collapse ensues. Pupillary size is not changed by barbiturate intoxication, but secondary anoxia may cause fixed, dilated pupils. In persons who have adequate respiratory function, pinpoint pupils usually indicate an opiate overdose or the combined ingestion of barbiturates and opiates. Such patients should be observed carefully for increased lethargy and progressive respiratory depression. Appropriate measures for treating overdoses should be instituted as necessary. Patients should not be left unattended until all signs of intoxication have cleared.

Because there is no cross-tolerance between narcotics and barbiturates, patients receiving methadone maintenance who continue to abuse sedative–hypnotics present special problems. If a barbiturate overdose is suspected, the methadone-treated patient should be given a narcotic antagonist to counteract any respiratory depression caused by methadone. We recommend naloxone hydrochloride (Narcan) 0.4 mg IM or IV because it is a pure narcotic antagonist and it has no respiratory depressant effect even in large doses. If the respiratory depression does not improve after treatment with naloxone, the patient should be treated for a pure barbiturate overdose. Supportive measures include maintenance of adequate airway, mechanical ventilation, alkalinization of the urine, correction of acid–base disorders, and diuresis with furosemide or mannitol. Severe overdose cases may require dialysis or charcoal resin hemoperfusion.[21]

Withdrawal

The sedative–hypnotic withdrawal syndrome can present a wide variety of symptoms (e.g., anxiety, insomnia, hyperreflexia, diaphoresis, nausea, vomiting, and sometimes delirium and convulsions). As a general rule, individuals who ingest secobarbital 600 to 800 mg daily for more than 45 days develop physiologic addiction and show symptoms after withdrawal. Minor withdrawal symptoms usually begin 24 to 36 hours after the last dose. Pulse and respiration rates are usually elevated, pupillary size is normal, and there may be postural hypotension. Fever may develop, and dangerous hyperpyrexia can occur in severe cases. Major withdrawal symptoms, such as convulsions and delirium, indicate addiction to large doses (secobarbital 900 mg or more daily).

Because of the danger of seizures, barbiturate withdrawal should be managed only on an inpatient basis. Grand mal seizures, if they occur, are usually seen between the third and seventh days, although some reported cases occurred as late as 14 days into a medically controlled detoxification. Withdrawal seizures are thought to be related to a rapid drop in the blood barbiturate level. Treatment therefore should be carefully controlled so that barbiturates are withdrawn gradually with minimal fluctuation in the blood level, which theoretically decreases the danger of seizures. Treatment with phenytoin does not reliably prevent seizures caused by barbiturate withdrawal.

Delirium occurs less frequently than do seizures; it rarely appears unless preceded by seizures. It usually begins between the fourth and sixth days of withdrawal and is characterized by both visual and auditory hallucinations, delusions, and fluctuating levels of consciousness. The presence of confusion, hyperreflexia, and fever helps distinguish this syndrome from schizophrenia and other non-toxin-related psychoses.

Treatment for Withdrawal

Several techniques are available for managing barbiturate withdrawal. The basic principle is to withdraw the drug from the addicting agent slowly to prevent seizures. First, the daily dosage that produces mild toxicity must be established. Because barbiturate addicts tend to underestimate their drug use, it is dangerous to accept the patient's history as completely accurate. Treatment should begin with an oral test dose of the short-acting barbiturate pentobarbital (200 mg). If no physical changes occur after 1 hour, the patient's habit probably exceeds 1200 mg of pentobarbital per day. If the patient shows only nystagmus and no other signs of intoxication, the habit is probably approximately 800 mg per day. Evidence of slurred speech and intoxication and no sleep suggests a habit of 400 to 600 mg per day. The patient can then be given the estimated daily requirement divided into four equal doses administered orally every 6 hours. Should signs of withdrawal appear, the estimated daily dosage can be increased by 25% following an additional IM dose of 200 mg of pentobarbital. After a daily dose that produces only mild toxicity has been established, phenobarbital is substituted for pentobarbital (30 mg phenobarbital equals 100 mg pentobarbital) and then withdrawn at a rate of 30 to 60 mg per day (Table 15–1).[24] An alternative method is to treat withdrawal symptoms orally with 30 to 60 mg phenobarbital hourly, as needed, for 2 to 7 days. After the patient has received similar 24-hour doses

TABLE 15–1 Equivalent Doses of Common Sedative–Hypnotics

GENERIC NAME	DOSE (mg)
Barbiturates	
Phenobarbital	30
Secobarbital	100
Pentobarbital	100
Benzodiazepines	
Alprazolam	1
Diazepam	10
Chlordiazepoxide	25
Lorazepam	2
Clonazepam	0.5-1
Others	
Meprobamate	400

for 2 consecutive days, the 24-hour stabilizing dose is given in divided doses (every 3 to 6 hours). A gradual taper is then instituted as described previously. At MGH, we recommend this latter method because the use of a long-acting barbiturate produces fewer variations in the blood barbiturate level and should produce a smoother withdrawal.

Inpatient Management and Referral

Sedative–hypnotic users, like many other substance users, can present a variety of psychological management problems. Effective treatment requires a thorough evaluation of the patient's psychiatric problems and the development of long-term treatment plans before discharge. Treatment for withdrawal or overdose presents an opportunity for effective intervention in the patient's self-destructive lifestyle. Patients who abuse drugs have a reputation for deceit, manipulation, and hostility. They frequently sign out against medical advice. It is rarely acknowledged that these problems are sometimes caused by clinicians who fail to give appropriate attention to the patient's psychological problems. Most of these difficulties can be eliminated by effective medical and psychiatric management. The patient's lack of cooperation and frequent demands for additional drugs are often the result of anxiety and the fear of withdrawal seizures. This anxiety is greatly relieved if the physician thoroughly explains the withdrawal procedure and assures the patient that the staff knows how to handle withdrawal and that adverse effects will not occur if the patient cooperates with a schedule of medically supervised withdrawal.

Physicians sometimes fail to realize that the patient's tough, demanding behavior is a defense against a strong sense of personal inadequacy and a fear of rejection. Addicts have been conditioned to expect rejection and hostility from medical personnel. The trust and cooperation necessary for successful treatment cannot be established unless physicians show by their behavior that they are both genuinely concerned about the patient and medically competent to treat withdrawal. Physicians can expect an initial period of defensive hostility and testing behavior and should not take this behavior personally. Patients need to be reassured that their physician is concerned about them.

If the patient manifests signs of a character disorder and has a history of severe drug abuse, the setting of firm limits is necessary to ensure successful detoxification. Visitors must be limited to those individuals of known reliability. This may mean excluding spouses and other relatives. Urine should be monitored periodically for illicit drug use. Family counseling should be started during hospitalization and should focus on the family's role in helping the patient develop a successful long-term treatment program. Hospital passes should not be granted until detoxification is completed; however, passes with staff members as escorts should be used as much as possible. An active program of recreational and physical therapy is necessary to keep young, easily bored patients occupied. Keys to successful inpatient treatment are summarized in Table 15–2.

The story of a 21-year-old man who was hospitalized after having a grand mal seizure illustrates several of the problems that may occur.

TABLE 15–2 Inpatient Management and Referral

KEYS TO SUCCESSFUL INPATIENT TREATMENT
Perform a psychiatric evaluation.
Develop a long-term treatment plan.
Demonstrate explicit concern and expertise.
Expect testing behavior.
Set appropriate limits.
Limit and monitor visitors.
Supervise passes.
Monitor urine for illicit drug use.
Encourage ward activities and recreation.
Initiate family–network therapy.
Treat with respect.

CASE 4

The son of an eminent attorney described several years of episodic barbiturate and alcohol use and admitted to 3 months of daily barbiturate use after dismissal from college for failing grades. Three days before the patient's seizure, his father discovered that he had been ingesting secobarbital tablets taken from the medicine cabinet. The patient agreed to stop using barbiturates but did not realize that he was addicted. After admission to the hospital, the patient became a management problem. He demanded additional medication and refused to obey hospital regulations. Twice he left the floor without permission, and on one occasion he returned obviously high. A discussion with his physician turned into an angry shouting match. The patient denied any unauthorized drug use and insisted that he be permitted to leave the unit. He threatened to file a lawsuit for violation of his civil rights. When seen by the psychiatric consultant, the patient was hostile and provocative. He denied having any psychiatric problems and suggested that his physician was trying to have him committed to a psychiatric hospital.

The patient's hostility disappeared after the psychiatrist indicated that he had no interest in committing him but was concerned that his arguments with his physician and the nurses were interfering with his medical treatment. Once reassured that the psychiatrist did not think he was crazy, he admitted his fear of having more seizures. He did not know what to expect during detoxification and was too frightened to admit his fears to his physician. He finally admitted that he was meeting friends in the hospital cafeteria and they were giving him additional drugs. A meeting was then arranged between the patient and his physician. The physician explained the detoxification procedure in detail, including possible causes of seizures and the need for diagnostic tests. The patient was relieved to receive this information and readily agreed to appropriate limitations on visitors and hospital passes. The remainder of his hospitalization passed without incident, and he agreed to continue seeing the physician after his discharge.

Because treatment for detoxification or an overdose rarely cures an addict, referrals for long-term outpatient or residential care should be made early in the treatment process. Ideally, the patient should meet the future therapist before discharge. Alcoholics Anonymous and Narcotics Anonymous are useful adjuncts to any outpatient treatment

TABLE 15–3 Equivalent Doses of Narcotic Pain Medications

GENERIC NAME	DOSE (mg)
Morphine	10
Oxycodone (Percocet, OxyContin)	5-10
Hydrocodone (Vicodin, Lortab)	10
Meperidine (Demerol)	100
Hydromorphone (Dilaudid)	2.5
Methadone	5
Heroin	10

program. If transferring to a halfway house or residential program, the patient should move there directly from the hospital. Addicts are not likely to execute plans for follow-up care without strong encouragement and support.

MIXED-DRUG ADDICTION

Increasing numbers of patients are addicted to varying combinations of drugs, including benzodiazepines, cocaine, alcohol, and opiates. Accurate diagnosis is difficult because of confusing, inconsistent physical findings and unreliable histories. Blood and urine tests for drugs are required to confirm the diagnosis. A patient who is addicted to both opiates and sedative–hypnotics should be maintained on methadone while the barbiturate or other sedative–hypnotic is withdrawn. Then methadone can be withdrawn in the usual manner. Dose equivalents of narcotics are provided in Table 15–3.

Behavioral problems should be dealt with as previously described. Firm limit-setting is essential to the success of any effective psychological treatment program. Some patients who overdose or have medical problems secondary to drug abuse, such as subacute bacterial endocarditis and hepatitis, are not physiologically addicted to any drug despite a history of multiple-drug abuse. Their drug abuse behavior is usually associated with severe psychopathology. These patients should receive a thorough psychiatric evaluation and may require long-term treatment.

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16 Functional Somatic Symptoms, Deception Syndromes, and Somatoform Disorders

Ilana M. Braun, M.D.
Donna B. Greenberg, M.D.
Felicia A. Smith, M.D.
Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.

Called by Lipowski[1] "the borderland between medicine and psychiatry," somatization presents an important challenge to psychiatrists. It is defined as experiencing and reporting of physical symptoms for which there are no discoverable organic causes. Kellner[2] noted that 60% to 80% of the general nonpatient population experiences one or more somatic symptoms in any given week and that, when a patient approaches a physician with a somatic complaint, no organic cause can be found between 20% and 84% of the time. The most common somatic symptoms include palpitations, chest pain, headache, fatigue, and dizziness. For patients with functional symptoms, the strategy of pursuing a medical cause with invasive diagnostic procedures, unnecessary surgeries, and misdirected drug trials can be life-threatening, and the unwarranted costs of these measures strain limited medical resources.

The approach to patients with a host of unexplained symptoms must be thorough and include: taking a history (medical, psychiatric, psychosocial, and family), performing a physical examination, listing current medications, and obtaining appropriate laboratory tests. Because symptoms can occur in the context of serious medical illness, a systematic differential diagnostic approach is required; one of the first questions asked by a clinician should be "What organic disease could account for these symptoms?" Reading both the current and often formidable old medical records is indispensable. A psychiatrist may be the first clinician to diagnose a physical disease because the patient's personality, behavior, affect, or odd cognition has distracted the primary physician and other consultants from the task at hand. Table 16–1 lists diagnoses likely to produce functional somatic complaints.

DIFFERENTIAL DIAGNOSIS OF FUNCTIONAL SOMATIC SYMPTOMS

Depressive Disorders

Somatoform disorders should not be the first consideration when evaluating a patient whose physical symptoms seem out of proportion to objective findings. Major depressive disorder (MDD) is far more commonly a source of physical findings. Indeed, 75% of primary care patients with MDD or panic disorder seek treatment from their physicians for exclusively somatic symptoms.[3,4] This is likely the case for several reasons. First, the vegetative symptoms of MDD are physical in nature; they include insomnia, fatigue, anorexia, and weight loss. Second, depressed patients report more functional somatic symptoms (aches and pains, constipation, dizziness, and the like) than do other patients. Among primary care patients in an American health maintenance organization,[5] disabling chronic pain was present in 41% of those with MDD compared to 10% of those without MDD. Those patients with both chronic pain and MDD tended to have more severe affective symptoms and a higher prevalence of panic disorder. Even across cultures, the majority of patients with MDD spontaneously report only somatic symptoms; when pressed, however, 89% will also offer psychological symptoms.[6]

When MDD is diagnosed in the context of unexplained bodily complaints, depression should be treated promptly. Ordinarily both affective and somatic symptoms abate with psychological treatment, although, as shall be discussed, sometimes only the mood improves, leaving functional somatic symptoms still to be managed. (For further coverage of affective disorders, see Chapter 9.)

Anxiety Disorders

Anxiety frequently co-occurs with functional somatic symptoms, distorting the cognitive appraisal of somatic symptoms and making even benign bodily sensations seem ominous and alarming. Anxious patients tend to catastrophize normal physiologic sensations and ailments. As noted in Chapter 13, many of the symptoms of panic disorder are somatic; they include dyspnea, palpitations, chest pain, choking, dizziness, paresthesias, hot and cold flashes, sweating, faintness, and trembling. As a result, patients in the midst of a panic attack may fear that they are unable to breathe or that they are dying. Panic disorder is far more prevalent among patients with medically unexplained symptoms than was once thought (especially in cardiology,

TABLE 16–1 Differential Diagnosis of Functional Somatic Symptoms

Physical Disease
Axis I Disorders
Depressive disorders
Anxiety disorders
Substance abuse disorders
Psychotic disorders
Organic mental disorders
Voluntary symptom production
Malingering
Factitious disorders
Somatoform disorders
Personality Disorders (Axis II)
Antisocial
Avoidant
Borderline
Dependent
Histrionic
Narcissistic
Obsessive–compulsive
Paranoid
Schizoid
Schizotypal

gastroenterology, and neurology practices).[7] Anxiety is also one of the most common features of MDD.[8]

When co-morbid with pain, anxiety can lower the pain threshold dramatically. In fact, some patients cannot distinguish anxiety from pain ("No, I am not frightened; I hurt!"). Health care providers must be on guard against mistakenly attributing the marked discrepancy between pain complaints and objective findings to other conditions, for instance drug abuse or a personality disorder (see later).

Substance Abuse Disorders

Physicians should always consider the diagnosis of alcohol abuse in a patient with multiple, vague somatic symptoms. Whether the patient consciously conceals alcohol dependency or fails to make the connection, the diagnosis may be elusive. Information from the patient's family may help ("What he calls headache and chest pains, Doctor, I call a hangover."). Because alcohol abuse systematically disrupts sleep, patients may begin using sedative–hypnotic substances as well. Insomnia, morning cough, pains in the extremities, dysesthesias, palpitations, headache, gastrointestinal (GI) symptoms, fatigue, bruises—none are strangers to the alcoholic. The effects of other addictive drugs may be similarly confounding. (See Chapters 14 and 15 for the diagnosis and treatment of substance abuse disorders.)

Psychotic Disorders

Patients with psychotic depression may have somatic delusions (such as the conviction that one's abdominal organs are decomposing). Such patients are much more likely to be misdiagnosed as having schizophrenia than a physical illness. The somatic delusions of schizophrenia are generally so bizarre and idiosyncratic (e.g., that foreign bodies are inside an organ or orifice, or that body parts are missing or deformed) as to be easily recognized. But when a patient with schizophrenia complains of a functional symptom that is not of delusional proportions (e.g., a headache or weakness), psychosis may be missed. Making such a diagnosis with a thorough psychiatric history and examination is ordinarily no problem. Patients with schizophrenia can also have conversion symptoms (e.g., hemiparesis). In such a case, the proper diagnosis is of a conversion symptom in a patient with schizophrenia, not "conversion disorder."

Organic Mental Disorders

Somatizing cannot be localized to either a specific brain structure or a particular neurotransmitter system; however, patients with organic brain disease can have functional somatic complaints. The clinician's careful examination will detect cognitive dysfunction that may have gone unnoticed.

Personality Disorders

Although included in the differential diagnostic list of Table 16–1, personality disorders do not "cause" functional somatic symptoms. Rather, for the patient with an Axis II disturbance, the somatic symptom is a means to an end. For the individual with an antisocial personality, pain may be a means to get narcotics, to get out of work, or to escape trial. For the person with a dependent personality, functional weakness gains the attention and nurturance of others.[9] The borderline patient's somatic symptoms can become the focus for physicians and nurses, who may engage in a sadomasochistic struggle with the patient. The process begins with a helping relationship and ends with the rejection of a disappointed and outraged patient accused of wrongdoing. The "end" for this patient is the emotionally charged (usually hostile) relationship, and the failure to palliate the symptoms means to the patient that the physician simply does not care enough. Sometimes symptoms are reinforced by personality styles. Somatic symptoms are exaggerated by patients with a histrionic personality and may be the object of such intense fixations by those with compulsive, paranoid, schizotypal, and schizoid personalities as to make these patients take on a hypochondriacal character.

Factitious Disorders

Factitious illness is also on the differential of functional somatic symptoms. It is a complicated disorder that is marked by the conscious production of symptoms without clear secondary gain beyond assumption of the sick role; in fact, these patients often put their health at considerable risk. They may fake, exaggerate, intentionally worsen, or simply create symptoms. They do not admit to self-harm, but rather hide it from their doctors. The paradox, then, is that those with factitious illness come to health care providers requesting help, but intentionally hide the self-induced cause of their illness.

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) describes three subtypes of factitious disorder: that with predominantly physical signs and symptoms, with predominantly psychological signs and symptoms, and with combined psychological and

physical signs and symptoms. Finally, factitious disorders not otherwise specified (NOS) includes the notable example of factitious disorder by proxy, or Munchausen syndrome by proxy (see later).

In *factitious disorder with predominantly physical signs and symptoms*, the most common presentation is that of a general medical condition. Examples of faked clinical problems run the gamut from fever, bleeding, hypoglycemia, and seizures, to more elaborate productions of cancers and infection with the human immunodeficiency virus (HIV).[10–14] Whereas the term *Munchausen syndrome* is often used interchangeably with the physical type of factitious disorder, the classic Munchausen syndrome is reserved for the most severe and chronic form of the disorder, which is marked by the following three components: recurrent hospitalizations, travel from hospital to hospital (peregrination), and *pseudologia fantastica*.[14] Pseudologia fantastica is the production of intricate and colorful stories or fantasies associated with the patient's presentation. It is a form of pathological lying characterized by an overlapping of fact and fiction (with a repetitive quality, grandiosity, or an assumption of the victim role by the storyteller).[15] In some cases, it may be difficult to determine whether these lies are delusions or conscious deceptions. Munchausen patients often make a career out of their illness. Serial hospitalizations render employment or sustained interpersonal relationships impossible. Moreover, patients who produce significant self-trauma or develop untoward complications from medical or surgical interventions become further incapacitated. The prognosis is generally poor in these cases, and patients may die prematurely from complications of their own self-injurious behavior or from iatrogenesis.

Whereas Munchausen syndrome is the most dramatic form of factitious illness, *common factitious disorder* is more frequently encountered.[15] As opposed to those with Munchausen syndrome, patients with common factitious disorder do not typically use aliases or travel from hospital to hospital, but rather frequent the same physician. They are well known in their health care system because of numerous hospitalizations. They still misrepresent symptoms and feign illness, but are not as prone to pseudologia fantastica. Although conflicting data exist with regard to whether factitious disorders are more common in males or females, some suggest that common factitious disorder is more prevalent in women. Other risk factors include being unmarried, being in one's thirties, having experience in the health care profession, and having a cluster B personality disorder. Munchausen syndrome, on the other hand, may be more frequently seen in men in their forties who are single and have antisocial traits.[15] The co-morbidity with personality disorders may result from a rigid defensive structure, poor identity formation, and prominent dependency needs.[16]

Typical hospitalizations for those who feign medical illness share common characteristics. First, patients often come to emergency departments (EDs) after hours (at night or on the weekend), when it is less likely that medical personnel familiar with their cases are available. Patients use medical jargon and generally know what diagnoses or conditions will merit hospitalization. Their histories are often quite dramatic and convincing, and such patients persuade their physicians to provide care by appealing to narcissistic qualities, such as omnipotence. Once hospitalized, treatments are marked by demands for specific interventions (e.g., surgery or particular medications) and by increasing needs for attention. When the demands are not met, patients become angry and may accuse staff of misdiagnosis and mistreatment. If staff uncovers the deception, strong countertransference feelings of hatred ensue. Patients are then rapidly discharged or elope from the hospital only to seek "treatment" at another facility soon thereafter.

The types of physical symptoms and diseases that have been faked are limited only by the imagination of those who feign them. Table 16–2 lists some common categories. Modern day laboratory tests and diagnostic modalities may be particularly useful in distinguishing factitious symptoms from true medical illness. For example, in the case of suspicious infection, polymicrobial culture results that indicate an uncommon source (e.g., from urine or feces) is highly suggestive. Those who inject insulin to produce hypoglycemia will have a low C-peptide level on laboratory analysis, whereas glyburide can be measured in the urine of those suspected of taking oral hypoglycemics. Laxative abuse to cause ongoing diarrhea is confirmed by testing for phenolphthalein in the stool.[17] Finally, diagnostic studies in cases of suspected thyrotoxicosis (from surreptitious ingestion of thyroid hormone) reveal elevated serum total or free thyroid hormone levels, undetectable serum thyrotropin levels, low serum thyroglobulin concentration, normal urinary iodine excretion, suppressed thyroidal radioactive iodine uptake (RAIU), absence of goiter, and absence of circulating antithyroid antibodies.[18]

Detection of other types of physical factitious illness may require more astute physical examinations or observational skills (not to mention catching the patient "in

TABLE 16–2 Typical Clinical Presentation of Factitious Disorder

TYPE	CLINICAL FINDINGS OR SYMPTOMS
Acute abdominal (laparotomaphilia migrans)	Abdominal pain; multiple surgeries may lead to true adhesions and subsequent bowel obstruction
Neurologic (neurologic diabolica)	Headache, loss of consciousness, seizure
Hematological	Anemia from bloodletting or use of an anticoagulant
Endocrinological	Hypoglycemia from exogenous insulin; hyperthyroidism from exogenous thyroid hormone
Cardiac	Chest pain or arrhythmia
Dermatologic (dermatitis autogenica)	Rash; skin erruptions
Febrile (hyperpyrexia figmentatica)	Thermometer manipulation to produce fever
Infectious	Wound infected with multiple organisms (often through fecal material)

Adapted from Viguera AC, Stern TA: Factitious disorders. In Stern TA, Herman JB, editors: *Massachusetts General Hospital psychiatry update and board preparation,* ed 2, New York, 2004, McGraw-Hill, pp 145-147.

the act"). For example, fever of unknown etiology may be caused by warming thermometers on light bulbs or radiators, or with a flame (though this is more difficult with the advent of the electronic thermometer). Hematuria may be produced by bloodletting from another body area (commonly from a finger prick) into the urine sample. Though finding suspicious cuts may be suggestive, direct observation may be the only way to prove factitious disorder in this instance. Likewise, with nonhealing wounds where self-excoriation or "picking" behavior is suspected, witnessing the act either directly or with the use of video monitoring is diagnostic. Of note, the latter brings up ethical considerations unless done with the consent of the patient. Finally, among the numerous other possible physical manifestations, those that rely on more subjective report (including joint or muscle pain, headache, renal colic, or abdominal pain) may be present for months or years before a factitious etiology is even considered, much less proven.

Although the majority of published cases of factitious disorder involve physical symptoms, some patients primarily feign psychological symptoms. Psychological complaints encompass a broad spectrum of symptoms (including depression, anxiety, psychosis, bereavement, dissociation, posttraumatic stress, and even homicidal ideation).[19–23] As with primarily physical symptomatology, separating the motive of playing the sick role from one of secondary gain (malingering) is difficult and often imperfect. In the case of factitious bereavement, for example, the patient may report a dramatic or recent loss of a child or other loved one with a display of emotion that invokes significant sympathy by medical treaters. When the truth is discovered, the reported deceased may either be still alive, have died long ago, or perhaps did not really play a major role in the patient's life.

Diagnostic Approach. As previously suggested, making the diagnosis of factitious illness is often difficult. However, there are several elements of a general strategic approach that may be helpful. When suspecting factitious illness as a cause for somatic symptoms, one should first obtain information from all pertinent collateral sources. These may include previous or current caregivers, family members, current and old medical records, and laboratory and diagnostic studies. Verification of the "facts" presented by the patient is critical. Next, one should look for historical elements suggestive of factitious disease. Some of these are outlined in Table 16–3. Recognition of typical presentations (including all of those outlined in Table 16–2) may provide further clues. When one is lucky enough to find medical paraphernalia or to observe the patient intentionally inducing his or her own symptoms, the diagnosis is assured. Of note, room and personal belonging searches without the patient's permission are controversial and, in many cases, considered an invasion of privacy. Before embarking on such an endeavor, it is prudent to consider the potential ramifications carefully and to seek legal counsel. There is no doubt, however, that in most cases the diagnosis relies on significant detective work based on a high level of suspicion.

True physical disorders (especially rare or unusual diseases with few objective findings) may mimic factitious disorders. It is essential to consider this possibility before prematurely diagnosing factitious illness. Somatization disorder (Briquet's syndrome) and conversion disorder (see later) may also be mistaken for factitious disorder. These diagnoses, however, are distinguished from factitious illness, in that their symptoms are not under voluntary control. Factitious illness may also be confused with malingering, in which symptoms are also intentionally feigned. Malingerers, however, produce symptoms for obvious secondary gain (often financial, legal, or drug seeking).

TABLE 16–3 Historical Elements Suggestive of Factitious Disorder and Malingering

Factitious Disorder
Multiple hospital admissions—"hospital shopping" or peregrination
Many forms of identification or hospital numbers under various names
Ease with medical jargon
Current or prior employment in a medically related field
Lack of verifiable history
Few interpersonal relationships
Early history of chronic illness
Unexplained physical findings, multiple scars, or both
Failure to respond to typical treatments
Co-morbid personality or substance abuse disorders
Malingering
Legal involvement (e.g., the patient is referred for examination by an attorney)
A significant discrepancy between objective findings and reported symptoms or disability
A failure to cooperate with the evaluation or prescribed treatment
The presence of an antisocial personality disorder

From American Psychiatric Association: *Diagnostic and statistical manual of mental disorders, fourth edition, text revision*, Washington, DC, 2000, American Psychiatric Association.

Treatment Approach. No specific psychiatric treatment has been shown to be effective in the management of factitious disorders. There are, however, a few principles that generally prove helpful. The first is to avoid confrontation, especially when making the diagnosis. Direct confrontation or accusation often results in defensiveness, increased elusiveness, or flight from the hospital. Moreover, confrontation appears to be ineffective in most patients; few of them actually admit to their deception.[12] Interventions that allow the patient to save face (which require significant skill to carry out) may be effective.[24] Being aware of negative countertransference is also essential if one is to avoid being judgmental or acting on the hostility so often evoked by these patients. Making an early diagnosis is one of the most important interventions, since an undiscovered diagnosis of factitious disorder exposes the patient to additional and potentially harmful interventions; avoiding iatrogenesis is a key element of treatment. Because this illness is often highly treatment-resistant, placing an emphasis on management over cure helps to reframe the treatment goals. Clear and open communication between the psychiatrist and medical and surgical colleagues is essential in this regard. Finally, legal interventions are sometimes prudent (and often

required), especially in cases of Munchausen syndrome by proxy, where children or the elderly are affected.

Factitious Disorder by Proxy

Factitious disorder not otherwise specified is reserved for disorders with factitious symptoms that do not meet criteria for factitious disorder. Factitious disorder by proxy, otherwise known as Munchausen syndrome by proxy, is perhaps the most notable of these and often presents as unexplained somatic symptoms. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) defines *factitious disorder by proxy* as "the intentional production or feigning of physical or psychological signs or symptoms in another person who is under the individual's care for the purpose of indirectly assuming the sick role."[25] The perpetrator in this case is most often the biological mother of a young child, although the elderly and those under the medical care of others are also at risk. The perpetrator deceives medical personnel by altering records, falsifying medical history, contaminating laboratory samples, or directly inducing injury or illness on the victim.[26] In a review of 451 cases of Munchausen syndrome by proxy, Sheridan found that victims are typically 4 years old or younger, with equal percentages of males and females. She further discovered that an average of 21.8 months elapsed between the onset of symptoms and diagnosis, and 6% of victims died.[27] Perhaps even more alarming is her finding that 61% of siblings had illnesses similar to those of the victims, and 25% of the victims' known siblings were dead.[27]

Much like general factitious disorder, the symptoms in factitious disorder by proxy are more commonly physical than psychological, and may involve any symptom within the scope of imagination. The most common presentations seem to be apnea, anorexia, feeding problems, diarrhea, and seizures.[27,28] These may be induced in a variety of ways, from smothering the child to feeding the child laxatives or ipecac. Perpetrators often have some medical training or exposure to the illness that affects the child (e.g., a mother who has a seizure disorder herself). Other clinical indicators or red flags include a patient who does not respond to appropriate treatments, symptoms that improve when the mother does not have access to the child, unexplained illnesses with other children in the family, a mother who becomes anxious when her child improves, or a mother who encourages invasive tests.[26]

As with all factitious illnesses, diagnosis may prove difficult unless one directly witnesses a perpetrator harming the victim. When the victim is a child or is elderly, both legal obligations and privacy rights may differ from those of a typical adult patient. This is particularly pertinent with regard to mandated reporting (which varies by state), as well as when video surveillance is proposed as a mechanism to uncover intentional harm. In general, whenever diagnostic or treatment strategies outside the usual standard of care are considered, it is best to consult with both professional medical and legal colleagues before undertaking them.

Treatment Approach

The first consideration once a diagnosis of Munchausen syndrome by proxy is made is that of protecting the victim. In many cases this means placing the child in a foster care situation (at least temporarily). Treatment then addresses both the victim and perpetrator. Although no effective treatment for victims has been established, it is generally thought that therapy to address co-morbid other psychiatric diagnoses is a good place to start. Therapy for perpetrators is generally the mainstay of treatment; however, because many perpetrators never admit to wrongdoing, this often proves difficult.

Malingering

The DSM-IV-TR describes malingering in the following manner: "The essential feature of malingering is the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution, or obtaining drugs. Under some circumstances, malingering may represent adaptive behavior, for example, feigning illness while a captive of the enemy during wartime."[25] Table 16–3 outlines clinical indicators suggestive of malingering. Patients always have a clearly definable goal or external motivation for their behavior (this differentiates malingering from factitious disorders). Though the prevalence of malingering is unknown, it is thought to be more common in men than women and is often co-morbid with antisocial personality disorder. Settings where these conditions intersect (e.g., prisons) likely see a higher incidence.

Malingerers most often pick symptoms that are highly subjective and difficult to prove (or disprove). Vague pains, such as headache, tooth pain, or back pain, are common. The goal may be to obtain narcotics or to be placed on disability from work. The presence of a lawsuit after a reported injury should also raise suspicion that the patient is malingering. As with factitious disorders, the primary symptomatology of malingering may also be psychological in nature. Malingerers may report symptoms of anxiety or depression, and try to convince the examiner of how much their function is impaired and how much they are bothered by the symptoms. The malingerer may say something like this: "My panic attacks come back every time I go to work. All I want to do is to be able to work, but the panic won't allow me to. Please help me, doc."

The presence of clearly identified secondary gain is not absolute evidence of malingering—one must be careful not to miss the diagnosis of a true medical condition in this population. When malingering is suspected, however, objective tests are crucial. When these are normal, psychological testing may be in order. The Minnesota Multiphasic Personality Inventory–2 (MMPI-2) may pick up distortions or exaggerations in both physical and psychological symptoms.[29] Direct confrontation is not advised because this often results in the patient becoming angry and fleeing from treatment. Strategies that allow the patient to save face, for instance, suggesting that the illness will improve soon, are generally more successful. Avoiding iatrogenesis and remaining aware of one's own anger toward the patient (so as not to act on it) are also keys to appropriate treatment.

Somatoform Disorders

The somatoform disorders are characterized by bodily symptoms that suggest a physical disorder, but for which there are no demonstrable organic causes or known

physiological mechanisms severe enough to result in significant distress or functional impairment; there is also a strong presumption that the symptoms are linked to psychological factors or to conflict.

Conversion Disorder

Conversion disorder is perhaps the classic somatoform disorder; it involves a loss or change in sensory or motor function that is suggestive of a physical disorder but that is caused by psychological factors. Common signs and symptoms include paralysis, aphonia, seizures, disturbances of gait and coordination, blindness, tunnel vision, and anesthesia. The primary evidence for the psychological cause consists of a temporal relationship between symptom onset and psychologically meaningful environmental precipitants or stressors. A patient who developed conversion blindness, for instance, may have seen her husband with another woman before she complained of being unable to see. The conversion symptom is not under voluntary control, although the patient may be able to modulate its severity. A patient with a functional gait disturbance or a weak arm, for example, may, with intense concentration, be able to demonstrate slightly better control or strength. DSM-IV has eliminated pain and sexual dysfunction as conversion symptoms. Reviewing conversion, Ford and Folks[30] recommended that it be considered a symptom rather than a primary diagnosis. In children with conversion symptoms, the gender ratio is equal; in adults, conversion is two to five times more common in women than men.

Predisposing factors are important considerations for both diagnosis and treatment. A prior medical illness is a common source for the symptom. If a viral illness is accompanied by vertigo while a patient is under stress, the illness may bring secondary benefits of attention and support from loved ones. At a later time, when stress recurs, the symptom of vertigo may develop again, this time as a conversion symptom. By definition, the symptom is not intentionally produced or feigned. It is presumed that the unconscious secondary benefit of the condition that alleviates conflict sustains the condition. Patients with seizures, especially complex partial seizures (in which consciousness is preserved), are repeatedly exposed to a phenomenon that removes them from responsibility, evokes sympathy, and brings help from a loved one. Pseudoseizures commonly co-exist with true seizures and can be exceedingly hard to discriminate, particularly when the electroencephalogram (EEG) fails to demonstrate spiking activity or shows only nonspecific slowing. Epileptic and nonepileptic seizures can be temporally related, and in patients with partial seizures, organic ictal changes may also facilitate the development of conversion symptoms.[31]

Preexisting psychopathology is another factor that predisposes to conversion symptoms. The most common Axis I disorders associated with conversion are depression, anxiety, and schizophrenia. Axis II personality disorders (especially histrionic, dependent, and what was formerly known as passive-aggressive personality disorders) are common in these patients.

Conversion symptoms may be precipitated by exposure to others with specific symptoms. Such "figures of identity" may be psychologically important people in the patient's life (such as a parent who has just died), or may be strangers whose symptoms the patient observes under extreme and sudden stress, as occurs in mass psychogenic illness ("epidemic hysteria"). Extreme psychosocial stress is likely the most important of all precipitating factors. Some authors have presented evidence for a predominance of conversion symptoms, when unilateral, and on the nondominant side in females.[32,33] More recently, the tendency for motor and sensory symptoms to occur on the nondominant left has been questioned.[34]

Often, confidence in the diagnosis is based on demonstration that function is normal in the symptomatic body part. Depending on the deficit being investigated, electromyograms (EMGs), evoked responses of vision and hearing, slit lamp examinations, funduscopic examinations, retinoscopic examinations, pulmonary function tests, and barium swallows should be normal. This negative evidence is critical and requires meticulous review by the clinician. Positive evidence includes not only the psychological data but also any demonstration of normal function in the supposedly disabled body part. Detective work begins with close observation of the patient, including during periods when the patient is unaware of the observer's presence. In part, one is trying to distinguish the presentation from that of the malingerer. If the patient moves his or her arm normally when unaware of being observed and displays a frail arm when watched, the patient is most likely malingering.

The diagnosis of conversion cannot rest comfortably only on the absence of organic disease. Caution in diagnosing conversion symptoms is based on early reports that 13% to 30% of those with this diagnosis went on to develop an organic condition that, in retrospect, was related to the original symptom.[35] The rate of misdiagnosis of conversion has dropped; a recent report revealed only 4% who were subsequently found to have a documented medical illness.[36]

Functional brain imaging has added another dimension to the study of patients with conversion disorder; there have been reports of functional neuroanatomical abnormalities in patients with conversion (i.e., sensorimotor loss).[37] Black and co-workers[38] have summarized the lessons from neuroimaging, suggesting that conversion results from dynamic reorganization of neural circuits that link volition, movement, and perception. Disruption of this network may occur at the stage of preconscious motor planning, modality-specific attention, or right frontoparietal networks subserving self-recognition and the affective correlate of selfhood.[38]

Conversion symptoms are usually sustained, but sometimes only for a certain activity. The patient who cannot lift his leg adequately in walking may be observed to cross it over his good one during conversation. Deviation of the eyes toward the ground, no matter which side the "semicomatose" patient lies on, is functional, and sometimes demonstrates lack of an organic disorder.[39] One may lead the patient with functional blindness around obstacles (e.g., chairs); the patient with conversion usually avoids them (a malingerer is more likely to bump into them). Carefully watching the "blind" patient's eyes and face while quietly taking a roll of money out of one's wallet, or suddenly menacing (being careful to avoid creating a draft or noise) or making a face at the patient is another way to assess vision. Sensory testing on the patient in both prone and supine positions checks for consistency. A malingerer is more likely to become hostile and uncooperative during the examination, probably in the hope of shortening it.

Prognosis and Treatment. The literature supports an optimistic outlook for these patients, at least in the first few years. Folks and co-workers[40] recorded a complete remission rate of 50% by discharge in those with conversion disorder in a general hospital. However, the long-term course is less favorable, because a sizable fraction of these patients develop recurrent conversion symptoms (20% to 25% within 1 year). Unilateral functional weakness or sensory disturbance diagnosed in hospitalized neurological patients persisted in more than 80% (of 42 patients over a median of 12.5 years).[41] Patients with one conversion symptom may also develop other forms of somatization or eventually meet criteria for somatization disorder.

The most common form of treatment is to suggest that the conversion symptom will gradually improve. This ordinarily begins with reassuring news that tests of the involved body system show no damage and therefore that recovery is certain. Predicting that recovery will be gradual, with specific suggestions (e.g., vague shapes will become visible first; weight bearing will be possible and then steps with a walker; standing up straight will come before full steadiness of gait; strength in squeezing a tennis ball will be followed by strength at the wrist and then elbow joints; and feeling will return to the toes first) usually succeeds, provided that the diagnosis is conveyed with serene confidence and the suggestions provided with supportive optimism. Lazare[35] pointed out that the psychiatrist should also discuss the patient's life stresses and try to detect painful affects to assess the nonverbal interpersonal communication embodied by the symptom.

Confrontation is seldom helpful. Patients are particularly sensitive to the idea that an authoritative person has dismissed their suffering; their anger and sensitivity may be based on a history of abuse or neglect. Stonnington and associates[42] suggested that the best context for discussion of the diagnosis of pseudoseizure comes after the patient and the family have agreed that key representative events have been captured by video EEG monitoring.

Some patients sense that there is a relationship between the stressful psychosocial conditions and the conversion symptomatology. An approach acceptable to some of these individuals has been to say that the body, mysterious in many ways, can be smarter than we are; it may tell us something is wrong before we realize we need help. When the stress in our lives becomes excessive, especially when our nature is more to overlook it or to grit our teeth and prevail, our body, by its symptoms, may blow the "time-out" whistle, forcing us to stop, to take a rest, and to get some help. This approach invites the patient to greater insight.

Further intervention may not be necessary. However, if the conversion symptom persists, if the precipitating stress is chronic, or if there is massive secondary gain, resolution of the situation becomes a target of the intervention. Because the stresses are often social, couples or family therapy may be instrumental in achieving a final resolution. Treatment, for instance, for nonepileptic seizures, should consider risk factors, including perpetuating and triggering events. Co-morbid psychiatric diagnoses should be treated. Behavioral interventions, physical therapy, and reassurance are crucial, particularly for less verbal patients.[42]

Some hospitalized patients fail to improve with suggestion. Because they occupy a nonpsychiatric bed, they must be told that if they insist that they are not well enough to leave the hospital, transfer to a psychiatric hospital or to a psychiatric unit will be arranged. Symptoms that have not responded to earlier suggestion may then improve sufficiently to permit discharge. One would have to entertain in such a patient the possibility that the correct diagnosis is malingering. In general, a favorable outcome depends more on the patient's psychological strengths and on the absence of other psychopathology than on the specific nature of the conversion symptom itself.

Somatoform Pain Disorder

The predominant feature of somatoform pain disorder (termed simply *pain disorder* in DSM-IV) is chronic, severe, and preoccupying pain that has no adequate medical explanation. Either there is no medical disease at all, or the patient's pain is grossly disproportionate to demonstrable histopathologic findings. The pain is severe enough to warrant clinical attention and to impair role function. It is constant and often inconsistent with known neuroanatomical innervation. Psychological factors must be judged to play a significant role in the precipitation, maintenance, or exacerbation of the pain, but it is neither intentionally produced nor feigned. Pain is the subject of Chapter 18. Patients with somatoform pain disorder are often severely disabled by their symptoms, live like invalids, and work infrequently. They have long histories of medical care and many surgical interventions. They are often completely preoccupied with their pain and view it as the sole source of all their difficulties. Depression is commonly co-morbid with somatoform pain disorder.

In practice, the problem is often that organic causes of pain cannot be completely disregarded. Co-morbid medical illness, concerns about neuropathic pain, myofascial pain, or an undiagnosed medical problem, challenge the diagnosis of the psychiatric disorder. Questions about substance abuse and personality disorder complicate the picture. A multiaxial record of the data related to a patient may help clarify the course, treatment effectiveness, and relative contributions of medical and psychiatric data. Mayou and associates[43] have suggested a method of somatoform classification that would include medical diagnoses, the presence or absence of depressive or anxiety disorder, history of narcotic use, health beliefs, illness behavior, stressors, and social benefits (e.g., disability payments or unemployment). Each parameter could be followed over time to shed light on the patient's condition.

Treatment. The spectrum of reactions of these patients is likely to mimic that for conversion and the same therapeutic approach is recommended: Provide reassurance that the body parts in question appear to be normal (or no worse) and then suggest that the pain will gradually subside. Some patients can accept their manifest need to resolve the stress that has been uncovered in psychiatric consultation (and can be told that it is worth working on even if it does not appear to be related to the pain). Results of psychological testing can be presented to them as helpful evidence of the existence of concerns in their subconscious or unconscious mind. The "wisdom" of their body in warning them about

their stress, by means of pain, may be helpful as well. Early treatment of patients with this disorder is usually limited to individual, marital, or family therapy. If it has continued for a longer time, multimodal, behavioral, and more comprehensive approaches (including relaxation response training and physical therapy) are indicated. Attention to triggers and perpetuating factors is important.

Somatization Disorder

Originally termed *hysteria* or *Briquet's syndrome* and now given the DSM-IV designation of *somatization disorder*, this condition has been solidly established as clinically and epidemiologically distinct. It is a chronic syndrome of multiple, recurring somatic symptoms that are not explainable medically and are associated with psychosocial distress and with medical help–seeking behaviors. The disorder is much more common in women as compared to men. It tends to occur in those of low socioeconomic status, often in non-Caucasians who live rurally, and has a 1-year prevalence rate of 0.3% in the general population.[44–46] Of first-degree female relatives, 10% to 20% suffer the same disorder, whereas male relatives show an increased incidence of alcoholism and sociopathy.[47]

Women with this disorder tend to have histories as children of missing, disturbed, or defective parents, and of sexual or physical abuse.[48–51] The tendency to somatization has been linked to childhood trauma via insecure attachment and maladaptive patterns of interpersonal communication in seeking care.[52,53]

These women marry sociopaths more often than chance would predict, and they tend to be poor parents themselves.[48–50] Given these unfortunate circumstances, and their roughly 75% chance of having one or more additional psychiatric diagnoses (the most common being an affective or anxiety disorder, or drug and alcohol abuse[54]), it is no surprise that marital discord and unsatisfactory work histories are also common.

DSM-IV diagnostic criteria include at least the following: four different pain symptoms (e.g., headache; back, joint, extremity, or chest pain; painful urination, intercourse, or menstruation); two GI symptoms (e.g., nausea, bloating, diarrhea, and food intolerance); one sexual symptom (e.g., menstrual symptoms, erectile or ejaculatory dysfunction, or sexual indifference); and one pseudoneurological symptom other than pain (e.g., deafness, paralysis, a lump in the throat, aphonia, fainting, anesthesias, or blindness). The symptoms must be disproportionate to demonstrable medical disease and severe enough to result in medical attention or significant role impairment.

The diagnostic symptoms are numerous and can be cumbersome for the busy clinician. Othmer and DeSouza[55] have addressed the first problem by developing an abbreviated list of seven symptoms that can be employed to screen for the disorder. If two or more of the symptoms in their clever mnemonic (Table 16–4) are present, there is a high likelihood of somatization disorder. The presence of three symptoms accurately identified 91% of the patients with somatization disorder with a sensitivity of 87% and a specificity of 95%. However, despite this list of symptoms, the clinical diagnosis almost always requires review of past records; these tend to be voluminous, scattered among a host of hospitals, lost, or a combination of the three. In the absence of the chart, contact with prior treating physicians or family members may help in establishing the symptom count. Notoriously poor historians, these patients will be unable to recall past admissions or clinic visits, and they will deny a history of a symptom that the chart lists as a chief complaint on a past visit.

TABLE 16–4 Seven-Symptom Screening Test for Somatization Disorder

MNEMONIC	SYMPTOM	SYSTEM
Somatization	Shortness of breath	Respiratory
*D*isorder	Dysmenorrhea	Female reproductive
*B*esets	Burning in sex organ	Psychosexual
*L*adies	Lump in throat (difficulty swallowing)	Pseudoneurologic
*A*nd	Amnesia	Pseudoneurologic
*V*exes	Vomiting	Gastrointestinal
*P*hysicians	Painful extremities	Skeletal muscle

From Othmer E, DeSouza C: A screening test for somatization disorder (hysteria), *Am J Psychiatry* 142:1146-1149, 1985.

During the interview, the patient usually presents complaints in a histrionic fashion ("Why I bled so much—I've never seen so much blood!!—that I passed out on the bed and my family said I was in a coma for 3 days!"), with symptoms so exaggerated that a psychogenic cause may be suspected from the outset. The other consistent trait these patients possess is a peculiar communication style. Histories are vague and details are either elusive or downright inconsistent. Efforts at clarification may be fruitless and frustrating. ("Is your pain worse in the morning?" "Yes, and it's worse in the afternoon, too.") Emotional distress is openly expressed ("I'm not getting *anywhere*, Doctor! No one can tell me anything! What's happening to me?"), but if one tries to identify the emotion, for example, telling the patient she seems very anxious, that emotion is more likely to intensify ("Well, wouldn't anybody be? It's been a whole month and nobody—nobody, Doctor—knows what's going on with me!"). This type of response tends to drive the physician back to a cognitive search—onset, duration, radiation, intensifying or relieving factors—only to encounter once again the fogbound and trackless waste of imprecision, inconsistency, and lapsing memory.

Contemporary medicine's shift from clinical to economic priorities has only heightened attention to somatization disorder. Smith and associates[56] have documented that the typical patient with this disorder spends an average of 7 days per month sick in bed (compared with 0.48 days for the average person), and accrues (mostly unnecessary) annual hospital care rates many times higher than those of the average person in the population between the ages of 15 and 64 years. This happens despite their remarkably stable clinical course, with a 90% probability of not developing a new medical or psychiatric disorder in the subsequent 6 to 8 years following diagnosis. New evidence suggests that somatizing patients experience functional disability and role impairment equal to or greater than that associated with many major, chronic medical conditions.[57]

Treatment. The management of somatization disorder has been well formulated by Murphy.[58] It is best carried out by primary care physicians (PCPs) according to a conservative plan based on being a consistent care provider, preventing unnecessary or dangerous medical procedures, and inquiring in a supportive manner about the areas of stress in the patient's life. The last occurs during the physical examination, without inferring that the real cause for the increase in the patient's somatic complaints is psychosocial stress (which is what most authors believe). The basic goal is to help the patient cope with the symptoms rather than to eliminate them completely. In short, the aim is palliation, rather than outright cure. Psychotropic medication and prescription analgesics generally are not very helpful, except when used to treat a clear-cut, co-morbid psychiatric condition, such as major depression or panic disorder.

Smith and associates[59] codified treatment recommendations in a letter to the PCPs of somatization disorder patients. These included regularly scheduled appointments (e.g., every 4 to 6 weeks); a physical examination performed at each visit to look for true disease; the avoidance of hospitalization, diagnostic procedures, surgery, and the use of laboratory assessments, unless clearly indicated; and advice to avoid telling patients, "It's all in your head." In a randomized controlled trial (RCT), this intervention reduced quarterly health care charges by 53%, largely as a result of decreases in hospitalization.[60] Neither the health of the patients nor their satisfaction with their care was adversely affected by implementation of the advice.

Cognitive-behavioral therapy (CBT), when compared to standard medical care, has also reduced symptoms, ratings of disorder by evaluators, and health care costs. The intervention focused on stress management, activity regulation, emotional awareness, cognitive restructuring, and interpersonal communication.[61]

Undifferentiated Somatoform Disorder

The diagnostic criteria for somatization disorder are quite restrictive, and most chronic somatizing patients in medical practice do not cross this stringent threshold. In an attempt to provide a diagnostic home for such patients, DSM-IV now includes the entity *undifferentiated somatoform disorder*. This diagnosis requires one or more physical symptoms that persist for at least 6 months and are medically unexplained. Several researchers, including Kroenke and co-workers[62] and Escobar and associates,[63,64] have sought to define a more inclusive entity that requires fewer somatic symptoms than are required for somatization disorder, but that nonetheless identifies patients who have the clinical and behavioral features characteristic of the disorder. Multi-somatoform disorder is based on current unexplained symptoms. It requires three or more unexplained symptoms within the past 2 weeks out of a list of 15, along with a 2-year history of somatization. Escobar's abridged somatization disorder is based on at least six lifetime unexplained symptoms in women and four in men. Multisomatoform disorder has a high concordance with somatization disorder and perhaps a more efficient diagnostic algorithm. It is less correlated with abridged somatization disorder, but all three diagnoses are associated with similar medical utilization rates and declining physical function over a year.[65]

Hypochondriasis

While extensive research has crystallized the concept of somatization disorder, the nosology of hypochondriasis remains more ambiguous. Concern about health is common, and the point at which preoccupation becomes pathological is not always clear. Hypochondriacal thinking may occur in the form of a primary disorder or as a nonspecific correlate of other Axis I illnesses, including affective and anxiety disorders. Tendencies to amplify benign, unpleasant symptoms and to misconstrue them as pathological have both trait-like and state-like properties. In a study of a military population, Noyes and colleagues[66] found that personality measures, mainly neuroticism, explained much of the variance in hypochondriacal concerns. Based on evidence such as this, some nosologists have argued that hypochondriasis is better thought of as a personality disorder to be denoted on Axis II.[67]

DSM-IV identifies the predominant feature of hypochondriasis as a preoccupation with the fear or belief that one has a serious, undiagnosed disease. This concern is based on a misinterpretation of benign physical signs and symptoms as evidence of disease. Other diagnostic criteria include the absence of a physical disorder that accounts for the patient's symptoms; persistence of the disease fear or belief despite appropriate medical reassurance; clinically significant distress or role impairment; and duration of at least 6 months. By this definition, hypochondriasis is quite prevalent. It is found in approximately 5% of medical outpatients and occurs equally between the genders.[68]

Fundamentally, hypochondriasis represents an overconcern about illness and a fearful attitude toward one's health. Afflicted patients are absorbed by their bodies and preoccupied with their symptoms. Their assessment of their health becomes both a way of reacting to life's stresses and demands, and a nonverbal language for communicating with others. Such inclinations and beliefs share similarities with those of the somatizer. The cognitive style of the typical hypochondriac is obsessive, whereas the cognitive style of the typical somatizer is histrionic.

The origins of hypochondriasis are not fully understood. Both genes and early upbringing may serve as conditioning factors. There is evidence, for instance, that hypochondriacal patients tend to amplify and augment somatic and visceral sensations more than nonhypochondriacal patients.[69,70] Predisposing events in childhood include disease in the patient or in a family member, and adversity, including neglectful and abusive parents.[71] Context also plays a role. The onset of the syndrome can be triggered by illness or by the death of a loved one.

Prognosis and Treatment. Hypochondriasis can be a chronic and disabling disease. Barsky and Ahern[72] note a time course of approximately 11 years in the group they studied; Kenyon[73] found that among hospitalized patients with hypochondriasis, only 20% were judged as recovered or much improved at the time of discharge, and twice that many were either unchanged or worse than on admission. There may be some room for optimism, however, particularly when the illness has lasted less than 3 years and is not co-morbid with a personality disorder.[74]

When confronted with hypochondriasis, a treater's first step should be to screen for co-morbid affective and anxiety disorders (including obsessive–compulsive disorder [OCD]). These are likely easier to treat, and their resolution may greatly diminish or bring an end to exaggerated disease fears. Isolated hypochondriasis is more difficult to cure. Although there have been a few reports suggesting a role for selective serotonin reuptake inhibitors (SSRIs).[75–77] the most successful psychiatric interventions for primary hypochondriasis are cognitive, behavioral, and educational.[78,79] Barsky and Ahern[72] have recently shown that the treatment combination of education of the PCP and time-limited CBT for the patient improves a range of hypochondriacal symptoms, with modest treatment effect. The manualized treatment for the patient targets cognitive and perceptual mechanisms of illness, including *hypervigilance* to visceral experience, *beliefs* about symptom etiology, *context* in which the hypochondriasis occurs, sick role *behaviors*, and *mood*.

Patients with hypochondriasis tax the general physician. Such patients are difficult to reassure; their care is both time-consuming and expensive; and they often provoke strong negative reactions in their frustrated providers.[73] Psychiatrists can be instrumental in easing anxieties and offering management recommendations. An internist's goals when treating a hypochondriacal patient should be threefold[78]: to avoid unnecessary diagnostic tests and to obviate overly aggressive medical and surgical intervention; to help a patient tolerate the symptoms, rather than striving to eliminate them; and to build a durable doctor–patient relationship based on the physician's interest in the patient as a person and not just in the symptoms. Once a physician views his or her task as palliative, not curative, the doctor–patient relationship becomes less contentious and adversarial. Further, the patient is likely to loosen the grip on symptoms when he or she feels that the physician has acknowledged and accepted them as real.

Several practical measures may be helpful. The physician can forge a personal connection with the patient by paying particular attention to social history and by complimenting the patient on the ability to persevere despite great discomfort. Rather than providing as-needed appointments, the doctor can schedule meetings at regular intervals, thereby decoupling professional attention from symptom severity. Patients with hypochondriasis tend to develop iatrogenic complications and treatment side effects. This has given rise to the clinical maxim, "Don't just do something, stand there." In other words, the best medical interventions are modest, simple, and benign (e.g., heating pads, ointments, frequent physical examinations, vitamins, as well as the offering of tangible evidence of discomfort, including canes, braces, and elastic bandages).

Monosymptomatic Hypochondriasis and Body Dysmorphic Disorder

Monosymptomatic hypochondriasis refers to several distinct syndromes characterized by a single, fixed, false belief that one is diseased. The disease conviction is generally delusional and grossly disproportionate to any objective disease or deformity. This belief is tightly circumscribed; no other thought disorder is present; and the remainder of the patient's personality remains intact and unaffected.[80] *Body dysmorphic disorder* (BDD), is one of the most common of these syndromes, and it is singled out in the DSM-IV as a separate diagnosis under somatofom disorder.[81,82] Other forms of monosymptomatic hypochondriasis include the delusional belief that one is infested with a parasite or insect and the delusion that one emits an offensive odor (olfactory reference syndrome).

The patient with BDD believes he or she is physically misshapen and unattractive, although objective appearance is unremarkable. Self-reported prevalence of the disorder in the German population is 1.7%.[83] The defect or deformity in appearance is most commonly in the face, breasts, or genitals. The average age of onset for these patients is younger than age 20, with males and females equally represented. Typical males seek plastic surgeons with the conviction that their noses are too large or disfiguring. The typical female, convinced that her facial skin is "scarred," making her appearance grotesque, will seek a plastic surgery or dermatological consultation. BDD is commonly accompanied by a mood disorder (including atypical depression with rejection sensitivity), social phobia, OCD, and substance use disorders. The rate of suicidal ideation, suicide attempts, and completed suicide is notable,[84] and the course chronic with a remission rate probably lower than that reported for mood and anxiety disorders alone.[85]

Patients with delusions of infestation believe that parasites, insects, or vermin are under their skin, and as a consequence they have often severely excoriated themselves. These individuals tend to be in their mid-50s at onset, and approximately two thirds are women. They may complain of itching or tickling sensations and frequently produce bits of skin or hair as evidence of their infestation.

In olfactory reference syndrome, the patient is falsely convinced he or she emits a foul odor, for example halitosis, which offends others. The patient engages in elaborate rituals, such as frequent bathing and changes of clothing, and uses excessive amounts of perfume and deodorants. Olfactory reference syndrome is more common in men than women, and the typical patient is in his mid-20s.

The three forms of monosymptomatic hypochondriasis share certain clinical characteristics. Despite the encapsulation of their thought disorder, these patients are profoundly anguished about their symptoms, and their lives are severely disrupted. Their lives are completely devoted to the pursuit of medical and surgical remedies, and they tenaciously resist psychiatric referral or treatment. They are intensely ashamed and feel that they are under constant scrutiny and derision. This generally leads to profound social withdrawal and disability. Severe anxiety, paranoia, and depression are prevalent. Alcohol abuse is common, especially in younger males.

Treatment. SSRIs and clomipramine (a tricyclic antidepressant [TCA]) are the agents of choice in the treatment of BDD, with doses in the upper therapeutic range. BDD may remit along with major depression, but treatment often fails or is only partially effective. Olanzapine, but not pimozide, has been shown to be effective to augment fluoxetine.[86,87] Electroconvulsive therapy (ECT) has also been used successfully when the patient was frankly delusional.

These patients are difficult to treat, in part because they are so ashamed of their appearance and resistant to psychiatric help. Psychopharmacologic agents may be effective, but the patients are frequently unwilling to take them.

They do not believe that a psychotropic drug could correct a physical defect; or once begun on an agent, they may stop taking it without informing their physician.

Maintenance therapy is generally necessary.[81] Even with successful pharmacotherapy, most patients retain some concern about their problem, but its intensity is blunted sufficiently to permit them to lead more normal lives. One may never be able to get some patients to acknowledge the delusional nature of their symptom, even after significant improvement. Hard-pressed to justify the recommendation of a neuroleptic, the physician may even tell the patient that these insects or odors are best "cleansed" from within the system, hence the need for a drug. On the other hand, a few patients will accept the notion that the body is more vulnerable to parasitic infestation or odor generation during times of greater stress. When major depression is present in BDD, medication is more readily accepted.

Functional Medical Syndromes

Although somatoform disorders are characterized by complaints that seem far out of proportion to any abnormalities found, common functional medical syndromes also lack laboratory confirmation. Like the diagnoses in DSM-IV, these diagnoses depend on consensus criteria, description of symptoms, and a natural course of illness. There is substantial overlap in the phenomenology, epidemiology, and co-occurrence of these various syndromes.[88,89]

Chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS) are three of the functional medical syndromes named for the dominant symptom complex. Those patients who seek medical care for functional medical syndromes are more distressed, depressed, and under more life stress than community residents who have the same symptoms but who never seek out a physician. Once the patient acquires a functional diagnosis (either by strict research criteria or by looser clinical criteria), that diagnosis is granted greater authority and legitimacy than a co-morbid psychiatric diagnosis. Physician and patient often collude to focus attention only on the somatic syndrome. A symptom (such as disturbed sleep) can be seen either as part of a medical or a psychiatric diagnosis. Whether the patient is diagnosed with a functional medical condition, mood disorder, or somatoform disorder depends on whether the key symptoms are attributed to the physical or psychiatric realms. The fact that the patient carries a functional medical diagnosis should not limit aggressive treatment of co-morbid psychiatric diagnoses.

The principles of care for somatoform disorders apply here as well. Rule out organic disease; diagnose and treat affective disorder, substance abuse, and the other psychiatric diagnoses. Knowing the patient, listening with respect for his or her suffering, setting limits, and keeping an ear for changes in medical complaints remain pivotal concepts. CBT is emerging from a number of rigorous intervention trials as an effective treatment for many of these syndromes.[90–92] The status of antidepressant pharmacotherapy for them has been systematically reviewed.[93]

Chronic Fatigue Syndrome

Many more patients complain of chronic fatigue without a medical cause than meet formal criteria for CFS. Fatigue itself is a vague symptom that requires exploration of exacerbating factors, timing, mood, and meaning. Patients with MDD have fatigue that is worse in the morning. They have difficulty initiating activity, as do patients with Parkinson's disease. Sometimes fatigue actually turns out on exploration to be agoraphobic avoidance of leaving home, or a tendency to avoid the risk of social embarrassment. Fatigue may also mean daytime sleepiness, seen in sleep apnea. Fatigue with dysphoria is central to a mood disorder. Apathy—lack of motivation and lack of dysphoria—is more characteristic of a neurologic disorder or hypothyroidism. Patients who value their productivity and strength are especially frustrated by fatigue, and its personal meaning will exacerbate the symptom.

By consensus, CFS is defined by several features: self-reported, clinically evaluated, unexplained, persistent or relapsing chronic fatigue with a definite onset that lasts more than 6 months. It is not due to exertion or relieved by rest, but it substantially reduces the patient's activities; and it includes four or more other symptoms (impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain without joint swelling or redness; new headaches, unrefreshing sleep, and postexertional malaise lasting more than 24 hours), which came after onset of fatigue.[94]

The formal diagnosis of CFS, like that of a somatoform disorder, requires exclusion of the common psychiatric diagnoses. Patients, according to the most recent research criteria, do not qualify if they have a fatiguing medical condition that has not yet resolved or if they use fatiguing prescription medications. A formal diagnosis of past or current MDD with psychotic or melancholic features, bipolar mood disorder, schizophrenia, delusional disorder, dementia, substance abuse within the previous 2 years, and anorexia nervosa or bulimia precludes a formal diagnosis of CFS.

The patient may have CFS and also have a co-morbid anxiety disorder, somatoform disorder, nonmelancholic depression, neurasthenia, multiple chemical sensitivity disorder, or FM. The challenge for the psychiatrist is to treat what can be treated using either psychopharmacologic or psychological approaches. Anxiety disorders and nonmelancholic depression remain potentially fatiguing aspects of the syndrome. The psychiatrist should consider the role of personality disorder or the possibility of bipolar disorder, a diagnosis not easily ascertained by history, especially when seen between flagrant episodes. Exploration of the description and meaning of the most prominent symptom is indicated.

Although fatigue may follow a viral infection, no single virus has been shown to cause persistent, debilitating CFS. In the primary care setting, patients with postinfectious fatigue after 6 months are more likely to have had fatigue and psychological distress before the infection.[95] A history of dysthymia and more than eight medically unexplained symptoms not already listed in CFS criteria may predict prolonged disability in CFS patients.[96]

Suggested screening laboratory tests include a complete blood count, a sedimentation rate, liver and renal function tests, calcium, phosphate, glucose, thyroid-stimulating hormone (TSH), and urinalysis. Further tests, such as a magnetic resonance imaging (MRI) scan of the head to search for multiple sclerosis, should be guided by clinical findings. Lyme disease, for instance, is unlikely to cause

fatigue as the only finding.[97] Acute mononucleosis in adolescence might produce a similar picture, but it is not likely later on in life. The acute diagnosis could be documented by antibody evidence of recent infection.

There is no specific medical treatment for formal CFS. The choice of antidepressant for co-morbid mood disorder depends on its capacity to improve sleep but limit sedation. Graduated aerobic exercise programs are important to improve physical conditioning. CBT programs increasingly appear to have established their effectiveness.[98,99] The goal is to help the patient achieve maximal function.

Fibromyalgia

Fibromyalgia is a syndrome of generalized muscle pain and tenderness at specific trigger points, detected by physical examination.[100] For diagnosis, pain must be bilateral, above and below the waist, and include the axial-cervical spine, chest, or lower back. Criteria require 11 of 18 (9 bilateral) trigger points. Secondary FM occurs with rheumatoid arthritis and Lyme disease.

Affective disorders are common among FM patients who seek out rheumatologists. The diagnosis of FM, originally associated with chronic fatigue and sleep disorder, now only includes pain and trigger points, according to the American College of Rheumatology; however, patients with FM, fatigue, and unrefreshing sleep may meet diagnostic criteria of CFS.

For FM, amitriptyline (25 to 50 mg/day) and cyclobenzaprine (10 mg at bedtime) (both TCAs) to relieve pain and improve sleep seem to work at least briefly in some fraction of patients.[101,102] There have been single RCTs of fluoxetine, duloxetine, and venlafaxine.

Irritable Bowel Syndrome

Functional GI disorders are recurrent medical syndromes without known biochemical or structural abnormalities. Irritable bowel symptoms occur in 15% to 20% of the population, but people with the disorder who seek medical help compose a major component, 25% to 50%, of referrals to gastroenterologists.[103] The disorder effects females more than males and, although its causes are unknown, does appear to have a genetic component.[104,105]

The international criteria for IBS include continuous or recurrent symptoms (for at least 3 months) of abdominal pain or discomfort relieved by defecation, or associated with a change in stool frequency or consistency *and* an irregular pattern of defecation at least 25% of the time (three or more of the following): altered stool frequency; hard, loose, or watery stool; straining, urgency, or feeling of incomplete evacuation; passage of mucus; and bloating or a feeling of abdominal distention.[106]

Those who visit physicians have more severe symptoms and are more likely to have co-morbid psychiatric diagnoses than those who do not. Mood disorder,[107] panic with agoraphobia (especially fear of leaving the house because of diarrhea),[108] history of childhood abuse, and neuroticism[109] are more prevalent among patients than among the general population.[110]

Again, diagnosis depends on criteria, natural history of illness, and absence of laboratory confirmation of another diagnosis. The clinical approach to IBS is similar to that for the somatoform disorders: rule out organic and psychiatric diagnoses. In the context of a relationship in which the physician continues to learn about the patient, the physician chooses somatic treatments that target the predominant symptom of pain, constipation, or diarrhea. A TCA has an analgesic effect at low doses but tends to cause constipation and be preferable for a patient with recurrent diarrhea. An SSRI seems the better choice for co-morbid panic disorder or OCD,[111] particularly in patients with constipation. Paroxetine is most studied of the SSRIs for this use and results have been mixed.[112] If the patient tends to have diarrhea, loperamide, a constipating agent, may be useful. Fiber and dietary adjustments may relieve constipation. The principles of pain management in IBS parallel the principles of management in somatoform pain disorder.

Cognitive-behavioral therapy and interpersonal psychodynamic therapy appear to be effective for improving well-being and quality of life.[113–115] Education about amplification of visceral symptoms and the vicious circle of anxiety, increased vigilance for symptoms, and resultant increase in symptoms and pain; relaxation training; and stress management techniques are helpful to both individuals and groups.

CONCLUSION

When one thinks of psychologically driven somatic symptoms, the somatoform disorders may be the first diagnostic category to come to mind. But among general hospital inpatients and outpatients, other psychiatric diagnoses (particularly affective disorders, anxiety disorders, and organic mental syndromes) are more likely to be discovered at the end of the history and examination. These require specific treatment, and when the psychiatric disorder remits, the somatic symptoms usually subside. The diagnostic tests we find helpful are the MMPI-2, an excellent screening device for conversion or a somatoform disorder, and Axis II parameters; projective tests, to help both physician and patient understand conflicts in the patient's life that may not be in the patient's awareness; and full neuropsychological test batteries, which delineate precise areas of cognitive deficiency (see Chapter 7).

In the case of complex medical patients, some have suggested that disorders defined solely by unexplained somatic symptoms should be described as a multidimensional functional medical diagnosis without reference to etiology. Disorders such as chronic pain, FM, or IBS would be listed as medical diagnoses. Somatic symptoms associated with depression would be classified with depression, and those associated with anxiety would be classified with anxiety. A multiaxial diagnostic system would allow anxiety disorders, anxiety and hypochondriasis, and specific illness fears to be listed together. Personality disorders, including those seen in somatization disorder, would be on a personality axis, and specific stressors (including difficult interactions with the health care system) could be specified. A multidimensional descriptive system for somatic symptoms should document the type and number of somatic symptoms and the nature of the acute, chronic, or recurrent course. Known organic disease pathology should be listed as well as health beliefs, illness behavior, associated psychiatric disorders, and social factors such as employment or social benefits.[43]

The treatment ultimately depends on the diagnosis. Smith and associates[56] have shown that an intervention with the PCP significantly reduced costly and potentially harmful medical interventions for somatizing patients without compromising the health or satisfaction of these patients. Psychological treatments such as CBT that focus on initiating and perpetuating factors improve the outcome.

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17 Patients with an Eating Disorder

Anne E. Becker, M.D., Ph.D., Sc.M.
Jennifer J. Thomas, Ph.D.
Kristin S. Russell, M.D.
Esther Jacobowitz Israel, M.D.

Eating disorders are common among adolescent and young adult women and are associated with serious morbidity and mortality. Patients with eating disorders present a multidimensional clinical challenge in the general hospital setting. These disorders frequently have medical complications and go undetected in clinical settings, and the patients are often reluctant to seek or accept treatment. Patients with anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), or atypical eating disorders (known as eating disorder, not otherwise specified [EDNOS]) almost always benefit from integrated multidisciplinary care, with a team that includes primary care and mental health clinicians as well as a nutritionist. Medical and nutritional stabilization are often clinical priorities in the general hospital setting and can enhance the effectiveness of the management of psychological and psychiatric dimensions of these disorders.

EPIDEMIOLOGY

Although their prevalence is highest in westernized and postindustrial societies, eating disorders appear to have a global distribution. Notwithstanding a previous clinical stereotype that associated eating disorders with affluent white girls and women, eating disorders are also prevalent among women of ethnic minorities in the United States. Rates among Latinos and non-Latino whites may be comparable, and rates among Native American women may exceed those among whites.[1,2] Moreover, rates of binge eating and BED may be elevated in black and Latino women compared with white women in both community- and clinic-based samples.[3–9] Whereas eating disorders and clinically significant disordered eating most commonly occur in the young adult female population, they also occur in men and boys, albeit at lower rates (5% to 15% of cases of AN and BN occur in males).[10] The lifetime prevalence of AN among individuals residing in the United States is 0.9% for women but just 0.3% for men.[11] Lifetime prevalence of BN is slightly greater, affecting 1.5% of women but just 0.5% of men.[11] The most prevalent eating disorder, BED, has a more equal sex distribution, with a lifetime prevalence of 3.5% in women and 2.0% in men.[11] The prevalence of BED in weight-treatment–seeking populations ranges up to 30%.[12,13]

Although various guidelines have been proposed to assess subthreshold eating disorders,[14–16] the consensus is that they are prevalent among United States girls and women, pose a risk for significant impairment and distress, and often feature psychopathology of commensurate severity to the officially recognized eating disorders.[17] Even higher prevalence rates are reported for specific individual symptoms (e.g., in 2007, 6.4% of adolescent girls in the United States reported purging, and 16.3% reported fasting in the past month to lose weight).[18] Although the clinical significance of isolated symptoms is debatable, substantial evidence supports the notion that subthreshold presentations are commonly precursors of full-syndrome eating disorders[19,20] and thus very likely part of a spectrum of eating disturbances.[14,15]

ONSET AND COURSE

The etiology of eating disorders is multifactorial with biological, psychodevelopmental, and sociocultural contributions to risk. AN and BN most commonly have an onset in adolescence; eating disorders are relatively rare in young children compared with postpubertal adolescents and young adults. Although AN can be seen in young children,[21] it is far less common (i.e., only 5%) in prepubertal girls.[22–25] Moreover, the onset of BN is usually in late adolescence,[23] and prepubertal bulimic behavior is reportedly uncommon.[26] Longitudinal twin data indicating that the heritability of eating disorder psychopathology increases substantially from early to mid adolescence raise the intriguing possibility that epigenetic processes—through which pubertal hormones trigger the phenotypic expression of latent genotypic vulnerabilities—may work in tandem with environmental ones to promote risk.[27] Finally, the onset of BED is typically in the early twenties.[4,28] Despite rapidly evolving pharmacologic and psychosocial treatment strategies for the eating disorders, approximately half of cases of AN and BN follow a chronic course,[29,30] and 43% of individuals with BED continued to be symptomatic in a 6-year longitudinal study of BED.[31] It is very common for individuals with AN, BN, or BED to transition from one diagnostic category to another during the course of their illness.[20] When diagnostic crossover occurs, trajectories typically feature movement away from restrictive eating patterns and toward binge eating or purging patterns, or both, at follow-up.[32,33]

In addition to their considerable prevalence, eating disorders are associated with serious medical co-morbidity and mortality. Eating disorders and substance abuse are associated with the highest risk of premature death among all

psychiatric illnesses.[34] The mortality rate from AN alone is 0.56% annually.[35] Moreover, AN is associated with an all-cause death risk five times what is expected, and BN with a risk nine times that expected. It is also important to note that whereas some of the deaths associated with AN were directly attributable to self-starvation, the mortality risk for suicide was 33 times the amount expected.[34] Because of the serious medical complications associated with eating disorders, patients often present to primary care, emergency departments, or hospital inpatient settings with an undisclosed or previously unrecognized eating disorder. Given that up to half of eating disorder may be undetected in primary care settings,[36–41] inpatient and outpatient medical and pediatric services provide significant opportunities to make a new diagnosis of an eating disorder and to initiate treatment. Furthermore, it appears that initiating treatment earlier in the course of the illness may improve outcome.[42]

DIFFERENTIAL DIAGNOSIS AND INITIAL ASSESSMENT OF EATING DISORDERS

Selection of an optimal treatment strategy for an eating disorder depends on an accurate diagnosis. Both identification and differential diagnosis of an eating disorder can be challenging. Differentiating between AN, BN, and EDNOS must address both substantial symptom overlap (Table 17–1) and crossover among diagnostic categories. Moreover, eating disorder symptoms can be masked by certain medical complaints, particularly those associated with gastrointestinal (GI) symptoms and weight loss, which can obscure an underlying or associated eating disorder. For example, some individuals attribute their restrictive diet to efforts to minimize severe bloating, nausea, or constipation, but a restrictive diet can, in fact, *cause* or contribute to these symptoms.[43] Patients sometimes initially present for medical care[44] and only come to psychiatric attention after an extensive medical evaluation has excluded a medical cause, unless an eating disorder is suspected on the basis of history. In other cases, the etiology of symptoms remains unclear and psychiatric consultation is sought to clarify contributions from an eating disorder or other mental illness. Using the same example, in the vast majority of such cases, GI symptoms caused by disordered eating often improve or remit with nutritional rehabilitation, psychiatric care, and conservative management.[43] However, it is always appropriate to consider the panoply of medical and psychiatric differential diagnoses that could contribute to symptoms. This is particularly true for unexplained weight loss in a demographic group not generally associated with AN, or for patients who do not clearly exhibit the excessive concern with weight associated with AN. But it is also true for patients with what appear to be classic symptoms of an eating disorder, given the frequent association between acute weight loss of medical origin and the onset of an eating disorder.

Clinical Detection of an Occult Eating Disorder

Clinical detection of an eating disorder can also be undermined by the limited capacity or motivation of patients to acknowledge and receive care for their illness.[45] Patients with AN are commonly reluctant to seek or accept treatment for their symptoms, and some even go to great lengths to avoid clinical detection of symptomatic behaviors or low weight. For instance, patients may avoid clinic visits, laboratory tests, or weighing. They may layer their clothing to give the appearance of normal weight, or, if they anticipate being weighed, they may "water load" (i.e., drink excessive quantities of water) or even tape weights to themselves to make their weight appear closer to normal. Individuals with BN also commonly postpone seeking treatment. For these reasons, individuals may come to medical attention for their eating disorder only after they arouse clinical suspicion on a medical or pediatric service, either by unexplained weight changes or by other medical symptoms, or when family members report concerns. For instance, family members might notice restrictive food intake (e.g., a girl becomes a vegetarian or vegan and progressively narrows food selections), secretive behavior concerning food (e.g., parents notice large quantities of food are consumed after the rest of the family has gone to bed, or cafeteria charges are very high on a term bill), or a pattern of excessively frequent bathroom use after meals.

Given the prevalence and associated mortality and morbidity of the eating disorders, clinicians should maintain appropriate vigilance for eating disorders in general hospital settings as well as an awareness that they can be difficult to detect. For patients with limited capacity or motivation to report symptoms, some probe questions can yield useful clinical data. These include questions about weight and dieting history. Frequent fluctuations in dieting and weight sometimes suggest restrictive or binge patterns of eating, or both. It is quite useful to ask patients their current and desired weights as well as what and when their minimum and maximum weights have been. This information can help to identify a range suggesting capacity for nutritional compromise. It can also help clinicians gauge how the patient's presenting weight compares to his or her healthiest and most compromised weights in order to develop reasonable clinical goals and a timeline for therapeutic intervention. Finally, an unrealistic or unhealthful desired weight can reveal body image disturbance, whether the patient desires to be unreasonably thin, and whether the patient and clinician are likely to negotiate successfully for mutual treatment goals. For younger patients whose parents are involved in their care, a question about desired weight is also useful as a probe to discover whether parental expectations are aligned with therapeutic goals. Psychoeducational information about appropriate weights for height can be reviewed with the patient and others involved in supporting participation in treatment.

When an eating disorder is identified or suspected, information about dietary patterns (such as meal skipping or food restriction) and inappropriate compensatory behaviors (e.g., vomiting, laxative or diuretic misuse, fasting, and excessive exercise) should be elicited. Questioning should be approached with sensitivity because patients are frequently embarrassed to discuss these behaviors. Data from participants in a national eating disorders screening program indicate that 91% of individuals who had not previously volunteered eating and weight concerns to a health professional ultimately disclosed such concerns when directly asked.[46] Clinicians should ascertain the presence

TABLE 17–1 Differential Diagnosis of Eating Disorders

	PHYSICAL SIGNS	COGNITIVE OR EMOTIONAL SIGNS AND SYMPTOMS	BEHAVIORAL SIGNS AND SYMPTOMS	ASSOCIATED DISTRESS OR IMPAIRMENT
Anorexia nervosa (AN)	Inappropriately low weight for height, age, and sex (e.g., BMI of ≤17.5 kg/m^2 or BMI of <85% expected body weight in an adult) Amenorrhea	Fear of weight gain or fatness Body image disturbance	No specific symptoms required to meet DSM diagnostic criteria Almost always associated with restrictive pattern of eating Associated with bingeing or purging behavior in 50% of cases	None specified under DSM-IV diagnostic criteria; in fact, individuals with AN are often in denial of the serious nature of their illness
Bulimia nervosa (BN)	BMI can range from normal to overweight; a diagnosis of AN would most likely be made for low-weight individuals with BN symptoms	Excessive impact of body shape or weight on self-evaluation Frequently excessively preoccupied with body shape and weight	Frequent and regular binge eating (at least twice weekly for at least 3 months) Frequent and regular inappropriate compensatory behaviors to prevent weight gain (e.g., purging, fasting, excessive exercise; at least twice weekly for at least 3 months)	None specified under DSM-IV diagnostic criteria, although many individuals are markedly distressed by their symptoms
Binge-eating disorder (BED)	No weight criterion, but overweight is commonly associated with BED	None required to meet DSM-IV diagnostic criteria, but weight and shape concerns are frequently present	Frequent and regular binge eating (on at least 2 days weekly) Binge eating often associated with • Eating rapidly • Eating alone • Eating while not hungry • Eating well past satiety to the point of discomfort No regular inappropriate compensatory behaviors to prevent weight gain	Marked distress about the binge eating is present
Eating disorder, not otherwise specified (EDNOS)	No weight criterion, but low weight is likely to shift the diagnosis to AN	All of the above are possible	All of the above are possible, but full-syndrome criteria for AN or BN would be mutually exclusive of the EDNOS diagnosis Can be associated with chewing and spitting out food and inappropriate compensatory behaviors after small or normal quantities of food as well	Distress can be present or absent

From American Psychiatric Association: *Diagnostic and statistical manual of mental disorders, fourth edition, text revision,* Washington, DC, 2000, American Psychiatric Association.

of the full range of possible behaviors; although many of these questions can be asked in a relatively straightforward manner, appropriate clinical discretion should be used in taking an inventory of compensatory behaviors. Although information on extreme dieting is readily accessible via the Internet and social networks, patient reports of learning about managing weight through withholding insulin (for those with insulin-dependent diabetes) are sobering. Health risks associated with extreme dieting and compensatory behaviors are not always obvious to patients or their parents, and appropriate education is essential.

Because clinical history does not always elicit accurate or complete data, collateral history, physical signs, observable behaviors, and longitudinal clinical course should be used when possible to augment evaluation. These potentially informative sources also have limitations. With the exception of low weight in AN, eating disorders can and do present without physical signs. Laboratory studies may yield data suggestive of purging or nutritional compromise but do not have sufficient specificity or sensitivity to be useful in screening. When suggestive physical signs are present—for example, parotid hypertrophy, excoriations on the dorsum of the hand (Russell's sign), or characteristic

dental erosion—they can launch further evaluation. Whereas collateral data can be helpful for establishing the presence of eating and weight concerns, family members may not be aware of or may not recognize symptomatic behaviors. If a patient does not endorse or disavows weight and shape concerns, observed behaviors (such as body checking in a mirror, excessive weighing, undue sensitivity to weighing, or evidence of behaviors undermining weight gain) can suggest the diagnosis.

Differential Diagnosis

For patients who are more forthcoming about their symptoms, the differential diagnosis is relatively straightforward. AN is characterized in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) by an inappropriately low body weight for height and age (the DSM-IV gives an example of a weight less than 85% of expected body weight, or body mass index [BMI] ≤ 17.5), a fear of fatness, some type of body image disturbance (e.g., excessive impact of body shape or weight on self-evaluation, feeling fat when actually thin, denial of seriousness of low weight), and amenorrhea (in women who have passed menarche) (see Table 17–1).[47] Heterogeneous rationales for food restriction are reported in Asian as well as Western populations, and the fear of fatness is sometimes not reported or not discernible,[48–50] so there may be cultural diversity in the presentation of AN. Moreover, the usefulness of amenorrhea as a diagnostic criterion for AN has been questioned.[51,52] AN occurs as two subtypes, restricting and binge eating/purging. In the latter type, individuals binge and/or purge in addition to maintaining their low weight; bingeing and/or purging occurs in approximately half of individuals with AN.

BN is characterized by regular binge eating and by inappropriate compensatory behaviors (both at least twice weekly for 3 months) to control weight. Like AN, BN is characterized by excessive concern with body shape or weight, which has a major impact on self-evaluation (see Table 17–1). BN can occur as one of two subtypes: purging (i.e., regularly inducing vomiting or using laxatives, diuretics, or enemas) or nonpurging (i.e., inappropriate compensatory behaviors that exclude the aforementioned methods, such as restrictive eating or excessive exercise).[47] The purging subtype is much more commonly seen in clinical practice. Although AN and BN can have substantial phenomenological overlap in symptoms (i.e., excessive concern with weight, binge or restrictive pattern eating, and purging), they are best differentiated by weight and menstrual function. Specifically, a low-weight individual with bingeing and purging and excessive concern with weight is likely to best fit diagnostic criteria for AN. Similarly, although menstrual abnormalities can occur in individuals with BN,[53] amenorrhea is required for a diagnosis of AN.

BED is primarily characterized by recurrent binge eating over a period of 6 months or more. A diagnosis of BED requires that binges (1) occur at least 2 days weekly for the past 6 months; (2) are associated with three or more of the following qualitative characteristics: rapid eating; eating past satiety to the point of discomfort; eating a large amount without being hungry; eating alone to avoid embarrassment by the amount one plans to eat; feeling disgust, guilt, or dysphoria after a binge; and (3) are accompanied by marked distress. A diagnosis of BED is excluded in the presence of AN, BN, or regular purging or inappropriate compensatory behaviors to control weight (see Table 17–1).[47] BED is frequently complicated by obesity. Hospital psychiatric consultation often does not initially identify a patient's BED unless there is a known history or there is a concern about obesity. For these reasons, clinicians should remember to ask about associated symptoms and should be especially vigilant for BED in certain populations of adult patients—for example, those with current obesity, a history of weight fluctuation and dieting, or a history of an eating disorder.

Approximately 40%[54] to 60%[55] of patients who present with an eating disorder do not meet full criteria for AN or BN, notwithstanding clinically significant psychopathology. These patients are diagnosed with EDNOS. Despite its designation as a residual category, EDNOS is associated with significant eating pathology, general psychopathology, and medical risk.[17] Common presentations of EDNOS include individuals who present with AN-like symptoms but do not meet the weight or amenorrhea criterion, and patients with BN-like symptoms who do not binge and purge at the requisite frequency or duration. EDNOS also includes distinct syndromes, such as BED, purging disorder (i.e., repeated purging in the absence of objectively large binge episodes),[56] and night eating syndrome (i.e., habitual and distressing nocturnal overeating associated with sleep disturbance).[57]

Because diet and fitness concerns are virtually socially normative and often appropriate in American society, it can sometimes be difficult to differentiate appropriate concern with diet, weight, and exercise from excessive concern. For instance, the prevalence of obesity in children is 12% and has more than doubled over the course of the last generation.[58] Moreover, the prevalence of obesity among United States adults has steadily increased over the past two decades,[59,60] with an estimated 65.7% of adults currently overweight and 30.6% obese.[61] Finally, obesity is associated with substantial medical and psychological complications in both children and adults, and it is the second highest cause of preventable death in the United States.[62] For these reasons, appropriate attention to diet, fitness, and weight is necessary, but the appropriate level of physical activity should be evaluated with regard to health and fitness guidelines, social context, and presence of an eating disorder. For example, physical activity that appears motivated by inappropriate weight goals or compensation for binges, that results in significant distress or impairment, that exceeds or violates coaching recommendations, or that cannot be adjusted for sickness or injury warrants concern as inappropriate. The administration of a brief self-report measure querying the personal, social, and cognitive impairment associated with disordered eating can also assist clinicians in evaluating whether potentially problematic behaviors are clinically significant.[63]

Because many patients with disordered attitudes about eating feel that even normal food intake is excessive, it is helpful to establish that binge episodes are consistent with the established definition in the DSM-IV.[47] Thus, for the purposes of meeting criteria for BN or BED, a binge includes both the consumption of an unusually large

amount of food in a discrete time period (i.e., 2 hours or less) and is associated with diminished control over eating.[47] Subjective binge episodes are distinguished from objective binge episodes (requisite to meet diagnostic criteria for BN or BED) by food consumption with loss of control that appears excessive to the patient but is not actually excessive for its context by objective standards.

Assessment of the severity and patterning of the binge eating is aided by requesting that a patient keep a self-monitored record of daily food intake. To do this, patients should be instructed to record the contents of each meal, snack, or binge directly after it is consumed. Patients are also directed to record the feelings they experienced before, during, and after consumption. Although this record will be generally less useful in the hospital setting given the limited dietary choices and rather structured setting, it can still yield useful diagnostic information. Food records are, moreover, a core intervention of cognitive-behavioral therapy for both eating disorders because such records provide a detailed picture of the patient's typical eating habits, thus aiding in diagnostic formulation and assessing treatment response, and they help patients increase real-time awareness of behaviors that may have previously seemed automatic and beyond their control. Once completed, patients can review food records with clinical staff to identify probable binge triggers (e.g., undereating earlier in the day or negative affective states) and behavioral solutions (e.g., eating a morning snack or engaging in pleasurable activities).

Clinicians should maintain vigilance for a broad spectrum of purging and other inappropriate compensatory behaviors in their assessment. Vomiting is the most common means of purging associated with eating disorders, but some patients also misuse laxatives, diuretics, enemas, stimulants, and other naturaceutical preparations purported to suppress appetite or otherwise aid weight loss in addition to or instead of vomiting. Clinicians should also inquire about fasting or dietary restrictions and exercise behavior as modes of preventing weight gain. A recent survey of health food stores, pharmacies, and grocery stores identified 248 laxative,[64] 167 appetite-suppressant, and 25 diuretic[65] products readily available over the counter. Thus, clinicians should bear in mind the plethora of purging possibilities when assessing a patient with a suspected eating disorder and inquire about prescription stimulants (e.g., methylphenidate), herbal supplements (e.g., senna or aloe vera), and so-called cleansing or detoxifying products (e.g., Evercleanse), in addition to more conventional over-the-counter laxatives and diuretics. Herbal product use for weight loss is widespread among women with an eating disorder; a recent study reported a lifetime prevalence of 64% and a 1-month point prevalence of 14.1% among women with an eating disorder ($N = 100$).[66]

Patients with co-morbid insulin-dependent diabetes should also be assessed for inappropriately withholding their insulin. This behavior places them at risk for diabetic ketoacidosis, as well as long-term complications of poorly controlled blood sugars, and may necessitate inpatient care for stabilization and safety. As noted earlier, assessment of this mode of purging or weight control should be made with special clinical discretion, because some patients have reported learning about this strategy for weight control during a clinical evaluation. Finally, some individuals with an eating disorder induce vomiting with syrup of ipecac. Again, the ready over-the-counter availability of this medication is often misleading for individuals who wish to use it to purge, and the Food and Drug Administration (FDA) has considered elevating it to prescription status because of its toxicity and potential for abuse.[67] Because chronic ipecac use can result in cardiomyopathy, myopathy, and death,[68–71] patients should be educated about its associated risk. Patients who have used it should be instructed to discontinue it immediately, and they should be evaluated for possible further medical investigation. Ongoing ipecac use is an indication for inpatient care, and patients assessed as unable or unwilling to discontinue use should remain hospitalized until they are able to abstain from this behavior.

Although there is substantial phenomenological overlap and some crossover between AN, BN, and BED, by definition, they are mutually exclusive diagnoses. As can be seen from the diagnostic criteria, binge eating can be present in all three disorders, and purging and fasting can each be present in AN and BN. In addition, overvaluation of shape and weight is one of the diagnostic criteria of BN, but it is also common in patients with BED,[72] so the presence or absence of purging behavior is the best criterion for differentiating the two disorders. Finally, individuals with BN sometimes have amenorrhea, but by definition, if they have an inappropriately low weight, they meet the diagnostic criteria for AN instead.

Medical and other psychiatric causes of poor appetite and weight loss (e.g., the anorexia of depression) or vomiting (e.g., secondary to achalasia) should be excluded with appropriate history, examination, and diagnostic tests. Medical illnesses that the practitioner needs to differentiate from eating disorders include endocrinologic disorders (such as diabetes mellitus and hyperthyroidism), brain tumors, cancer, occult infections, and GI disorders. Moreover, because all of the eating disorders are frequently co-morbid with mood and anxiety disorders, personality disorders, and substance abuse, a complete assessment of mental status and psychiatric history should be included in the evaluation. Finally, a careful assessment of suicide risk is essential, and clinicians should bear in mind the frequent association of suicidal ideation and attempts with eating disorders.

Weight Assessment

Evaluation of an eating disorder routinely includes weight assessment. Weight assessment is inexpensive, straightforward, and informative; it is not only integral to the diagnosis of AN but also necessary for therapeutic management across the spectrum of eating disorders. For some patients, weight management—or medical management of weight-related conditions and complications—is a central therapeutic concern. Weight and height should be measured during the initial assessment. These should be obtained in privacy and with sensitivity. In some cases, patients benefit from the option of not seeing or knowing their weight. The calculated BMI is the clinical standard for weight assessment for adults. The formula for men and women is as follows:

$$\text{BMI} = \text{height (in meters)} \div \text{weight (in kilograms)}^2$$

For children, the BMI generally increases with age, and therefore BMI centiles are a more accurate measure. They can be assessed by measuring height and weight and plotting on the U.S. Centers for Disease Control and Prevention BMI-for-age charts.[73]

Other methods for weight assessment for adults include comparing the patient's actual weight with expected body weight (EBW) as a percentage:

$$\%\text{EBW} = (\text{actual weight} \div \text{expected body weight}) \times 100\%$$

EBW can be estimated with one of the following formulas:

$$\text{EBW (women)} = 100\text{ lb for the first 5 feet} + 5\text{ lb / inch above 5 feet}, \pm 10\%$$

$$\text{EBW (men)} = 106\text{ lb for the first 5 feet} + 6\text{ lb / inch above 5 feet}, \pm 10\%$$

The EBW percentage is preferable for both scientific and clinical use, but the estimated EBW is more intuitive for patients and can be calculated by hand.

Obtaining an accurate weight is critical to care. Because some patients may attempt to disguise a low weight by adding weight through jewelry, clothing, and hidden items, weights should be measured with the patient in a hospital gown only. If water loading is suspected, patients can be asked to void prior to weighing; urine specific gravity may be informative if it is relatively low. Some patients endeavor to increase their weight by taking in calories prior to a weight check; fortunately, eating to promote weight gain is consonant with therapeutic goals.

INTERVENTIONS

Although acute treatment of medical complications, nutritional compromise, and associated acute psychiatric symptoms can begin in the general hospital setting, treatment duration is generally lengthy and is likely to eventually require transfer to a psychiatric specialty or outpatient setting. Therefore, the consulting psychiatrist has a critical role in establishing a diagnosis and the level of severity to guide inpatient management, disposition, and a comprehensive care plan. Additional potentially useful interventions in a general hospital setting include (1) education of the clinical staff caring for the patient; (2) patient engagement in treatment and psychoeducation; (3) identification of referral resources for either specialized inpatient eating disorder care or for an outpatient multidisciplinary clinical care team; (4) implementation of behavioral strategies to control symptoms, when appropriate; (5) initiation of pharmacotherapy, when appropriate; and (6) implementation of a plan for nutritional rehabilitation, as appropriate. Also, on occasion, a formal behavioral treatment protocol is implemented on a general medical or pediatric floor.

Education of the clinical staff on the general medical or pediatric service is essential for two main reasons. It ensures that a thorough targeted work-up is complete, and that nutritional and medical complications of restrictive eating, binge eating, and inappropriate compensatory behaviors are addressed. For example, potassium repletion for a patient with chronic vomiting or diuretic or laxative abuse and ensuing hypokalemia, or a suitable bowel regimen for a patient tapering off laxatives, can be prescribed. Moreover, monitoring and prophylactic treatment for refeeding syndrome can be implemented for patients with severe nutritional compromise in consultation and collaboration with other specialty care teams with relevant expertise in the hospital.

Psychiatric consultation can also assist staff in the management of countertransference feelings toward patients, which can range from rescue fantasies to anger. Many hospital staff may be unfamiliar or inexperienced in responding in therapeutically constructive ways to patients who evade or undermine their care. Moreover, because patients with eating disorders often function quite highly in some domains, staff may underestimate their pathology or spend excessive time in well-intentioned—but ineffective—efforts to talk the patient out of his or her choices. On the other hand, the helplessness that can be engendered in staff and the appearance that the patient is choosing the symptoms (e.g., not to eat or to purge, whereas the patient in the next bed may be wasting away from cancer or nauseated by chemotherapy) can lead to anger. Similarly, the frequency with which eating-disordered patients comment on treatment providers' own weight, appearance, and eating habits can promote self-consciousness among clinical staff.[74] Consultation can assist treatment providers in setting appropriate (nonpunitive) limits, formulating realistic expectations, and maintaining an empathic stance.

Engaging the Reluctant Patient

Several unique features of AN serve to maintain the illness; even if AN patients are able to recognize their symptoms as an illness, they commonly perceive substantial benefits associated with it.[75,76] For the patient who is unable to admit the extent of the symptoms or to acknowledge that symptoms are problematic, gentle confrontation is essential. Although AN patients commonly disregard or disavow even the most objective evidence of medical complications, they should still have the benefit of education about clinical signs that are worrisome, availability and efficacy of treatment, and the substantial risks of not pursuing treatment. In addition, psychoeducation of patients with AN, BN, and EDNOS is useful to clarify their diagnosis of an eating disorder for them, to discuss the serious medical and psychological risks associated with symptoms, and to convey available treatment options that will be beneficial in focusing appropriate energy toward an intervention.

Anticipation of patient ambivalence about engaging in treatment and relinquishing symptoms may be helpful to identify resources, strategies, and supports that can advance therapeutic goals. Collaboratively creating a cognitive–behavioral formulation that highlights the predictable and self-defeating links among eating-disordered behaviors can be especially illuminating for patients who perceive symptoms as disparate or uncontrollable. Many individuals with either AN or BN believe their symptoms have an important primary gain—controlling their weight. By definition, individuals with AN and BN unduly base their self-worth on their body shape, weight, and appearance. Sometimes, an initial experience of positive social feedback and self-efficacy is so reinforcing that it

induces them to continue to lose weight. Not infrequently, the restrictive eating gives way to bouts of binge eating, which in turn can segue to purging and other inappropriate compensatory behaviors. Not surprisingly, this cycle is generally ineffective in achieving the desired weight loss. For example, laboratory studies of binge eating and purging indicate that the majority of calories are retained in the digestive tract after vomiting[77] or laxative use.[78] When patients rededicate their efforts to restrict their diet—often in a pattern in which they bank their calories for the end of the day—their hunger later in the day may trigger a binge. This binge eating can be further complicated by a preoccupation with food—so extreme that many patients report a constant distraction concerning the tally of calories they have consumed or that they plan to consume during the day. Thus, a viciously self-reinforcing cycle ensues.

Individuals with eating disorders are not always aware of the substantial secondary gains of their symptoms. Many patients experience distraction and emotional numbing as a result of their restrictive and binge-pattern eating and purging behaviors. Studies utilizing ecological momentary assessment paradigms—in which patients record symptoms and moods in real time on palmtop computers—indicate that individuals with BN are at higher risk for binge eating and purging on days characterized by consistently high levels of negative affect or increasing negative affect throughout the day,[79] suggesting that binge eating may serve as a self-soothing mechanism to individuals who perhaps cannot readily access higher-level defenses. Thus, the behavioral symptoms eventually become a core coping strategy for many individuals with eating disorders. Whereas some patients are completely unaware of this function of their symptoms, others have a clear sense that they could not tolerate relinquishing them. Moreover, most patients are convinced that they will gain weight if they establish normal dietary patterns. For these reasons, patients are understandably reticent to disclose their symptoms and reluctant to embark on any treatment plan that they perceive will result in weight gain and deprive them of sometimes highly valued coping strategies. In addition, extremely low weight AN patients often manifest cognitive inflexibility that can undermine insight and therapeutic engagement.

Thus, engaging a patient in treatment for eating disorders is often challenging, because the patient may perceive this as a threat to all the gains he or she experiences from the symptoms. Others, especially those who engage in binge eating, may quite willingly enter treatment when the symptoms lose their efficacy or purpose in self-soothing, have unwanted weight gain effects, or are too time-consuming or expensive. In one study, individuals with BN reported spending an average of $1600 per year on binge food, and $240 per year on purging aides (such as laxatives, diuretics, and diet pills).[80] In addition, some patients finally seek treatment when their living situation (i.e., a roommate and shared bathroom) puts their secrecy in jeopardy or when they are confronted about their symptoms by someone who has adequate leverage to steer them to treatment for their problem.

For reluctant patients, motivational enhancement therapy (MET) may galvanize the therapeutic alliance and promote patient readiness. Eating disorders are notoriously ego-syntonic; patients who perceive treatment providers as forcing them to change may ironically become increasingly less willing to do so. The goal of MET is to cultivate cognitive dissonance between the patient's current eating disorder symptoms and future life goals. Rather than attempting to convince the patient to recover, the skillful MET therapist introduces nonjudgmental exercises that allow the patient to identify and verbalize his or her own arguments for change. Techniques, such as brainstorming the pros and cons of the eating disorder, imagining life 5 years from now with and without the eating disorder, and identifying inconsistencies between eating disorder symptoms and core life values (i.e., autonomy, friendship) can be effective to this end. Short-term group MET has been associated with increases in self-reported motivation[81,82] and reductions in premature termination[82] among individuals in treatment for eating disorders. MET techniques can be readily adapted for use in individual psychotherapy.

For general hospital inpatients reluctant to discuss or allow treatment of their symptoms, engaging the patient around mutually identified goals and identifying key points of leverage are first-line strategies. In many cases, the patient can be asked why he or she has agreed to meet or speak with the consultant and what he or she hopes to get out of it. Even if the patient provides a seemingly bleak reply (e.g., an AN patient hopes to get her parents "off her back," a BN patient would like to lose weight), the stated rationale can prompt the development of specific goals with which to ally with the patient, such as autonomy or health. In addition to informing the patient and family about medical complications and risks associated with the disorder, concrete evidence about adverse health impact (e.g., the results of a dual-energy x-ray absorptiometry [DXA] scan of the lumbar spine showing osteopenia, or of laboratory analysis indicating hypokalemia) can be presented as a strategy to motivate treatment engagement.

When appropriate, clinicians should work collaboratively with parents, teachers, coaches, or school administration to identify incentives for patients to meet therapeutic goals. For example, patients may be required to meet specific clinical benchmarks to be eligible to participate in school or extracurricular activities. In addition to considering local mandatory reporting requirements, voluntary notification of employers, regulatory boards, and school administrators should be discussed when there are concerns about occupational impairment and safety. Clinicians with preexisting good therapeutic alliance should be enlisted in establishing incentives as well.

Especially when motivation is in question and when adherence to treatment or risk of decompensation is high, a treatment agreement specifying interim goals as well as the patient's responsibilities provides clarity to the team and the patient. For example, the patient may be asked to agree to attend all appointments, to allow weighing and laboratory work at intervals specified by the team, and to consent to communication among all members of the treatment team. In addition, parameters to be used in considering intensification of care should be specified, so that if a patient's weight is unstable, all team members and the patient are in agreement about the point at which an increased intensity of care (e.g., adding a group, adding medication, or being admitted to an inpatient unit for eating disorders) is necessary. To be maximally therapeutic, treatment

nonnegotiable outcomes—such as inpatient hospitalization at low body weight—should have a sound rationale, be consistently implemented throughout treatment, not take the patient by surprise, and provide clear opportunities for the patient to prevent implementation by altering undesirable behaviors.[83]

Involuntary hospitalization[84] may be necessary when patients are at imminent risk for self-harm or are unable to care for themselves (e.g., as evidenced by ongoing untreated serious medical complications). Although compulsory treatment raises challenging ethical considerations, available data suggest that patients may gain an understanding of treatment necessity after engaging in care. For example, one study found that 43% of patients with an eating disorder, who initially denied the need for hospitalization, retrospectively admitted its necessity within 2 weeks of admission.[85] Another study reported that legally committed patients exhibit similar rates of weight restoration during inpatient hospitalization compared to their voluntarily admitted peers.[86]

By contrast, some patients appear very eager to begin treatment for an eating disorder. Although this eagerness can be genuine, it can also eventually be revealed to have been only superficial compliance.[87] An abrupt eagerness to address an eating disorder in the setting of an ongoing treatment may also be motivated by difficulty tolerating the intensity or emotional charge in other areas of the therapy. In other words, a change in therapeutic focus to eating behaviors provides a diversion. In such a situation, the consultant can address with the patient and treatment team whether adjunctive treatment is advisable and appropriately timed with respect to other treatment goals and priorities.

Considerations in Initiating Treatment

Goals of the inpatient hospitalization are guided by the severity and duration of the disease as well as its medical complications. Initial goals generally encompass stabilization of medical parameters and behavioral symptoms, safety and containment (when appropriate), and a plan for nutritional rehabilitation. Therapeutic interventions that address cognitive and behavioral symptoms are integral to enhancing motivation to engage in treatment, consolidating nutritional and medical recovery, enhancing capacity to tolerate weight and behavioral changes, and preparing the patient for continuing in a less intensive level of care treatment setting, such as residential care, partial hospitalization, or multidisciplinary team outpatient care.

Depending on clinical staffing, a behavioral protocol can be implemented on a general medical or pediatric service to promote refeeding or control inappropriate compensatory behaviors. Some services have standardized protocols, and in others the consulting psychiatrist and staff can develop a plan to meet the needs of individual patients. A description of such protocols is beyond the scope of this chapter, but they include medical and nutritional monitoring and may also include supervised regularly scheduled meals, expectations for participation in meal selection with a nutritionist, expectations for duration of meals, restrictions of bathroom trips within an hour of meals, privileges (e.g., leaving the floor) contingent on meeting a dietary plan and weight goals, and restriction of physical activity.

Some patients who have been hospitalized on a medical service because of complications of their eating disorder will benefit from, or require transfer to, an inpatient setting for specialty psychiatric care. Others who are well stabilized, or for whom the eating disorder was an incidental finding, will be discharged home for outpatient care. Table 17–2 shows criteria for inpatient-level care of patients with an eating disorder. Although psychotherapeutic care (with the exception of supportive or psychoeducational treatment) may not be feasible in the general hospital inpatient setting, behavioral treatment to support adequate dietary intake can be initiated, pharmacologic therapy—when appropriate—can be started, and an outpatient team can be assembled to ensure smooth transition in care.

There are well-established treatment approaches for patients with eating disorders that should inform and guide treatment planning. However, general hospital clinicians should bear in mind the potentially limited generalizability of findings from clinical trials in outpatient or specialty care settings to the patients admitted to their care. Flexibility may be required to meet the multifaceted treatment goals in a general hospital setting.

The utility and necessity of a multidisciplinary team approach to treatment for eating disorders is well established. Generally, treatment benefits from the inclusion of the primary care clinician, a nutritionist, and a mental health clinician or clinicians, although it is not essential that the clinicians comprising this team be in one program or institution. A clear demarcation of responsibilities and roles (e.g., who will monitor weight, if necessary, or who will monitor frequency of purging behaviors that may require medical monitoring) and frequent and open communication about the treatment plan, progress, and concerns is optimal. Clinicians should strongly encourage patient consent to communicate all clinical information relevant to treatment planning among members of the team and should carefully scrutinize how exceptions will have an impact on treatment. Because splitting and miscommunication are both strong possibilities in such treatment situations, the team should make every effort to reach a consensus about the treatment plan and contingencies for changes depending on patient progress or difficulties and should present a unified front to the patient.

When evaluating an ongoing treatment or the development of a new treatment plan, clinicians should bear in mind that medical, nutritional, and psychological goals are integral to treatment; sometimes, progress with psychological symptoms is predicated on medical and nutritional stabilization. Likewise, if psychological symptoms are not addressed, medical complications and nutritional compromise can recur. With respect to the mental health component of treatment, psychosocial therapies and pharmacotherapies both have a role, but the former appear to be more effective. Thus, pharmacotherapy is more appropriately used as an adjunctive treatment to psychotherapy or when access to psychotherapy is otherwise limited. Although case reports and open trials have provided emerging support for the potential pediatric efficacy of agents with better-understood therapeutic effects in adult populations, such as olanzapine in AN and fluoxetine in BN,[88] data on efficacy and safety for pharmacologic management of eating disorders in children are too limited to support general recommendations for pediatric populations.

TABLE 17–2 Clinical Signs and Criteria Warranting Inpatient-Level Care to Stabilize or Treat an Eating Disorder

DOMAIN	GENERAL SYMPTOM*	EXAMPLE†
Weight	Substantially low weight for height and age	<75%-85% expected body weight
	Rapidly falling weight	
Behavioral	Acute food or water refusal	
	Episodes of bingeing and purging of very high and/or escalating frequency	Bingeing and/or vomiting multiple times per day resulting in social or occupational impairment and/or serious medical complications; ongoing ipecac use; inappropriate withholding of insulin
	Compensatory behaviors likely to result in acute and severe medical complications	
Other medical compromise	Abnormal vital signs reflecting nutritional compromise	Severe hematemesis
	Severe medical complications	Severe neutropenia and/or thrombocytopenia
		Severe hypokalemia
		Uncontrolled type I diabetes
		Syncope
Psychiatric co-morbidity and risk of self-harm	Substantial risk of self-harm or suicide	
	Co-morbid psychiatric illness resulting in safety risk or seriously undermining treatment	Co-morbid substance use escalating in the setting of treatment for the eating disorder
	Inability to adhere to treatment plan that will sustain minimal level of safety	
Treatment-related	Lack of clinically meaningful progress in an outpatient setting resulting in social or occupational impairment or medical risk	An adolescent's low weight poses risk for decreased peak bone mass or short stature
	Necessity of close supervision to maintain symptom control	Sustained or persistent inability to eat without supervision or to abstain from intractable purging after food intake
	Previously agreed-on criterion for hospitalization based on patient history	Reaching a threshold weight at which the patient repeatedly has rapidly deteriorated

* These criteria may be sufficient but do not necessarily need to be present to indicate inpatient care.
† Weight, vital signs, metabolic, and other parameters for hospitalization are best interpreted in the context of the patient's overall health, medical and psychiatric history, support systems, and engagement in treatment.

Medical Intervention for Eating Disorders

Medical complications of eating disorders are common, can affect every organ system, and are potentially severe and even lethal (Table 17–3). Clinicians should be aware that complications are associated with behaviors that can occur across the spectrum of eating disorders. For example, they are associated with poor nutrition (both micronutrient and macronutrient deficiencies), underweight, overweight and obesity, bingeing, vomiting, misuse of prescription and over-the-counter medication and supplements (including ipecac, diuretics, laxatives, stimulants, insulin, and certain naturaceuticals), and excessive exercise.

Assessment for these possible sequelae, and their subsequent correction, is a necessary prerequisite to the management of the patient with an eating disorder. Clinical history and physical examination are routinely augmented with laboratory studies that screen and monitor associated medical conditions. Vital signs and weight require ongoing monitoring. Laboratory examination—including serum chemistries, complete blood count, bone densitometry, and electrocardiogram—is directed at detection of common and potentially life-threatening complications associated with poor nutrition and purging and other inappropriate compensatory behaviors. Common problems and the approach to their management are specified here. However, an exhaustive review of medical complications and treatment of the eating disorders is beyond the scope of this chapter.

Poor nutrition associated with a restricted diet and a low body weight in AN can result in a number of serious medical complications (see Table 17–3). Fluid and electrolyte disturbances require immediate attention. The correction of dehydration, hypokalemia, and metabolic alkalosis is a priority. Intravenous (IV) fluids and electrolytes sometimes need to be used to support these patients to improve these parameters. The optimal strategy for potassium repletion should consider the possibility of total body depletion in the setting of chronic vomiting, diuretic use, and laxative misuse.

Cardiac consequences of AN and BN may be asymptomatic or lethal. Dizziness, palpitations, orthostasis, or syncope may herald cardiovascular danger.[89] Myocardial hypotrophy occurs, often early, with reduced left ventricular mass and output.[90] Hypotension occurs early and orthostasis follows, possibly enhanced by volume depletion. Bradycardia is common in patients with AN, and it probably reflects cardiac impairment associated with reduced stroke volume. QT prolongation, which can be idiopathic in AN,[91] can also be a consequence of hypokalemia in AN and BN. Both QT dispersion and QT interval prolongation are predicted by both low BMI and weight loss in patients with eating disorders. These electrocardiographic

TABLE 17–3 Selected Important Medical Complications of Eating Disorders

Metabolic
Hypokalemia
Hyponatremia; hypernatremia
Hypophosphatemia; hyperphosphatemia
Ketonuria

Endocrine
Euthyroid sick syndrome
Amenorrhea, oligomenorrhea

Skeletal
Osteopenia/osteoporosis (rarely fully reversible)
Impaired peak bone mass

Developmental
Growth arrest; short stature
Delayed puberty; delayed menarche

Reproductive
Oligomenorrhea
Infertility
Miscarriage
Increased rate of cesarean sections
Increased risk for postpartum depression
Intrauterine fetal growth and birth weight
Decreased neonatal Apgar scores

Dermatologic
Acrocyanosis
Carotenemia
Brittle hair and nails
Xerosis
Pruritus
Lanugo
Hair loss

Cardiovascular
Decreased left ventricular mass
Decreased chamber size
Decreased contractility
Decreased stroke volume
Decreased cardiac output
Decreased exercise response
Increased ventricular ectopy
Pericardial effusion (small)
Bradycardia
Orthostatic and nonorthostatic hypotension
Dysrhythmias
ECG abnormalities (including QT interval prolongation and QT dispersion)
Acquired (reversible) mitral valve prolapse
Ipecac cardiomyopathy
Congestive heart failure

Gastrointestinal
Reflux esophagitis
Mallory–Weiss tear (usual cause of hematemesis)
Esophageal or gastric rupture (rare but often lethal)
Gastroparesis (often symptomatic)
Laxative abuse colon
Rectal bleeding
Superior mesenteric artery syndrome
Abnormal liver enzymes with fatty infiltration
Pancreatitis
Functional gastrointestinal disorders

Neurologic
Seizures
Myopathy
Peripheral neuropathy
Cortical atrophy

Immunologic
Blunted febrile response to infection
Impaired cell-mediated immunity

Hematologic
Bone marrow suppression

Renal
Renal calculi
Acute: azotemia
Long-term: renal failure from chronic hypokalemia
Secondary hyperaldosteronism

abnormalities require immediate medical intervention because they increase the risk of ventricular arrhythmia and sudden death.[92]

GI symptoms are common in patients with eating disorders. Constipation brought on by dehydration, or by long-term laxative abuse, often responds to stool softeners and to bulk-forming agents. These symptoms are sometimes accompanied by evidence of delayed gastric emptying and intestinal transit time. Although they may resolve with conservative treatment (including nutritional rehabilitation and establishing routine meals), they may also persist and exacerbate cognitive symptoms that maintain the eating disorder. Although GI signs and symptoms may in some cases be attributed to an eating disorder, primary GI illness should be evaluated in the entire clinical context.[93]

Gastric motility agents are not routinely recommended for alleviating these symptoms in AN patients.[94] Occasionally, marked dilation of the stomach can be seen in patients with AN or those with BN and BED and can augur a medical emergency. The placement of a nasogastric tube provides symptomatic relief with decompression and avoids the dire consequence of gastric rupture.[93]

Osteopenia and osteoporosis are among the most serious clinical concerns accompanying amenorrhea and weight loss in AN. The peak bone mass achieved as a young adult is the major determinant of bone density and fracture risk. AN is associated with markedly reduced bone density, especially at the lumbar spine, but also at the proximal femur and the distal radius. The importance of nutritional factors, lean body mass, and BMI in determining bone mass cannot be overstated. The duration of estrogen deficiency does not determine the severity of the osteopenia, and hormone replacement has not significantly increased bone mineral density in patients with AN,[95–97] and it may in fact be detrimental in that it creates a false sense of security from the monthly withdrawal bleeding without any tangible benefits to the bone. The primary therapy is weight gain. The most appropriate recommendations include a plan for nutritional rehabilitation, supplementation with 1500 mg/day of calcium and 800 IU/day of vitamin D. If the vitamin D level is low,

a higher dose can be given for 1 month. DXA scanning at the initial medical assessment of a patient with an eating disorder and at varying intervals every 12 to 24 months can assist in counseling those at high risk for fractures and bone loss. Bisphosphonates have been used in many conditions that lead to osteoporosis and have been considered for the bone loss of AN. Because data thus far are limited, and conflicting and long-term use of bisphosphonates has been associated with complications (including very rarely, osteonecrosis of the jaw) and with uncertain effects on future pregnancies, their use in treating patients with AN is currently not routinely recommended outside of clinical trials. Several experimental therapies are under investigation.

Medical therapeutic considerations for the comprehensive care of patients with BN, and with AN and EDNOS patients who purge, include a plan to monitor for and address the most common and serious medical complications, including hypokalemia and cardiac dysrhythmias. Potassium losses occur in the setting of chronic purging behaviors associated with either BN or AN (e.g., induced vomiting, laxative abuse, diuretic abuse). Laxative abuse results in diarrhea accompanied by cramping abdominal pain and, at times, rectal pain.[98] Fecal electrolyte losses can be very high as the daily output increases considerably. Large amounts of sodium may be lost, but hyponatremia is uncommon because of the concomitant loss of water. The resulting picture of dehydration with hypotension, tachycardia, postural dizziness, and syncope needs to be addressed acutely, usually with IV fluids and electrolytes. Chronic deficiency of sodium and water may lead to increased renin secretion and secondary hyperaldosteronism that may then become autonomous, persisting after the laxatives are removed, a pseudo-Bartter's syndrome. Hypokalemia, as a result of laxative-related losses and purging, may appear as generalized muscle weakness and lassitude. More profound levels of hypokalemia may be life-threatening with cardiac arrhythmias. Of particular note, hypokalemia can, and often does, appear asymptomatically, so patients with chronic losses through vomiting, laxative abuse, or diuretic abuse must be routinely monitored with serum electrolytes, even in the absence of symptoms. Hyperphosphatemia, hypermagnesemia, and hypocalcemia can also be seen as a result of excessive purging with laxatives. If motility is stimulated enough with the cathartic laxatives, absorption of nutrients may be impaired because of decreased transit time. Although laxatives may cause changes in the intestine itself, such as melanosis coli from pigment-laden macrophages in the submucosa of the colon secondary to anthraquinones, there does not appear to be any functional consequence to this. The "cathartic colon" has not truly been observed during the past few decades, presumably because the laxatives causing this are no longer in use.[99] However, the preference is to manage frequent complaints of constipation with stool softeners as opposed to cathartic agents (so as not to iatrogenically reproduce the purging behavior, promote caloric loss, or waste potassium). Polyethylene glycol solutions, and other osmotic agents such as lactulose, are used to ease evacuation.

GI symptoms are common in BN, and primary GI illness should be evaluated. GI symptoms most commonly seen in BN include bloating, flatulence, constipation, abdominal pain, and nausea. Although rare, gastric rupture has also been reported as a consequence of binge eating. Most of the GI symptoms associated with disordered eating improve with conservative management (nutritional rehabilitation).

Dental hygiene in eating-disordered patients with vomiting should also be addressed. Dental erosion and caries in patients with self-induced vomiting may occur because of the effects of gastric acid on teeth enamel. Preventive techniques to protect from further dental erosion include fluoride application, good brushing techniques, and even the use of mouth guards.[100] Patients who engage in vomiting should routinely be referred for dental care.

Patients who use ipecac to induce vomiting are at risk of a life-threatening cardiomyopathy caused by the emetine in this product.[101]

The comprehensive care of patients with BED includes addressing the medical co-morbidities and sequelae of the condition. Co-morbidities of BED include disorders associated with excess weight such as an elevated risk of type 2 diabetes, hypertension, cardiovascular disease, hypercholesterolemia, osteoarthritis, sleep apnea, gall bladder disease, and certain malignancies.

TREATMENT OF PATIENTS WITH ANOREXIA NERVOSA

Nutritional Rehabilitation

The most appropriate initial treatment strategy for patients with AN addresses weight restoration because of the serious medical consequence of low weight and poor nutrition. For example, the primary therapy for the amenorrhea associated with AN is nutritional rehabilitation. Most patients with eating disorders will recover menses within 6 months of reaching 90% of their ideal body weight.[102] A caveat to that is that menstrual recovery depends on attainment of optimal fat mass, and although some women may recover to normal body weight, they may have very little fat mass. Also, some girls may have undergone alterations in other neuroendocrine hormones, including cortisol, ghrelin, leptin, peptide YY, and adiponectin, all of which may be related to body fat but may also be independent of it.[103] Orthostasis has been observed to remit after several weeks, at about 80% of EBW in adolescents. However, a return to full health requires restoration of normal weight. Low BMI at referral predicts a poor prognosis[104,105] and is associated with significantly higher chronicity and mortality for patients with AN.[106] Relapse rises steeply as the percent of EBW at discharge falls, with 100% minimizing immediate relapse and readmission rising rapidly as discharge weight falls to 95%, 90%, and 85% of EBW.

Undernutrition is also suspected to underlie some of the neurocognitive features of AN that may contribute to poor treatment response. Clinical experience suggests that cognitive inflexibility (e.g., relating to overvalued ideas about body weight) may impede treatment efforts for AN. Indeed, subtle abnormalities in abstraction and cognitive flexibility have been substantiated in studies of individuals with AN.[107,108] It is noteworthy that some of the cognitive abnormalities in those with AN that manifested in attentional domain tasks have been shown to at least partially improve with weight gain.[109] Interestingly, dilated ventricles and sulcal widening on computed tomography (CT)

scans as well as global hypometabolism seen in resting positron emission tomography (PET) studies of patients with AN improve at least somewhat with weight gain.[109,110] However, some aspects of cognitive inflexibility do not improve with treatment[109] and may be endophenotypic of AN. Pretreatment neuropsychological assessment coupled with individualized feedback highlighting the link between general cognitive inflexibility (i.e., a hyperfocus on detail at the expense of the bigger picture) and specific eating disorder symptoms (e.g., preoccupation with nutritional information at the expense of overall nutritional health) has demonstrated preliminary promise for enhancing motivation for treatment of AN.[111]

For AN patients without severe nutritional compromise, weight management can begin in the outpatient setting with the implementation of nutritional counseling (to make adequate dietary selections) and behavioral reinforcement for meeting weight goals. For example, the reinforcement might be to keep the privilege of working as an outpatient or to participate in an extracurricular performance. The treatment team and the patient should identify a weight goal and a timetable for interim goals at the outset of treatment. Generally, a goal weight should be chosen that is appropriate for the height and at which medical complications, such as osteopenia and amenorrhea, are reversed. Guidelines for appropriate duration and level of exercise should be addressed and adjusted as the patient recovers the weight.

Patients with eating disorders are often reluctant to meet with a nutritionist, with the excuse that they already know all there is to know about nutrition. However, they are often overly preoccupied with minor details of nutrition (such as calorie counting or carbohydrate avoidance), and their dietary knowledge may emanate from dubious sources such as fad diet books or websites. Nutritional counseling can also be framed as an activity to assist judgment and motivation. Especially with underweight patients, establishing a caloric requirement and developing a dietary plan to meet the weight goals that are set are highly useful. Minimally, this plan includes three meals daily to establish expectations of eating in alignment with social norms and nutritional adequacy, and it generally includes snacks or caloric supplements (or both) as well. When such a plan is in place, if a patient is unable to gain weight (e.g., the patient requires more calories or more help to adhere to the plan or needs to reduce physical activity), the need for additional measures can be assessed.

If patients are severely underweight (e.g., less than or equal to 75% of expected body weight), are underweight and have rapid weight loss, or remain chronically underweight with medical complications and are unable to gain a reasonable amount of weight as an outpatient, they will require inpatient or partial hospitalization care. Patients may require or benefit from hospital-level care at a higher percent EBW or if he or she has, for example, ongoing psychosocial stressors, a history of a pattern of rapid decompensation, or medical compromise. An inpatient hospital setting for nutritional rehabilitation offers diagnostic and therapeutic opportunities. For example, it promotes assessment of and rapid response to medical complications, and it allows dietary intake to be more carefully monitored, purging and exercise to be controlled, and behavioral reinforcement to be more easily implemented. In addition, if the patient withstands all feeding efforts, nasogastric feedings or parenteral feedings can be considered when there is extreme malnutrition and recalcitrance to treatment. However, most patients can be refed orally at experienced programs, so nasogastric tube feeding or total parenteral nutrition is very rarely required. Patients who require inpatient-level care to gain weight, but who recurrently relapse after discharge, may be best served in a residential care setting for an extended period to achieve and stabilize an adequate weight.

Calories should be increased incrementally, but rapidly, to achieve desired weight gains of 1 to 2 pounds weekly for outpatients and 2 to 3 pounds weekly in hospital settings. Patients vary widely in their caloric requirements for weight restoration, but it is not unusual to require up to 4000 calories a day as refeeding progresses. The measurement of the metabolic rate by indirect calorimetry can be helpful in determining the metabolic needs of the patient and thus the caloric goals. However, measurement of resting energy expenditure (REE) is not widely available, so an estimate of energy needs is usually required. Generally, most hospitalized patients with an eating disorder require at least 1500 kcal/day to maintain weight. Their reduced REE may be as low as 800 to 1000 kcal/day, and maintenance requirements are 130% to 150% of the REE. Approximately 1 g of weight is gained for every 5 calories in excess of output, so 5000 extra calories beyond maintenance is necessary for a weight gain of 1 kg. Weight gain may occur rapidly at first because of fluid retention and the baseline low metabolic rate.[112] Intake levels usually begin at 30 to 40 kcal/kg (1000 to 1600 kcal/day). As the patient with an eating disorder begins to gain weight, metabolic demands increase, and the intake needs to be increased considerably to continue to achieve ongoing weight gain.

Great care needs to be taken during nutritional rehabilitation to avoid the refeeding syndrome, a potentially catastrophic treatment complication that can result in heart failure, delirium, and death in undernourished patients who are being renourished. In this syndrome, the demands that a refilled circulatory system places on a nutritionally depleted cardiac mass result in cardiovascular collapse. This can be seen whether the nutrition is provided orally, enterally, or parenterally.[113] Patients most at risk are those who are the most undernourished. A range of electrolyte derangements can occur during refeeding. Much of the pathophysiology of the refeeding syndrome has been related to the rapid increase of insulin on refeeding.[114] Feeding stimulates insulin release, which, in turn, increases the cellular uptake of phosphate, glucose, and water, as well as stimulating protein synthesis. Insulin also increases sodium and water reabsorption in the renal tubules. Prolonged starvation results in a reduced cardiac mass and output. During the refeeding, ventricular volume returns to normal while left ventricular mass remains reduced, potentially leading to fluid retention and congestive heart failure. Sodium and fluid retention compound this problem. Serum phosphate levels may drop precipitously, leading to depletion of phosphorylated compounds, with impaired energy stores resulting from a decrease in intracellular adenosine triphosphate, and tissue hypoxia secondary to reduced levels of erythrocyte 2,3-diphosphoglycerate. Phosphate

depletion, in turn, produces widespread abnormalities, including cardiac arrest and delirium.[115] Potassium and magnesium also become depleted during starvation. On refeeding, these are deposited intracellularly and serum levels may fall if no supplementation is provided. Although refeeding syndrome generally emerges during the first 2 weeks of refeeding, delirium associated with refeeding can occur even later in the course.

Therefore, nutritional rehabilitation of the severely malnourished patient requires close monitoring for refeeding syndrome; the greatest caution is required during the first weeks after commencing the nutritional support. Specifically, vital signs and physical examination for signs of edema or congestive heart failure should be followed closely during this period—and daily for at least a week. Some patients develop edema without heart failure and may, indeed, have a rapid weight gain in the first few days of refeeding. Phosphorus, magnesium, and serum electrolytes should be closely monitored during at least the first 2 weeks of refeeding (e.g., it is recommended that this begin within 6 to 8 hours of feeding, continue daily for a week, and then continue at least every other day until the patient is stable). Cardiac telemetry is recommended during the first 2 weeks, and subsequent monitoring for complications of refeeding should continue until the patient stablizes.[116–120]

Due to concerns regarding refeeding syndrome, patients are cautiously refed with incremental increases of 200 to 300 kcal/day every 3 to 4 days as tolerated and as determined by individual weight gain. As patients near their target weight, they frequently require large amount of calories, upward of 3000 calories/day. Energy needs may be greater in young, growing adolescents and it often becomes difficult for that group of patients to ingest enough energy to gain weight consistently. Supplements need to be provided. Sodium at 1 mmol/kg per day, potassium at at least 4 mmol/kg per day, and magnesium at 0.6 mmol/kg per day should be given. Phosphate, up to 1 mmol/kg per day intravenously, and oral supplements up to 100 mmol/day can be given to try to avoid the hypophosphatemia associated with refeeding. Extra calcium may need to be given because hypocalcemia may occur during phosphate supplementation. Thiamine should be provided because acute thiamine deficiency can occur with refeeding.[121] Folic acid, riboflavin, ascorbic acid, pyridoxine, and the fat-soluble vitamins A, D, E, and K should be supplemented as well.[122] Trace elements, including selenium, may also be deficient. A good rule of thumb is to provide a multivitamin with minerals on a daily basis.

Psychosocial Therapies

Psychotherapy for patients with AN is often undermined by the effects of starvation and low body weight on cognition. Low-weight patients are often preoccupied with food and weight and relatively rigid in their dietary behaviors. Even modest weight gain can sometimes result in a remarkable improvement in cognitive flexibility, which facilitates further insight and behavioral change. However, persuading a patient to accept any treatment is often challenging. In a recent randomized prospective study of cognitive-behavioral therapy (CBT) and fluoxetine, 46% of patients dropped out before the completion of the study (most citing dissatisfaction with treatment).[123]

A number of psychotherapeutic modalities have been studied in the treatment of AN, including CBT,[124] psychodynamic psychotherapy,[125] and interpersonal psychotherapy.[126] For adolescents with AN, however, manualized family-based treatment (FBT) of adolescent AN has the strongest empirical support. This three-phase treatment lasts approximately 1 year and is based on the premise that the patient cannot control her symptoms, and thus her parents must temporarily claim complete responsibility for her eating.[127] In phase one, parents are encouraged to correct the patient's malnutrition by enforcing a regimented and calorie-dense meal plan. After steady weight gain has been established, food choices are gradually returned to the patient during phase two, and the family is invited to explore the ways in which the AN has affected family dynamics. In the final phase, when the patient has reached a stable weight, therapy focuses on enhancing the patient's autonomy and orchestrating a smooth return to normal adolescent development. FBT has demonstrated superiority to individual psychotherapy for adolescent AN,[128] and longitudinal follow-up studies suggest that approximately three quarters of patients receiving FBT achieve good outcome (normal weight and menstruation) at 4-year[129] and 5-year[130] follow-ups. However, data support efficacy of FBT only for adolescents—not for adults—with AN, and it is less effective in patients with a longer duration of illness. Moreover, it can only be implemented for patients whose families are willing to participate in treatment.

There are fewer empirical findings to guide psychosocial treatment selection in adults with AN. Outpatient CBT was superior to nutritional counseling alone in preventing relapse among a group of AN patients who had recently achieved inpatient weight restoration.[131] However, nonspecific supportive clinical management (a combination of case management and supportive psychotherapy) was as effective as CBT and superior to interpersonal therapy (IPT) in improving global outcome (a combined index of weight gain and reductions in eating disorder psychopathology) among outpatients with AN.[132] Conflicting randomized controlled trial (RCT) findings have prompted preliminary exploration of novel adjunctive treatments to target specific aspects of anorexic psychopathology. For example, graduated mirror exposure and response prevention, when added to a structured body image group treatment, was associated with significant reduction in the Body Dissatisfaction and Maturity Fears Subscales and significant improvement in the Interoceptive awareness subscale of the Eating Disorders Inventory at 6-month follow-up.[133] Similarly, exposure therapy encouraging AN patients to habituate to an unfamiliar, energy-dense test meal contributed to increased caloric intake of the same test meal after inpatient weight restoration compared with historical controls.[134]

Pharmacologic Management

Because of the desirability of weight gain in the early treatment of AN, there has been interest in identifying pharmacologic agents that promote weight gain in

patients with AN. Most efforts to identify pharmacologic agents to treat the primary symptoms of AN have been disappointing. Studies investigating the efficacy of chlorpromazine, pimozide, sulpiride, clomipramine, clonidine, and tetrahydrocannabinol[135] in addressing the primary symptoms of AN have all yielded negative results. It is important to emphasize the limited role for pharmacologic management of AN (Table 17–4), because patients with AN are frequently intolerant of medication side effects. Because there are no medications approved by the FDA for the treatment of AN, the use of pharmacologic agents to treat primary symptoms of AN is not only of questionable therapeutic value but also off-label.

Although few pharmacologic treatment strategies have shown promise, very preliminary data suggest that olanzapine, an atypical antipsychotic with a serotonin–dopamine antagonist profile, may have short-term clinical benefit in combination with day hospital treatment for AN. In a 10-week, double-blind, placebo-controlled flexible dose trial (to 10 mg/day), olanzapine resulted in a greater rate of weight gain and a greater rate of decrease in obsessive thoughts.[136] There are insufficient data to support recommendations for efficacy of olanzapine outside of concomitant structured treatment or beyond 10 weeks or for other atypical antipsychotic medications.

Empirical support for efficacy of serotonin selective reuptake inhibitors in the treatment of AN is also quite limited. Sertraline (50 to 100 mg/day) may promote some beneficial cognitive changes (e.g., reduction of perfectionistic attitudes and sense of ineffectiveness) in patients with AN, but there was no evidence that it promoted significant weight gain in AN patients compared with placebo in an open, controlled study.[137] Citalopram may have some efficacy in improving depression, obsessive-compulsive symptoms, and impulsiveness in this population.[138] Fluoxetine has been studied for stabilization in weight-recovered patients with AN in two RCTs. One of these demonstrated some efficacy (when adjunctive to elective psychotherapy) at a dosage of 20 to 60 mg/day, whereas the other failed to show efficacy compared with placebo when added to CBT (at a target dosage of 60 mg/day).[139] Whereas fluoxetine may have a role in stabilizing weight-recovered patients,[140] it does not appear effective in addressing symptoms of AN in patients who are underweight (i.e., those who meet weight criteria for diagnosis).

AN is frequently co-morbid with other mental disorders that can benefit from medication management, although clinical experience suggests reduced efficacy of antidepressant therapy in the setting of low weight. Agents that promote weight loss or diminish appetite should be avoided if possible. In addition, when agents that can prolong the QT interval or cause orthostatic hypotension are deemed essential, they should be implemented with extra caution along with appropriate monitoring and instruction to the patient. Finally, medications that promote appetite or weight gain can have the inadvertent effect of triggering binge episodes and should therefore be used judiciously—and with full transparency to the patient—if indicated for other symptom targets for patients with AN.

TREATMENT OF PATIENTS WITH BULIMIA NERVOSA

Individuals with BN are often eventually sufficiently distressed to seek and accept treatment, even if they remain ambivalent about relinquishing specific symptoms. As with AN, multidisciplinary team treatment to ensure adequate attention to nutritional and medical issues should be negotiated with the patient at the outset of treatment. Psychotherapy, with appropriate medical and nutritional monitoring and intervention, is the first-line treatment for BN. Although psychotherapy would not typically be feasible in a general hospital inpatient setting, patients can be informed about therapeutic options and provided with referrals. Among psychotherapeutic interventions studied, CBT has the strongest evidence supporting its efficacy in the treatment of BN.[141] Despite the high efficacy of CBT for many patients, a meta-analysis demonstrated that recovery rates (based on intention to treat) for subjects undergoing CBT for BN were only 38%.[142] Therefore, response to previous treatment, chronicity, severity of symptoms, co-morbid medical and psychiatric illness, psychosocial function, treatment availability, and patient preferences and capacities should inform treatment selection as well.[143]

CBT for BN is available in a manual for standardized care and is designed for completion in approximately 20 weeks. The treatment is based on educating the patient with a cognitive model of how symptoms of BN are perpetuated. That is, patients are introduced to a model in which low self-esteem, weight and shape concerns, dieting, binge eating, and purging operate in a self-perpetuating cycle.[144] The patient is asked to self-monitor intake with a food record to identify individualized triggers for binge eating and purging, which may include undereating, breaking self-imposed food rules, and negative affective states. The CBT therapist assists the patient in developing a schedule of regular eating (three meals and two snacks daily), and uses the information gained in the self-monitoring records to help the patient design relevant stimulus control strategies, such as keeping trigger foods out of sight or reach, and engaging in pleasant activities to distract from urges to binge (e.g., talking on the phone, going for a walk, or listening to soothing music). The CBT therapist also assists the patient in gently challenging cognitive distortions that perpetuate the disorder (e.g., "I must be thin to be happy"), reducing the body-checking and avoidance behaviors that exacerbate body dissatisfaction, and cultivating aspects of self-evaluation other than shape and weight. Last, the patient develops a relapse-prevention plan by identifying stressful situations (that may trigger future symptoms), and problem-solving potential solutions.

Up to 62% of the improvement seen in CBT treatment of BN occurs within the first 6 weeks.[145] A limitation of CBT has been that those who do not recover often remain substantially symptomatic and impaired in other domains.[142,143] An enhanced version of CBT (CBT-E) addresses this issue. It features an increased emphasis on mechanisms such as overvaluation of shape and weight, and emotion dysregulation. It also has optional modules specifically designed to target the features commonly encountered in treatment-resistant BN, including mood intolerance, clinical perfectionism, low self-esteem, and interpersonal difficulties.[146]

TABLE 17–4 Pharmacologic Agents with Efficacy in Treating Primary Symptoms of AN, BN, and BED, as Demonstrated in RCT Data*

	DOSAGE	COMMENTS OR CAVEATS
Anorexia Nervosa†		
Olanzapine	2.5-10 mg/day	Short-term efficacy in greater rate of weight gain when combined with day hospital treatment Potentially undesirable side-effect profile: somnolence, postural hypotension, QT interval changes, and metabolic effects
Fluoxetine†	20-60 mg/day	Stabilization of weight-recovered patients (i.e., patients at >85% EBW) in combination with elective adjunctive therapy Combination with adjunctive CBT did not show efficacy in trial
Bulimia Nervosa§		
Fluoxetine	60 mg/day	Best studied; well tolerated; only agent with FDA approval for this indication
Sertraline	100 mg/day	Data limited to one small, short-term RCT
Topiramate	Up to 250 mg/day Up to 400 mg/day	Potentially undesirable side-effect profile: sedation and cognitive changes, weight loss, renal calculi Both studies started at 25 mg/day and titrated upward as tolerated
Ondansetron	24 mg/day in six divided doses	High cost Effective for patients with severe BN
Of Limited Clinical Use		
Fluvoxamine‡	Up to 300 mg/day in divided doses	Inconsistent results in two RCTs, grand mal seizures in some study participants on active drug, but causal association unknown
Imipramine	Up to 300 mg/day	Potentially undesirable side effect profile: effects on pulse, blood pressure, and QT interval that potentiate medical complication seen in BN (e.g., QT interval lengthening associated with hypokalemia) High lethality in overdose
Desipramine	Up to 300 mg/day	Potentially undesirable side effect profile: effects on pulse, blood pressure, and QT interval that potentiate medical complication seen in BN (e.g., QT interval lengthening associated with hypokalemia) High lethality in overdose
Trazodone	Up to 400 mg/day	Potentially undesirable side-effect profile: sedation
Naltrexone‡	200-300 mg/day	Potentially undesirable side effect profile: hepatotoxicity Effective for patients who had not responded to a trial of antidepressant pharmacotherapy
BED‖		
Sibutramine‡	15 mg/day	Effective in a multisite trial
Topiramate	25-400 mg/day	Effective for patients with BED + obesity in a multisite trial Potentially undesirable side-effect profile: sedation, cognitive changes, paresthesia
Sertraline	50-200 mg/day	Effective for patients with BED + obesity
Fluvoxamine‡	50-300 mg/day	Effective for patients with BED + obesity in a multisite trial
Citalopram	20-60 mg/day	Effective for patients with BED + obesity
Fluoxetine‡	20-80 mg/day	Effective for patients with BED + obesity
Atomoxetine	40-120 mg/day	Effective for patients with BED + obesity
Orlistat (in combination with reduced calorie diet)	120 mg tid	Significant binge remission may not be maintained at 3 months Examined effects on BED in obese patients Was not effective at this dose in combination with CBT

*With the exception of fluoxitine or BN, none of these is FDA-approved for an eating disorder and thus use in treatment of an eating disorder is considered off-label.

† Cyproheptadine and zinc excluded because of mixed support and/or limited data, and because they are not in routine clinical use for AN.

‡ Negative study RCT data were also published on this agent for this indication.

§ Bupropion, phenelzine, and isocarboxazid excluded because of their potential for serious adverse reactions; bupropion and monoamine oxidase inhibitors are contraindicated in patients with BN; flutamide excluded because of limited support for efficacy and potential for hepatotoxicity and teratogenicity.

‖ Zonisamide 100-600 mg/day excluded because it was not well tolerated in the study sample.

AN, Anorexia nervosa; *BED*, binge-eating disorder; *BN*, bulimia nervosa; *CBT*, cognitive behavior therapy; *EBW*, expected body weight; *RCT*, randomized controlled trial.

CBT-E is designed to be offered to patients with any eating disorder diagnosis. An RCT comparing CBT to wait-list control for BN and EDNOS patients found that over half the sample endorsed eating-disorder features less than 1 standard deviation above the community mean at 60-week follow-up, indicating that CBT-E may be even more efficacious than the original version.[147]

With regard to alternative psychotherapeutic modalities for BN, IPT is as effective but generally takes longer to achieve a result than does CBT, thus increasing the length of time the patient is exposed to bulimic symptoms.[141,148,149] Other therapies that have some empirical support for the treatment of BN include dialectical behavioral therapy,[150] psychodynamic psychotherapies,[151] guided imagery,[152] and guided self-change (incorporating a self-care manual).[153]

In their work with BN patients at risk for relapse to more harmful self-destructive behaviors (such as cutting, suicide attempts, and substance abuse), clinicians need to weigh the benefits and risks of postponing focused efforts to reduce behaviors associated with eating disorders that may pose less medical risk. For example, some patients benefit from interim therapeutic goals focused on developing effective and constructive coping strategies if abstinence from eating disorder symptoms would jeopardize sobriety or safety. These treatment teams must closely monitor the frequency and severity of purging and focus on other inappropriate compensatory behaviors, and address medical safety and adjust treatment as appropriate. Moreover, it may not be medically safe or therapeutically appropriate to postpone a treatment focus on restrictive eating, bingeing, or purging behaviors. When there is an urgency to address eating symptoms, but there is concomitant concern that this treatment may precipitate a relapse of other self-harm behaviors, psychiatric inpatient care may be warranted.

Pharmacologic Management

Augmentation with medication with demonstrated efficacy in BN may further reduce symptoms, and fluoxetine 60 mg/day appears to be beneficial in reducing symptoms for patients with BN who have not responded well to CBT or IPT.[154] Several pharmacotherapies have modest short-term efficacy for BN, but remission rates are low (see Table 17–4)[155] and medication management is generally considered as an adjunctive—rather than a first-line—strategy for the treatment of BN. Fluoxetine is the only FDA-approved agent for the treatment of BN, and use of other agents is therefore considered off-label.

The decision to augment a psychosocial therapy with medication in the treatment of BN hinges on co-morbid illness, severity, past response to medication, patient preference, and patient commitment to adherence to a medication regimen. Choice of medication is guided by side-effect profile, history of response, and expense, because the data are insufficient to support greater efficacy for any particular agent. However, data do support consecutive trials if a patient does not respond to the first agent. If an agent is prescribed, it is essential to ensure that the dosing schedule is arranged so that the drug is sufficiently absorbed before the purging behavior.

Fluoxetine 60 mg/day is the first-line pharmacologic agent in the treatment of BN. It has shown efficacy in the reduction of symptoms of BN compared with placebo in two large RCTs, is generally well tolerated among individuals with BN, and shows efficacy in maintenance therapy over the course of a year.[156–158] Monotherapy with fluoxetine has also been found more effective than placebo for treatment of BN in a primary care settting.[159]

Sertraline was found to be effective in reducing the number of binge eating and purging episodes among patients with BN in a small RCT.[160] Fluvoxamine was evaluated in two clinical trials with inconsistent findings. One of these trials reported grand mal seizures among some study participants on active drug, although causal association is unknown.[161,162]

Other classes of agents also show promise for the reduction of symptoms of BN. Topiramate was found to significantly reduce symptoms when compared with placebo in two 10-week RCTs.[163–165] In addition, although naltrexone is not in routine clinical use, one study demonstrated that it had short-term efficacy at 200 to 300 mg/day versus standard dosages (50 to 100 mg/day) for patients with BN who had not previously responded to antidepressant therapy.[166] One RCT demonstrated short-term efficacy of ondansetron (24 mg/day divided into six doses) in severely symptomatic BN.[167] The risk for hepatotoxicity associated with naltrexone and cost associated with ondansetron limit clinical use of either of these options, however. Similarly, a small RCT suggested efficacy of flutamide for reduction of binge episodes (but not vomiting) in BN. However, given limited support for its clinical use and the associated risk of teratogenicity and hepatotoxicity with this agent, it cannot be recommended for the management of BN.[168]

Likewise, although imipramine, desipramine, and trazodone have been found effective in reducing symptoms in patients with BN, their side-effect profiles limit their use in this clinical population.[169–174] Finally, several agents should not be used for the treatment of BN. The risk of serious adverse events associated with both bupropion (seizures) and monoamine oxidase inhibitors (spontaneous hypertensive crises) in patients with BN contraindicates their use for the management of BN.[135,175–177] The use of these medications to manage co-morbid depression in the setting of BN is relatively contraindicated as well and warrants careful consideration of risk-to-benefit ratios in the context of each patient's individualized needs.

TREATMENT OF PATIENTS WITH BINGE-EATING DISORDER

Patients with BED are often quite willing to seek and accept treatment because of their high levels of distress and their eagerness to combat the co-morbid obesity (if present). Although BED is a recently described nosologic category in the DSM-IV (currently defined with research criteria), there has been rapid progress in identifying effective psychosocial and pharmacologic treatment. Because BED is frequently co-morbid with obesity, and because obesity is believed to contribute to risk for BED, weight reduction is often a primary goal of treatment and, unlike in patients with BN, it can be pursued concurrently or sequentially depending on the clinical situation.[178]

CBT, the best-studied psychosocial intervention for BED, has the strongest empirical support in the reduction

of the hallmark feature of the syndrome, binge eating.[179] Because the disorders share features, CBT for BED is similar to that for BN, featuring self-monitoring of food consumption, normalization of eating, implementation of distraction techniques, challenging of cognitive distortions, and development of a relapse-prevention plan. In an RCT comparing CBT to pharmacotherapy for BED, 61% of patients who received CBT plus placebo and 50% of patients who received CBT plus fluoxetine abstained from binge eating after treatment. Both CBT treatments were superior to fluoxetine (22%) or placebo (26%) alone.[180] Unfortunately, despite good efficacy in the reduction of binge eating, CBT is not associated with significant weight loss in obese patients with BED.[179,181,182] For this reason, clinicians have attempted to modify and augment the CBT protocol with medications and other psychosocial strategies in an attempt to improve results. For example, patients who complete experiential cognitive therapy (which incorporates a nutrition group, virtual reality therapy, daily moderate physical activity, and group therapy focused on increasing motivation and assertiveness) demonstrate lower rates of bingeing than those enrolled in traditional CBT or nutrition groups. Similarly, the addition of moderate exercise to CBT alone is found to further decrease the frequency of bingeing.[183]

Alternatives to CBT have demonstrated efficacy for BED as well. Specifically, substantial reductions in binge eating in the first 4 weeks of behavioral weight loss (BWL) treatment predict further reductions not only in binge eating but also in BMI. This finding has prompted speculation about the potential efficacy of a stepped care model in which patients begin treatment with BWL and subsequently transfer to CBT only if they are unable to achieve rapid BWL response.[184] As seen in results of studies comparing them for patients with BN, group IPT is as effective as group CBT in terms of posttreatment and follow-up binge eating recovery rates (i.e., approximately half of patients recover).[185] However, those participating in CBT are typically able to achieve change more quickly, usually through decreasing dietary restraint.[182] Participants in dialectical behavior therapy groups adapted for BED demonstrate significantly higher remission rates at the end of treatment in comparison to wait-list controls.[186] Finally, self-help versions of CBT delivered by book or CD-ROM are superior to wait-list control in reducing binge eating among individuals with both BN and BED, but the comparative efficacy of self-help versus traditional therapist-led CBT remains unknown.[187]

Pharmacologic Management

Pharmacologic therapies for the treatment of BED are being rapidly identified, and several medications have demonstrated efficacy in reducing symptoms of BED, or of BED with obesity, in RCTs, as a single or as an adjunctive treatment (see Table 17–4). However, none of these medications has FDA-approval for this indication, and the majority of the studies have investigated only relatively short-term use of the medication (3 months or less). Moreover, for the majority of agents, little is known about maintenance of symptom reduction after the drug is discontinued. Two agents have established efficacy for the reduction of symptoms associated with BED in multisite placebo-controlled trials: sibutramine for patients with BED[188] and fluvoxamine[189] and topiramate for obese patients with BED.[190]

Other agents with demonstrated efficacy in at least one RCT for reducing the symptoms of BED are sertraline,[191] citalopram,[192] fluoxetine,[193] atomoxetine,[194] orlistat in combination with a reduced calorie diet,[195] and zonisamide.[196] However, zonisamide was not well tolerated in the study population, and, in the or list at study, there was no significant difference in the rates of BED in the treatmetn versus control group at 3-month follow-up.[195]

Notwithstanding the promise of the emerging evidence of efficacy for pharmacotherapy for BED, long-term outcome data are not yet available on which to base recommendations for maintenance therapy strategies for this disorder. Evidence supports CBT as superior to pharmacotherapy. Although augmentation of CBT with topiramate (dosage range, 25 to 300 mg/day) was more effective than placebo augmentation in achieving BED remission in obese adults,[197] and fluvoxamine 300 mg/day augmenting CBT was more effective than CBT alone in reducing eating disorder pathology (as measured by the Eating Disorder Examination score) in the short term for patients with BED,[198] the efficacy of augmentation with other medications is not established.[199,200]

Because of the prevalence of BED in the weight-treatment–seeking population, a high percentage of patients seeking gastric bypass surgery for weight control have comorbid binge eating.[201,202] The long-term impact of bariatric surgery on binge eating is still unclear, as empirical data are mixed. One methodological issue that may account for differential findings across studies is the problematic definition of *binge eating* in postsurgical patients who may not be able to consume large amounts of food but who nonetheless experience bouts of loss of control and distress. Taken together, the evidence suggests that some patients who present with frank presurgical binge eating or BED continue to exhibit loss-of-control eating after surgery, and that postsurgical loss-of-control eating is associated with less weight loss, greater weight re-gain, and poorer psychosocial outcomes.[203] However, presurgical BED should not be viewed as a contraindication for bariatric surgery, because many other patients cease binge eating after surgery and the majority of patients experience weight loss and improved health even if some weight is re-gained.[204] Instead, presurgical psychiatric evaluation should be used as an opportunity to provide education about realistic weight loss expectations, identify potential barriers to meal-plan compliance, and recommend binge eating treatment (e.g., CBT, medication) if indicated.

SUMMARY

At Massachusetts General Hospital, and in many general hospital settings, patients with eating disorders frequently present with a serious, chronic, medically complicated, or co-morbid illness. For patients with previously unidentified or untreated eating disorders, an inpatient admission can present opportunities both to develop and coordinate a multidisciplinary team and for discussions about nutrition and psychoeducation. Inpatient assessment should ascertain the scope and severity of cognitive and behavioral symptoms associated with the eating disorder as well

as other psychological risks and psychiatric co-morbidities. Assessment of nutritional compromise and medical complications of the weight and behavioral symptoms are also essential to therapeutic planning. Interventions typically include assisting the medical team to complete an appropriate diagnostic work-up and address potential medical and nutritional complications as well as develop a plan for any behavioral interventions to be implemented during the admission. Psychoeducation and engagement of the patient and determination of appropriate disposition and available resources are two further goals of psychiatric consultation. Finally, in some cases, behavioral strategies (to stabilize weight, or to modify inappropriate compensatory behaviors) and pharmacotherapy can be implemented or initiated in a general hospital setting.

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18 Pain Patients

Shamim H. Nejad, M.D.
Menekse Alpay, M.D.

Of all human experience, pain is, as long as it lasts, the most absorbing; it is the only human experience that when it comes to an end, automatically confers a sense of relief and joy. Moreover, by its very nature it is solitary. However, the oddest thing about pain is that despite its intensity and its unequalled power over mind and body, it is difficult to recall when it is over.[1]

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[2] This definition recognizes the fact that pain has both an acute nociceptive aspect and an emotional and psychiatric dimension; these factors suggest that psychiatrists have a significant role in the treatment of the pain patient. Conceptualizing pain in this manner underscores the fact that pain is an important and complicated sensation, one that can occur in a multitude of ways.

In this chapter, we review the pathophysiology of pain, along with common pain syndromes and terminology. In addition, the role of the psychiatric consultant in the psychiatric assessment and management of the pain patient will be discussed. Furthermore, we will outline general principles of pain therapy, including use of medications commonly used for pain management, and review approaches to the treatment of pain behavior.

PATHOPHYSIOLOGY OF PAIN

To understand pain one needs to know about the pathophysiology of nociception and to realize that the threshold, intensity, quality, time course, and perceived location of pain are determined by central nervous system (CNS) mechanisms.[3] For example, neurosurgeons have shown that interruption of the specific pain pathways often does not eliminate pain; numbness does not confer analgesia. Peripheral nerve damage can result in changes in the receptive fields and recruitment of neurons at multiple levels of the nervous system (from the dorsal horn to the brainstem and to the thalamus and cortex). Somatic therapies directed only at nociceptive input may be ineffective.[4]

Detection of noxious stimuli (i.e., nociception) starts with the activation of peripheral nociceptors (somatic pain) or with the activation of nociceptors in bodily organs (visceral pain). Somatic pain is usually well localized, attributable to certain structures or areas, and described as stabbing, aching, or throbbing. In contrast, visceral pain may be poorly localized, is not necessarily attributable to the involved organ (as is the case with referred pain), and is characteristically described as dull and crampy.

Tissue injury stimulates the nociceptors by the liberation of prostaglandins, arachidonic acid, histamine, and bradykinin. Subsequently, axons transmit the pain signal to the spinal cord (to cell bodies in the dorsal root ganglia; Figure 18–1).

Three different types of axons are involved in transmitting a painful stimulus from the skin to the dorsal horn. A-β fibers are the largest and most heavily myelinated fibers that transmit awareness of light touch. A-δ fibers and C fibers are the primary nociceptive afferents. A-δ fibers are 2 to 5 μm in diameter and are thinly myelinated. They conduct immediate, rapid, sharp, and brief pain (first pain) with a velocity of 20 m/sec. C fibers are 0.2 to 1.5 μm in diameter and are unmyelinated. They conduct prolonged, burning, and unpleasant pain (second pain) at a speed of 0.5 m/sec. A-δ and C fibers enter the dorsal root and ascend or descend one to three segments before synapsing with neurons in the lateral spinothalamic tract (substantia gelatinosa in the gray matter).

Substance P, an 11-amino-acid polypeptide that is the major pain neurotransmitter, is released from the fibers at many of these synapses. Capsaicin, which is extracted from red hot peppers, inhibits nociception by inhibiting substance P. Inhibition of nociception in the dorsal horn is functionally quite important. Stimulation of the A-δ fibers excites some neurons and inhibits others. This inhibition of nociception through A-δ fiber stimulation might explain effects of acupuncture and transcutaneous electrical nerve stimulation (TENS). The lateral spinothalamic tract crosses the midline and ascends toward the thalamus. At the level of the brainstem more than half of this tract synapses in the reticular activating system (in an area called the *spinoreticular tract*), in the limbic system, and in other brainstem regions (including centers for the autonomic nervous system). Another site of projections at this level is the periaqueductal gray (PAG; Figure 18–2), which plays an important role in the brain's endogenous analgesia system. After synapsing in the thalamic nuclei, pain fibers project to the somatosensory cortex, located posterior to the Sylvian fissure in the parietal lobe (Brodmann's areas 1, 2, and 3).[5]

Developments in imaging technology have been helpful in understanding the relationship between pain pathways and cortical and limbic areas. These findings might help explain the relationship among emotions, cognition, and pain modulation that we observe in clinical practice as heightened pain perception in depressed patients and high rates of depression in those with chronic pain. Functional imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have shown that acute traumatic nociceptive pain

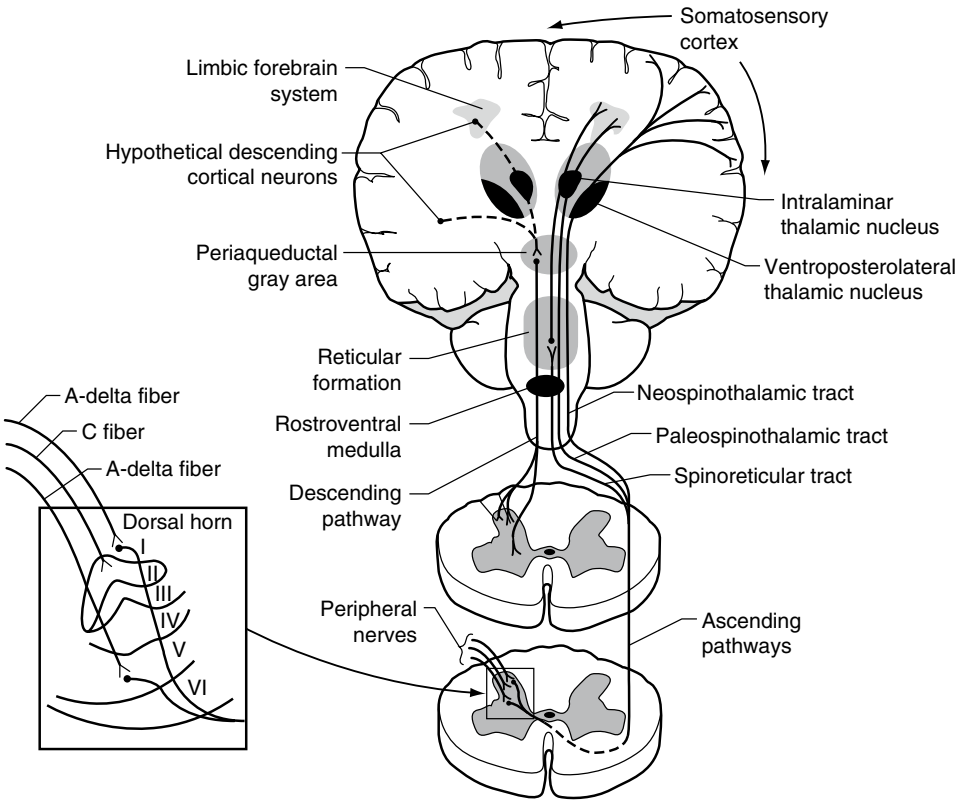

Figure 18–1. Schematic diagram of neurologic pathways for pain perception. *(From Hyman SH, Cassem NH: Pain. In Rubenstein E, Fedeman DD, eds.* Scientific American medicine: current topics in medicine. Subsection II. *New York, 1989, Scientific American, pp 1–17. Originally from Stern TA, Herman JB, editors:* Psychiatry update and board preparation, *New York, 2004, McGraw-Hill.)*

activates the hypothalamus and the PAG in addition to the prefrontal cortex (PFC), insular cortex, anterior cingulate cortex (ACC), posterior parietal cortex, primary motor and somatosensory areas, supplementary motor area (SMA), thalamus, and cerebellum.[6] Additionally, functional imaging studies have helped clinicians understand cognitive and emotional modulation of pain perception. Researchers have shown that with hypnotic suggestion the activity in the ACC depends on the intensity of the suggestion: The same stimulus with the suggestion of "highly unpleasant" induces significantly more ACC activation than when suggestions are less unpleasant.[7,8] In another study, when subjects were distracted during a painful stimulus, pain perception was attenuated in somatosensory regions and the PAG.[9] The short-acting opioid remifentanil and placebo analgesia have been shown to activate the ACC, which is rich in opioid receptors.[10] Analgesia induced by both opioids and placebos can be reversed with the opioid antagonist naloxone.[11] These findings suggest that cortical areas might exert control over lower brain areas involved in opioid analgesia.[10]

Endogenous analgesic systems involve at least 18 endogenous peptides with opiate-like activity in CNS (e.g., endorphins, enkephalins, and dynorphins). Different opiate receptors are involved in different effects of opiates. Mu receptors are involved in regulating analgesia, respiratory depression, constipation, and miosis. Mu receptors (located in the PAG, rostral ventral medulla, medial thalamus, and dorsal horn of the spinal cord) are mainly responsible for supraspinal analgesia. Kappa receptors are involved in spinal analgesia, sedation, and miosis. They are located in the dorsal horn (spinal analgesia), deep cortical areas, and other locations; pentazocine preferentially acts on these receptors. Delta receptors, like kappa receptors, mediate spinal analgesia, hypotension, and miosis. Enkephalins have a higher affinity for these receptors than do opiates. They are located in the limbic system, the dorsal horn, and other locations unrelated to pain. Delta receptors also mediate psychotomimetic effects (i.e., psychosis) in the CNS. Their effects are not reversed by naloxone, an opiate antagonist.[5]

In terms of anatomic organization, the centers involved in endogenous analgesia include, in addition to the PAG, the rostral ACC, amygdala, parabrachial plexus in the pons, and rostral ventromedial medulla.[10]

The descending analgesic pain pathway starts in the PAG (which is rich in endogenous opiates), projects to the rostral ventral medulla, and from there descends through the dorsolateral funiculus of the spinal cord to the dorsal horn. The neurons in the rostral ventral medulla use serotonin to activate endogenous analgesics (enkephalins) in the dorsal horn. This effect inhibits nociception at the level of the dorsal horn because neurons that contain enkephalins synapse with spinothalamic neurons.

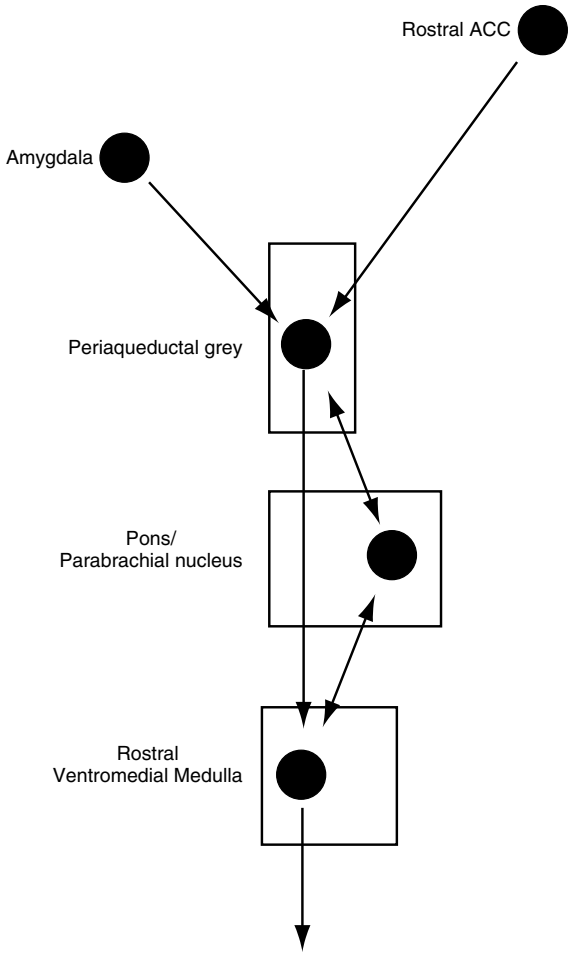

Figure 18–2. Endogenous opioid systems. *(From Petrovic P, Ingvar M: Imaging cognitive modulation of pain processing,* Pain *95:1–5, 2002.)*

Additionally, there are noradrenergic neurons that project from the locus ceruleus (the main noradrenergic center in the CNS) to the dorsal horn and inhibit the response of dorsal horn neurons to nociceptive stimuli. The effect of tricyclic antidepressants (TCAs) and other newer antidepressants is thought to be related to an increase in serotonin and norepinephrine that inhibits nociception at the level of the dorsal horn.[5]

PAIN TERMINOLOGY

Acute pain is usually related to an identifiable injury or to a disease; it is self-limited and resolves over hours to days or in a time frame that is associated with healing. Acute pain is usually associated with objective autonomic features (e.g., tachycardia, hypertension, diaphoresis, mydriasis, or pallor).

Chronic pain (i.e., pain that persists beyond the normal time of healing or lasts longer than 6 months) might have a neurologic origin. It has several features: lowered firing thresholds for spinal cord cells that modulate pain (triggering pain more easily); anatomic plasticity and recruitment of a wide range of cells in the spinal cord (so that touch or movement causes pain); convergence of cutaneous, vascular, muscle, and joint inputs (where one tissue refers pain to another); or aberrant connections (electric short-circuits between the sympathetic and sensory nerves that produce causalgia). Muscle pains often add to the pain experience. Vascular and other visceral mechanisms share features with neurologic mechanisms; however, these mechanisms involved are not mutually exclusive.[12,13] Table 18–1[14–26] summarizes the clinical implications of the mechanisms of chronic pain. Characteristic features include vague descriptions of pain and an inability to describe the pain's timing and localization. Unlike acute pain, chronic pain lacks signs of heightened sympathetic activity. Depression, anxiety, and premorbid personality problems are common in this patient population. Usually the major issue is a lack of motivation and incentive to improve. It is usually helpful to determine the presence of a dermatomal pattern (Figure 18–3), determine the presence of neuropathic pain, and assess pain behavior.

Continuous pain in the terminally ill tends to originate from well-defined tissue damage due to terminal illness (e.g., cancer). It is a variant of nociceptive pain. Stress, sleep deprivation, depression, and premorbid personality problems can exacerbate this pain.

Neuropathic pain is caused by an injured or dysfunctional central or peripheral nervous system; it is manifested by spontaneous, sharp, shooting, or burning pain that is usually distributed along dermatomes (see Figure 18–3). Neuropathic pain is often observed in deafferentation pain, complex regional pain syndrome (CRPS), diabetic neuropathy, central pain syndrome, trigeminal neuralgia, or postherpetic neuralgia.

Terms commonly used to describe neuropathic pain include *hyperalgesia*, an increased response to stimuli that are normally painful; *hyperesthesia*, an exaggerated pain response to noxious stimuli (pressure or heat); *allodynia*, pain with a stimulus not normally painful (e.g., light touch or cool air); and *hyperpathia*, pain from a painful stimulus with a delay and a persistence that is distributed beyond the area of stimulation.

CRPS, formerly known as reflex sympathetic dystrophy (RSD), is a syndrome of sympathetically maintained pain, or pain in an extremity that is mediated by sympathetic overactivity. The syndrome is usually caused by injury; however, the cause is unknown in approximately 10% of cases. Either microtrauma or macrotrauma (such as a sprain, a fracture, or a contusion) can cause it; iatrogenic causes include amputation, lesion resection, myelography, and intramuscular injections. CRPS may be related to disease, such as myocardial infarction, shoulder–hand syndrome, herpes zoster, cerebrovascular accidents, diabetic neuropathy, disc herniation, degenerative disc disease, neuraxial tumors or metastases, multiple sclerosis, or poliomyelitis. CRPS is divided into two types. In type I CRPS, which typically develops after minor trauma or fracture, no overt nerve lesion is detectable. In type II CRPS, a definable nerve injury is present. According to the diagnostic criteria set forth by the IASP, the diagnosis of CRPS can be made if the following criteria are met[27]:

TABLE 18–1 Chronic Pain: Nervous System Pathophysiology[14–26]

NEUROLOGIC MECHANISMS	PHYSIOLOGIC EFFECT	CLINICAL IMPLICATIONS
Neuroplasticity[14–15]	Recruitment of cortical and subcortical neurons so wide dynamic range cells can be activated by low-threshold mechanoreceptors Allodynia Allaesthesia	Early, concurrent, multimodal treatment of nociceptive, central, vascular, sympathetic, and psychiatric aspects of the pain Block glutamate, substance P Early use of anticonvulsants, membrane stabilizers, sympatholytics NMDA antagonists
NMDA excess and glutamate–GABA imbalance[16–19] Glutamate up, GABA down	Morphine tolerance Central hyperalgesia Hyperexcitability of peripheral and central pain cells	Normally nonpainful light touch, muscle and joint movements are painful Treatment options: benzodiazepines, baclofen, anticonvulsants, substance P antagonists, or other NMDA antagonists (e.g., ketamine), GABA agents
Neurotoxins[20]	Excitotoxic (e.g., quinolinic acid) neuropathy	AIDS pain: anticonvulsants, serotoninergic and noradrenergic agents, free radical scavengers
Opioid "off" mechanisms[21–22] Off cells in the medulla Morphine 3G and morphine up Side-effect intolerance	Hyperalgesia as narcotics increase (particularly intrathecal) Tolerance as morphine 3G increases Side effects greater than benefit	Maintain steady blood levels of narcotics, or decreased narcotic can increase pain Switch to a different narcotic if one does not work Trial off narcotics if narcotics not working
Sympathetic pain[15]	Mechanoallodynia, swelling Dystrophic changes	Sympathetic blockade and/or α-blocking drugs may be useful in CRPS, trauma, facial pain, arthritis
Monoamines (5-HT, NE, dopamine)[23–26]	5-HT increase lessens opiate analgesia 5-HT_1 dysregulation leads to vascular pain 5-HT_1 involved in affective disorders and suffering from pain	Full dosage, early use of antidepressant drugs, including tricyclics, SSRIs, and dopamine agonists, alone or in combination NE reuptake inhibitors (e.g., desipramine, venlafaxine) useful for pain whether depressed or not Pergolide and methylphenidate (Ritalin) are useful adjuvants
Psychiatric illness	Decreased sleep Decreased muscle relaxation Alienation, anxiety	Differential diagnosis of psychiatric conditions and appropriate treatments

5-HT, 5-hydroxytryptamine; *CRPS*, complex regional pain syndrome; *GABA*, gamma-aminobutyric acid; *NE*, norepinephrine; *NMDA, N*-methyl-D-aspartate; *SSRIs*, selective serotonin reuptake inhibitors.

- A preceding noxious event without (CRPS I) or with obvious nerve lesion (CRPS II)
- Spontaneous pain or hyperalgesia or hyperesthesia not limited to a single nerve territory and disproportionate to the inciting event
- Edema, skin blood flow (temperature) or sudomotor abnormalities, motor symptoms, or trophic changes are present on the affected limb, in particular at distal sites
- Other diagnoses are excluded

The clinical course (which can last up to 6 months) starts with an acute phase that involves pain, edema, and warm skin. Subsequently dystrophic changes dominate the picture with cold skin and trophic changes (3 to 6 months after the onset of the untreated acute phase). Irreversible atrophic changes (atrophy and contractures) eventually occur. Symptoms can improve with inhibition of sympathetic output; sympathetic blockade may be both diagnostic and therapeutic.[28]

Idiopathic pain, previously referred to as "psychogenic pain," is poorly understood. The presence of pain does not imply or exclude a psychological component. Typically, there is no evidence of an associated organic etiology or an anatomic pattern consistent with symptoms. Symptoms are often grossly out of proportion to identifiable organic pathology.

Jurisigenic pain results from perceived physical or emotional damage related to medical, personal, work, or product injury. Patients with this pain syndrome usually maintain the sick role for as long as possible to maximize financial return. It is important to recognize the existence of a conflict and to educate patients and attorneys; maintenance of a helping and neutral posture is critical.

Phantom-limb pain refers to severe and excruciating pain in the body part that is no longer present following amputation. The amputation of a limb is commonly followed by sensations that indicate that the deafferented body part is still present. These can include nonpainful phantom sensations such as specific positions, shape, movement, warmth, cold, itching, tingling, electric sensations, and other paraesthesias.[29] However, pain may also be present, and it occurs in 50% to 80% of all amputees.[30] Although this condition is most common after amputations of limbs, it can also occur

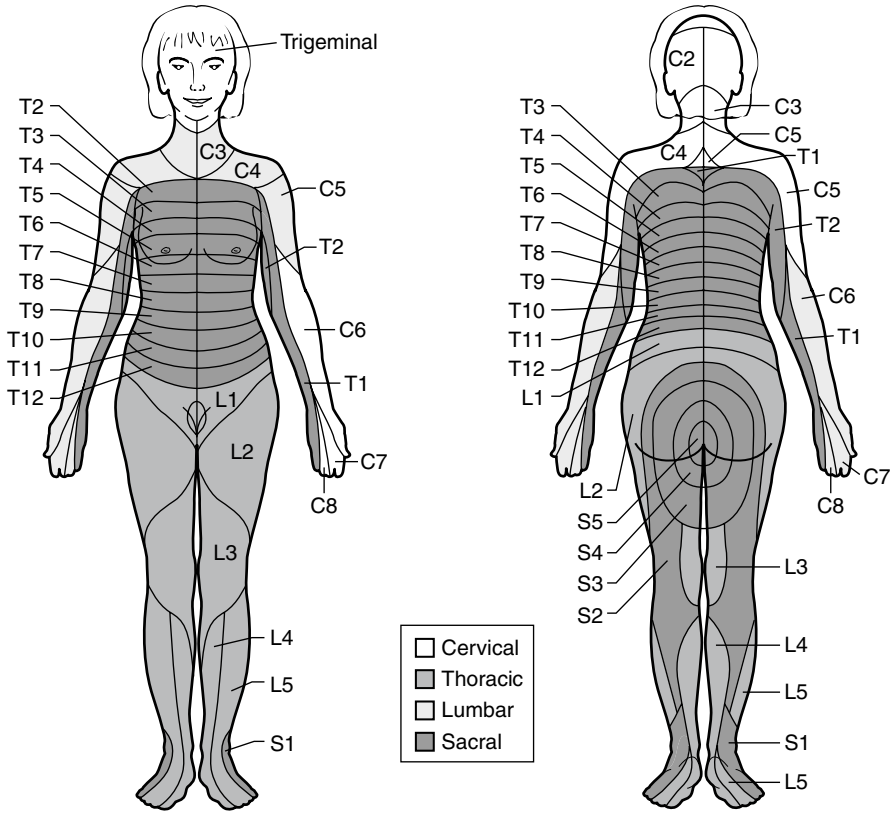

Figure 18–3. Schematic diagram of segmental neuronal innervation by dermatomes. *(From Hyman SH, Cassem NH: Pain. In Rubenstein E, Fedeman DD, eds,* Scientific American medicine: current topics in medicine. Subsection II. *New York, 1989, Scientific American; pp 1–17. Originally from Stern TA, Herman JB, editors:* Psychiatry update and board preparation, *New York, 2004, McGraw-Hill.)*

after the surgical removal of other body parts such as the breast, rectum, penis, testicle, eye, tongue, or teeth.[31] The pathophysiology of this pain is poorly understood; however, it is likely secondary to CNS[32–34] and peripheral (e.g., nociceptive input from the residual limb)[35] factors, with psychological factors influencing the course and severity of the pain.[36] Consistent with the impact of the psyche on pain, one study showed that it is possible to induce pain in an amputee by hypnotic suggestion.[37]

Myofascial pain can arise from one or several of the following problems: hypertonic muscles, myofascial trigger points, arthralgias, and fatigue with muscle weakness. *Myofascial pain* is generally used to describe muscle and connective tissue sources of pain. Myofascial pain can be a primary diagnosis (e.g., fibromyalgia) or, as more often is the case, a co-morbid diagnosis (e.g., with vascular headache or with a psychiatric diagnosis). Psychiatric symptoms are common in patients with muscle pain; other symptoms often include decreased energy, impaired sleep, and changes in psychomotor activity. Myofascial pain syndromes can involve muscle trigger points, hypersensitive skin, a subjective sense of swelling and numbness, somatoform pain disorder, affective and anxiety disorders, nonrestorative sleep, and pain of the head and neck. The diagnosis should be considered if there are multiple muscle trigger points in the temporalis, sternocleidomastoid, rhomboids, or trapezius muscles; if the person cannot get at least 5 hours of uninterrupted sleep; and if chronic fatigue is present.[38] Deficient stage 4 sleep is thought to underlie the lack of deep muscle relaxation, aching muscles, arthralgias, and general malaise.[39,40]

MEASUREMENT OF PAIN

The experience of pain is always subjective. Objective measurements of the patient's subjective response, however, are possible. Several sensitive and reliable clinical instruments for pain measurement are available. These include the pain drawing, the visual analogue scale, and categorical rating scales.

The pain drawing involves having the patient draw the anatomic distribution of the pain as it is felt in his or her body. The patient draws the outline of the body, labels where the pain is, and keeps this document as part of the medical record. The drawing serves as a clue to the anatomy of the problem, to the psychological state of the patient, and to the patient's level of knowledge.

The visual analog scale, a 100-mm scale with a 0 signifying no pain and 100 representing severe pain, is readily understood by most patients. It is also exquisitely sensitive to change; consequently the patient can mark this scale once a day or even hourly during treatment trials, if desired. Two separate scales can be kept for the least and the greatest pain. Concurrent scales for mood, overall progress, and

pain allow comparison of the relationship of pain to the total clinical picture, thereby rounding out the psychiatrist's understanding of the patient's syndrome.

Ad hoc categoric rating scales may be devised that comprise three to five categories for the ranking of pain severity.

THE PSYCHIATRY CONSULTANT AS PAIN PHYSICIAN

The Psychiatrist's Role

Physicians and patients alike seek knowledge, order, and relief when dealing with pain's chameleon-like manifestations; some of the common reasons pain patients or treating physicians seek consultation and treatment from psychiatrists are:

- To separate functional from organic factors. Unfortunately, the request to separate psyche from soma is often vexing. Through such consultations some physicians wish to absolve themselves of further responsibility.
- To resolve inconsistencies between symptoms and physical findings (or the lack thereof): "No anatomic lesion could account for this." The referring physician wonders if a psychiatric disorder or CNS pain is present or if he or she is missing something.
- To assess the patient for depression, anxiety, or some co-morbid disorder from the *Diagnostic and Statistical Manual of Mental Disorders*,[41] 4th edition, (DSM-IV) and the disorder's relation to the experience of pain.
- To address a patient's or physician's fear or misunderstanding of narcotics (e.g., use of high-dose narcotics, toxicity, and maintenance treatment).
- To determine if the use of psychopharmacologic agents might help alleviate pain and suffering.
- To satisfy the referring physician's personal desire to punish a "hateful" patient, one who will not take "yes" or "no" for an answer and who interferes with normal medical decision-making.

The psychiatrist begins with a clarification of the reason for the consultation, creates some initial hypotheses, and examines the patient. If possible, the psychiatric consultant should be brought into the case early on and introduced as a member of the medical team. The referring physician should take care to ensure that the patient does not interpret the referral as a sign that he or she is not believed, and the physician should state that a psychiatrist is routinely asked to evaluate patients with long-standing pain. When the referring physician is comfortable using the services of a psychiatrist, the patient typically accepts the examination without protest. When the psychiatrist is called in at the end of a long and frustrating stand-off, the patient typically balks.

Gathering Important Preliminary Information

The psychiatric consultant's job begins by answering five questions: Is the pain intractable because of nociceptive stimuli (e.g., from the skin, bones, muscles, or blood vessels)? Is the pain maintained by non-nociceptive mechanisms (i.e., have the spinal cord, brainstem, limbic system, and cortex been recruited as reverberating pain circuits)? Is the complaint of pain primary, as occurs in disorders such as major depression or delusional disorder? Is there a more efficacious pharmacologic treatment? Have pain behavior and disability become more important than the pain itself? Answering these questions allows the mechanism(s) of the pain and suffering to be pursued. Table 18–2 is a useful guideline to organize the questions, to test hypotheses, and to determine diagnosis.

Physical Examination

A psychiatrist's physical examination of the pain patient includes examination of the painful area, muscles, and sensation to pinprick and light touch (Table 18–3). The examination is essential to the psychiatric evaluation for pain and serves three purposes. First, examination of the patient allows better history-taking, therapeutic alliances, and integration of data; it also helps to eliminate the physical–mental dichotomy, which, left unspoken, often contributes to the patient's defensiveness. Second, the psychiatrist can search for signs of different types of pain and distinguish them from symptoms of a conversion disorder. Third, inconsistent findings suggesting a somatoform disorder may be uncovered.

Psychiatric Examination

Interviewing the patient with chronic pain demands close attention to both what was said and what was not said, as well as to mindfulness of the patient's style of discourse. Because patients with an extensive history of pain often delight in regaling the examiner with their odysseys through clinics, spas, and hospitals, it is helpful to ask them to write detailed accounts of their pain from its onset to the present. A detailed history of when and how the pain began, inquiring about the various treatments received, and the patient's relationships with other physicians are also important in the evaluation of the pain patient. Throughout the history, one should look for fluctuations in the course of the pain. Why did it improve? Did the medication help, or was it some other factor that proved palliative? In addition, one should explore the patient's past and present mental state and consider the family history and ethnic beliefs. Open-ended questions may include: "Have you ever suffered like this before? What do you do think about in the early morning hours when you cannot sleep? What do others think is the nature of the problem?" The psychiatrist also plays an important role in the treatment of the pain by his or her ability to recognize psychiatric conditions that can manifest with pain.

Diagnosis

Depression

Major depressive disorder (MDD) can be diagnosed by DSM-IV or similar research criteria in approximately 25% of patients who suffer from chronic pain. Recurrent affective illness, a family history of depression, and psychiatric co-morbidity (with anxiety and substance use) are often present. More often than not, depression predates the pain; overall, 60% to 100% of pain patients have depressive symptoms.

TABLE 18–2 Questions to Ask when Pain Persists

WHAT IS THE PROBLEM?	SELECTED DIAGNOSTIC CONSIDERATIONS	CONSIDER
Is there an ongoing physical disease? (e.g., infection, cancer)	MRI for anatomic pathology Gallium scan for infection ESR for infection, cancer PSA, CEA, p24 testing Pelvic, breast, prostate, gastrointestinal examination	Progression of disease Metastatic disease Visceral pain: adhesions, referred pain, central pain
Is there a problem with the use and response to narcotics? (misuse, lack of efficacy)	Central pain Narcotics masking a DSM-IV problem Narcotic dosing error or inconsistency Narcotic toxicity	Intravenous agents Antidepressants, anxiolytics, or sleep prescription Narcotic potency CYP 2D6 interaction: codeine or oxycodone with SSRI Meperidine toxicity
Is there a psychiatric disorder associated with pain?	Loss of all pleasure and mid or late insomnia Panic, depersonalization, benzodiazepine failure, anxiety	Depression often masked by narcotics or anxiolytics Co-morbid somatoform, mood, or anxiety disorders
Does CNS pain exist? (e.g., neuropathic pain)	not relieved by analgesics Hypochondriasis Increased sensory threshold, decreased pain threshold Nondermatomal distribution of pain Hyperpathia Allodynia, often narcotic resistant	Pain drawing and explanation helpful for diagnosis Sharp sensation perceived as light touch is common Light touch is painful and sustained and has a delayed crescendo Tuning fork and moving a hair examinations detect allodynia best
Is it a pain behavior syndrome?	Pain disorder (somatoform): rule out masked depression, drug abuse, physical or sexual abuse, missed physical disorder	Anger and anxiety: denied Counterdependent, demanding style Passive and endearing
Is the patient faking?	Malingering for drugs or disability benefits Factitious deception to maintain the sick role	Malingering or factitious disorders with physical symptoms are rare, much more likely to be something else
Is an unusual problem responsible for pain?	Muscle trigger points absent, deep sleep Laxative abuse, anorexia/bulimia Adhesions Hypoesthesia, allodynia Wasting illness, subcortical deficits, AIDS Conversion symptom, especially with pelvic, gastrointestinal, or head pain	Myofascial pain often is co-morbid with another pain syndrome Visceral pain is diffuse, nondermatomal, with sympathetic symptoms and can mimic DSM-IV Physical or sexual abuse history contributing to pain

CYP, Cytochrome P450; *ESR*, erythrocyte sedimentation rate; *MRI*, magnetic resonance imaging; *SSRI*, selective serotonin reuptake inhibitor.

TABLE 18–3 General Physical Examination of Pain by the Psychiatrist

PHYSICAL FINDING	PURPOSE OF EXAMINATION
Motor deficits	Does the patient give way when checking strength? Does the person try? Is there a pseudoparesis, abasia-astasia, or involuntary movements suggesting a somatoform disorder?
Trigger points in head, neck, shoulder, and back muscles	Are any of the common myofascial trigger points present, suggesting myofascial pain? Presence of evoked pain (such as allodynia, hyperpathia, or anesthesia) suggests neuropathic pain
Evanescent, changeable pain, weakness, and numbness	Does the psychological complaint preempt the physical?
Abnormal sensory findings	Detection of lateral anesthesia to pinprick ending sharply at the midline Presence of topographic confusion Presence of nondermatomal distribution of pain and sensation suggests either a somatoform or CNS pain disorder Presence of abnormal sensation suggests neuropathy or CNS pain
Sympathetic or vascular dysfunction	Detection of swelling, skin discoloration, or changes in sweating or temperature suggests a vascular or sympathetic element to the pain
Uncooperativeness, erratic responses to the physical examination	Detection of an interpersonal aspect to the pain, causing abnormal pain behavior, as in somatoform disease

Although some depressive syndromes are secondary to pain itself (e.g., an adjustment disorder with affective symptoms), many patients have major depression masked by denial or by medications that promote sleepiness. Denial of affect, particularly anger, is observed in nearly half of chronic pain patients referred to the Massachusetts General Hospital (MGH) Psychiatric Consultation Service. Diagnosing an affective illness when affect is minimized by the patient may be difficult, but the following tactics can be used to help ferret out affective illness.

One should ask questions about neurovegetative symptoms. Examples of questions to be posed include: How often do you wake from sleep at night? How long does it take you to return to sleep? Do you have early-morning awakening? When was the last time you really enjoyed yourself? Does food taste the same as it always has? Do you enjoy eating? What do you do for fun? Can you still smile? Do you have an interest in people, such as your grandchildren or friends? Do you have difficulty with decision-making? What do you do when you are angry? Do you sometimes feel you would rather be dead?

Clinicians should also evaluate the person's limbic (i.e., genuine and uncensored) response to emotionally charged stimuli. One should look for denial of any strong emotion, particularly anger or sadness, and note if the patient answers affective questions with affective responses or only with avoidance and denial. Denial, displacement, or suppression of emotions suggests psychopathology. One could ask questions such as "Can you laugh at a joke at your own expense? Can you acknowledge anger at yourself and others?" The Minnesota Multiphasic Personality Inventory (MMPI) may be of particular use in refining the differential diagnosis when denial or repression is suspected. Covert hostility is typically elevated, which adds some validity to the label of denier. The conversion V is present in about half of pain patients studied at MGH, and it occurs more often among those in denial. Patients with other chronic illnesses are more likely to have an inverted V configuration.

Anxiety Disorders

In the pain patient, denial of fear, worry, or nervousness is a more ominous sign than is the mere expression of modulated fear or worry about pain. Given that it is normal to worry about a painful threat to the body and the mind, pathologic denial of any anxious affect can suggest psychosis, hypochondriasis, conversion, factitious disorder, or personality disorder. Accordingly, the DSM-IV provides criteria to identify anxiety of sufficient intensity that can trigger or exacerbate pain. Inportant information may be gleaned by such questions as: Does the pain make you panic? Do you feel your heart beating fast, have an overwhelming feeling of dread or doom, or experience a sense of sudden high anxiety that overwhelms you?

Anxiety disorders are found in approximately 30% of patients with intractable pain (usually in the form of generalized anxiety or panic disorder). More than 50% of patients with anxiety disorders also have a current or past history of major depression or another psychiatric disorder. Alcohol and substance abuse are the most common co-morbid diagnoses; consequently, recognition and treatment of co-morbid depression and substance abuse are critical to long-term treatment outcome.

A variety of agents, including TCAs, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and clonazepam, alone or in combination, improve panic, anxiety, and depression as well as neuropathic pain, muscle tension, and sleep. Anxiety that results from disruptions of body integrity, sense of self, or attachment to caregivers occurs in one third to one half of patients with chronic pain. Disruption in body integrity or sense of self can block efforts at physical and emotional rehabilitation and they require a pragmatic psychodynamic treatment. Anger is often linked to anxiety, although it is typically denied and expressed in terms of somatic symptoms. One can uncover affect quickly by holding up a clenched fist and asking the patient what he or she would do with it. The response will often be telling regarding denied anger. SSRIs are helpful with anger, anxiety, and mood disorders. Existential anxiety can increase when cancer is first diagnosed, when death nears, or when pain engenders feelings of helplessness. Spending time with the person, telling the truth, accepting the situation, and reconnecting with family members (parents and children) often decreases existential anxiety.

Somatization Disorder

The somatoform disorders (see Chapter 16) comprise a group of disorders in which complaints and anxiety about physical illness are the predominant clinical features. These complaints exist in the absence of sufficient organic findings to explain the pain. Pain may be present in somatization disorder, conversion disorder, hypochondriasis, and pain disorder. Somatoform disorders occur in 5% to 15% of treated patients with chronic pain, and somatizers account for 36% of all cases of psychiatric disability and 48% of all occasions of sick leave.[42]

Among somatizers, pain in the head or neck, epigastrium, and limbs predominates. Visceral pain from the esophagus, abdomen, and pelvis associated with psychiatric co-morbidity, especially somatoform disorders, can be challenging to diagnose.[43] Missed ovarian cancers, central pain following inflammatory disorders, and referred pain are often overlooked because of the nonspecific presentations of visceral pain. In one study, 64% of women with chronic pelvic pain reported a history of sexual abuse.[44] The two most common co-morbid conditions associated with somatoform disorders among MGH pain patients are MDD and anxiety disorders. Surprisingly, drug and alcohol abuse and personality disorders are not significantly associated with somatoform disorders. Patients with somatization disorder consume health care resources at nine times the rate of the average person in the United States.[45]

Sufferers from somatoform disorders often have painful physical complaints and excessive anxiety about their physical illness. Most of their pain complaints to physicians do not have a well-defined cause, and a psychiatric diagnosis is often particularly difficult to establish (Table 18–4).

Conversion Disorder

Conversion disorder may be manifested as a pain syndrome with a significant loss or alteration in physical function that mimics a physical disorder. Conversion symptoms can include paresthesia, numbness, dysphonia,

TABLE 18–4 Somatoform and Related Disorders

DISORDERS	DIAGNOSTIC TIPS
Somatization disorder	Pain in at least 4 different sites of the body, 2 GI symptoms (other than pain), 1 sexual symptom, and 1 pseudoneurologic symptom
Conversion disorder	Real disease and conversion symptoms often co-occur
	An undiagnosed medical condition might underlie the psychiatric diagnosis
	Deciding if psychological factors are a cause or a response is often impossible in patients with chronic pain
	Culturally determined stress responses, numbness, total body pain, weakness, abasia-astasia, fainting, voices, and nonepileptiform seizure activity are transient and not included as conversion disorders
Hypochondriasis	Transient hypochondriasis is particularly common in the elderly
	Psychosis and depression may be concealed because of the patient's fears
Pain disorder	Pain is enmeshed in Axis II problems and complicated by drugs (narcotics, benzodiazepines, or alcohol)
	Central and visceral pain, especially pelvic pain, can mimic somatoform disorders
	Pain can improve with psychotropic drugs or psychological techniques without having a psychiatric diagnosis
Malingering and factitious disorder	Pseudomalingering with dissociative features (Ganser syndrome) manifests with malingering, but it also underlies real psychiatric illness
	Some classify it as a conversion, dissociative, or factitious disorder

dizziness, seizures, globus hystericus, limb weakness, sexual dysfunction, or pain. If pain or sexual symptoms are the sole complaints, the diagnosis is pain disorder or sexual pain disorder rather than conversion disorder. Pain, numbness, and weakness often form a conversion triad in the pain clinic.

Psychological factors are judged to be etiologic for the pain when a temporal relationship between the symptoms and a psychosocial stressor exists—the person must not be intentionally producing the symptom. A mechanism of primary or secondary gain needs to be evident before the diagnosis can be confirmed. *La belle indifférence* and histrionic personality traits have little value in making or excluding the diagnosis of conversion. A conversion V on the MMPI denotes the hypochondriacal traits and relative absence of depression that accompany conversion. Evoked responses, an electromyogram (EMG), an electroencephalogram (EEG), MRI and PET scans, and repeated physical examinations are useful for identifying patients with misdiagnoses of hysteria.[46]

Hypochondriasis

Hypochondriasis involves the persistent erroneous belief that one has a serious illness. Generalized anxiety disorder and depression are the common causes of hypochondriasis-like presentations.[47] Head and orofacial pain, cardiac and gastrointestinal (GI) pain, and feelings of pressure, burning, and numbness are common hypochondriacal concerns. Therefore, attention to head and neck pathology, cancer, visceral pains, degenerative disorders, and CNS syndromes should be ongoing.

Care of the hypochondriac begins with a comprehensive differential diagnosis and becomes longitudinal; the persistence of vague complaints helps to rule out the most serious diseases and to set the stage for an alliance with the patient by demonstrating an open and critical mind. A pain drawing may help reveal psychotic somatic beliefs. The psychiatrist should reassure and not reject the patient; one should label behavior that produces more symptoms maladaptive or dangerous and should openly discuss psychodynamic factors.

Pain Disorder

Pain disorder is defined in DSM-IV as a syndrome in which the focus of the clinical presentation is pain that causes significant impairment in occupational or social function, marked distress, or both. Organic pathology, if present, does not explain the pain or the associated social and occupational impairment. Pain disorder has three diagnostic subtypes: psychological, nonpsychiatric, and combined. In psychological pain, psychological factors play an important role in the onset, severity, exacerbation, or maintenance of the pain. Nonpsychiatric pain is associated with a general medical condition. If psychological factors are present, they play only a minor role in the genesis of pain. This medical pain disorder is coded as an Axis III diagnosis.

Pain disorder, as it is currently known, has been variously named during different epochs. Examples of such labels include psychogenic pain disorder, somatoform pain disorder, and pain behavior.[48] When behavioral disability predominates, chronic pain syndrome is the behavioral description of this same syndrome. The meandering history of nomenclature is best understood as reflecting the mix of pain behaviors, as well as interpersonal and affective characteristics, that emphasize disability and entreat attention from others.

Psychological antecedents of this syndrome can include a history of physical abuse, counterdependent personal relationships, a family history of alcoholism, and a personal developmental history of attachment problems. Co-morbid diagnoses should be sought, particularly depression, anxiety, and substance abuse. Treatment must address the triad of self-defeating behavior, affective dysfunction, and psychodynamic conflicts, which causes poor coping, disability, and disruptive rehabilitation efforts. Common treatments and their reasons for possible failure are outlined in Table 18–5.

TABLE 18–5 Treatment and Reasons for Treatment Failure in Pain Disorder

PROBLEM	REASONS (NOT MUTUALLY EXCLUSIVE)	TREATMENT
Physical diagnosis	Ignorance, transference, narcissistic fears, or dishonesty Drug abuse	Clarify which demands are and are not ignored, sidelined, mistreated Refer, if at any impasse Possible drug abuse
Behavior is abnormal	Axis I DSM-IV not applied Relaxation, yoga, physical rehabilitation methods have not been used No common ground or treatment plan agreed to	Reassure the patient about normal suffering, coping, rehabilitation, and distinguish from Axis I symptoms, ensuring treatment
Self-esteem hurts more than does the body	Coping methods have not been addressed The physician–patient relationship has not been acknowledged as a treatment aspect Locus of control is thought to be external	Address the muted anger Identify denial, avoidance, rationalization, projection Interpret the unrequited wish for dependency versus self-control
High affective suffering	Major depression or mood disorder complicating general medical condition might not get addressed because of the somatic focus and the patient's fear of being psychiatrically dismissed	Treat the covert depression Identify the hateful patient's psychodynamics

Factitious Disorder with Physical Symptoms

Factitious disorder with physical symptoms involves the intentional production or feigning of physical symptoms. Onset is usually in early adulthood, with successive hospitalizations forming the lifelong pattern. The cause is a psychological need to assume the sick role, and the intentional production of painful symptoms distinguishes factitious disorder from somatoform disorders, in which intention to produce symptoms is absent. Renal colic, orofacial pain, and abdominal pain are three of the common presenting gambits in factitious disorder; of these, abdominal pain and a scarred belly herald the diagnosis most often. Despite the seeming irrationality of the behavior, those with factitious disorder are not psychotic.

Pain may be described as occurring anywhere in the body, and the patient often uses elaborate technical detail to captivate the listener with *pseudologia fantastica*. Narcotic-seeking behavior, multiple hospitalizations under different names in different cities, inconclusive invasive investigations and surgery, lack of available family, and a suave truculence are characteristic of this disorder. An assiduous inquiry into the exact circumstances of the previous admission and discharge leads to a sudden outraged discharge against medical advice. Typically, there is no effective treatment. If the patient is willing to receive care, however, psychotherapy is the treatment of choice, coupled with addiction treatment when there is underlying opioid abuse or dependence.

Malingering

In malingering, the patient fakes a complaint, although no pain is felt, because of an external incentive (e.g., to obtain money, drugs, or privilege or to avoid work). The conscious manipulation by malingerers precludes much diagnostic help from amytal interviews or hypnosis because the patient willfully withholds information. The malingerer typically refuses psychological tests; this raises suspicion even before a diagnosis is made. Even when the patient agrees to testing, the MMPI can be skewed to normality by the clever malingerer, although differences (more than 7 points) between obvious and subtle scale scores and high L, F, K scale scores (T >70) may be suggestive nonetheless. A mnemonic for suspicion of the diagnosis is WASTE (*w*ithholding of information; *a*ntisocial personality; *s*omatic examination inconclusive and changeable; *t*reatment erratic with noncompliance and vagueness; *e*xternal incentives exist, such as occur in a medicolegal context). The psychiatrist's familiarity with the neurologic examination is always useful, but it is critically important for the diagnosis of malingering when nonanatomic findings arise. Once an organic etiology has been ruled out, careful scrutiny of old records and calls to previous physicians might unearth evidence of similar behavior in the past. Similar to lying, malingering tends to be a character trait used in times of stress from early adolescence through the senium. Once malingering is revealed, psychotherapy can be offered; unfortunately, noncompliance is typical.

Dissociative States

Dissociation is commonly caused by psychological trauma, and it involves a disturbance or alteration in the normally integrative functions of identity, memory, or consciousness. Pelvic pain, sexual pain disorders, headache, and abdominal pain are the most common pain complaints in developmentally traumatized patients. Walker and associates[49] reported that in 22 women with chronic pelvic pain, 18 experienced childhood abuse. Of the 21 women selected as controls (i.e., without pelvic pain), 9 had childhood abuse ($P < .0005$). Dissociation, somatic distress, and general disability were more common in the group with pain. Denial makes the diagnosis of dissociative disorders in pain patients a longitudinal process, because truth is shared slowly with the physician and only when the patient can tolerate it. Signs of an underlying dissociative disorder are periods of amnesia, nightmares, and panic as well as anxious intolerance of close personal relationships.

Psychosis

Pain can also be a symptom of psychosis. This is a problem of misreporting a delusional symptom as a physical ailment, hence demonstrating the need for assiduous screening of delusional thinking. The diagnostic problems are fourfold.

First, DSM-IV profiles of schizophrenia, affective psychoses, and organic psychoses are not typical presentations for psychosis with pain; covert delusional thinking and anomie may be the only symptoms. Second, psychotic thinking may be masked by denial, rationalization, concrete thinking, and fear; historical anamnesis is the last thing the patient wants. Third, the last person the patient wants to see is a psychiatrist because the patient knows the pain "is not in my head." Finally, the pain belief is erroneously attributed to hypochondriasis. The psychiatrist must always consider pain as a delusional symptom when there is a bizarre, variable distribution to the symptom (best proven by getting the patient to draw a picture of the pain); when the patient is not eager to have the discomfort removed; and when the patient complains persistently with vagueness and a flat affect. The question "What have you learned from the other doctors" leads to no useful information.

GENERAL PRINCIPLES OF PAIN THERAPY

Pain Is Not Psychological by Default

The patient should not have his or her pain called "psychological" or "supratentorial" merely because it is not understood or because it is unresponsive to treatment. The physician should assure the patient that there is no question about the degree of suffering involved. Psychological factors might play a role, but this by no means diminishes either the quality or the quantity of pain the patient endures. Education about the close relation of psyche and soma in the CNS is often useful to establish an effective doctor–patient relationship.

Long-standing pain is difficult to assess largely because what we learn about pain is based on our concept of acute pain. The patient with acute pain moans, writhes, sweats, begs for help, and gives every appearance of being in great distress. Those nearby someone in acute pain typically feel an urge to help. When pain persists over days and weeks, the individual adapts to it, often without realizing. The patient becomes able to sit in the physician's examining room and complains of agonizing pain while giving little or no evidence of actually being in agony. This adaptation means that the pain has become bearable, although there seems to be no change in intensity. This may be accounted for by several explanations: The sensation may become intermittent, the CNS inhibits the pain, or the sufferer becomes more capable of using distraction. It is ironic that the capacity to adapt to severe pain is often the patient's undoing because it causes the examiner to doubt the patient's veracity. The sufferer now is in the position of having to prove that he or she is in pain. The patient feels himself or herself to be on trial. To counter this end, the physician must know the pathophysiology of pain and employ the full range of neurologic, pharmacologic, and psychological therapies available.

Care Does Not Only Involve Managing Symptoms

An important principle of pain management is to assure the patient that treatment will continue even if there is no immediate improvement. The physician should also guard against being affected by the patient's sense of discouragement. One of the fears expressed by many patients who suffer from chronic pain is that of abandonment; they believe that if they do not improve, the physician will no longer see them. In this case, an endless series of medications, without continuing examination, psychotherapy, or critical thinking, is tantamount to noninvolvement or to abandonment. Education about relaxation techniques, yoga, acupuncture, TENS, ultrasound, and massage all have their place in the therapeutic armamentarium. The value is not only in soothing the pain but also in helping the person to feel more in control, that is, less of a victim, and to become an active, educated participant while under the physician's care.

Placebo Response Accompanies a Variety of Syndromes

Few phenomena are as misunderstood as the placebo trial. A placebo trial shows whether or not the patient is placebo-positive; it does not prove that the pain is not real or that the person is either an addict or a malingerer. Similarly, it does not demonstrate that the patient would not benefit from an active medication. The trial is of no assistance in separating psychogenic from organic pain because the placebo response cannot be linked with any type of psychopathology. In fact, patients with depression, somatoform disorder, or other varieties of emotional disturbance are no more apt to be placebo responders than are so-called normal people.

Whether the pain is from a metastatic lesion or is part of a major affective disorder, relief is experienced by the placebo responder. Following surgery, about one patient out of three obtains pain relief from saline or from some other inert substance and is therefore considered placebo-positive. For instance, Evans and Hoyle[50] used sodium bicarbonate to treat patients suffering from angina pectoris. In 38% of their subjects, they found this agent to be as effective as nitroglycerin.

The time-worn custom of slipping in a few saline shots for morphine and calling the deception a placebo trial only demonstrates the ignorance of the perpetrator. If a shot of sterile saline is substituted for a dose of narcotics and the patient responds by obtaining relief, the nature of his or her pain will be questioned even though relief is based on the conditioned response. Moreover, placebo effect and true effects are not independent. The mechanism for the placebo response is possibly the endogenous opioid pain-inhibiting system and is therefore co-influenced by psychological expectation. Placebo analgesia has been shown to be reversed with the opioid antagonist naloxone.[11]

In a valid placebo trial, the inert substance must be given to the patient in a randomized manner along with the usual narcotic under double-blind conditions. Without this control, the placebo trial is useless. The only place for a placebo trial is an informed blinded experiment in which both the patient and the physician have discussed the intention and methodology and are in agreement to find the best treatment for a patient's pain disorder. One of the chief hazards of placebo use is that the patient may feel tricked if he or she discovers that a placebo has been administered. In this case, it is natural for the patient to feel

on trial and wrongly accused; there is no psychiatric fix for this error once it has occurred. The physician who ordered the placebo needs to discuss it with the patient.

Deafferentation Surgery Is Usually Not the Answer

An abiding principle in the treatment of chronic pain is to avoid surgery whenever possible. Few surgical procedures on the CNS are persistently definitive in the cure or control of pain, and most carry with them a tax that is sometimes worse than the pain itself. In particular, CNS pain is notoriously refractory to surgery that interrupts afferent pain pathways. The pain is often made worse by procedures (such as neurectomies, rhizotomies, tractotomies, and cordotomies). Surgery, with the one exception of cingulotomy, is not a treatment for depression that manifests as pain. A central procedure, such as cingulotomy performed stereotactically using radiofrequency lesions, may be useful for intractable pain, especially because it has a low risk of psychiatric and physical morbidity. Personality changes, mental dulling, and memory impairment are rare. Unfortunately, even when pain is reduced with cingulotomy, it can return within 3 to 6 months. To exemplify this multiform plasticity of pain, consider the following account of an extraordinary case.

CASE 1

RC, a 28-year-old mechanic, was thrown from his motorcycle en route to his wedding. Injury occurred to his brachial plexus and arm, requiring an amputation at the shoulder. He then developed severe phantom limb pain. Six months later, the stump was revised and a neurectomy performed; the pain, however, remained unaltered. The nerve was then severed further into the stump with similar result. An unsuccessful rhizotomy was then performed, followed by a chordotomy with the same outcome. He embarked on individual psychotherapy for a year, but there was no improvement. After six sessions of electroconvulsive therapy (ECT), the pain was only intensified. A higher cervical chordotomy was performed without success, and then a mesencephalic tractotomy; again, there was no relief. He next had both dorsomedial thalamic nuclei ablated using stereotactic electrocautery. He emerged from this procedure with his personality intact but still with his original pain. Then electrolytic lesions were made bilaterally in the inferior mesial quadrant of the frontal lobe in stages; still, the pain remained. Following this, he had a left radiofrequency amygdalotomy followed by a left cingulotomy. Nonetheless, the pain continued as before. The pain remained for 4 years after the accident, as pristine as it was 2 weeks after the injury.

Talking and Listening Are Helpful

A strategy to evaluate the feelings and behavior observed in the pain patient is as necessary as the strategy for evaluating physical aspects of the pain. The skill required is not only a matter of diagnosing the major psychiatric illnesses that can manifest with pain—these patients often have a maladaptive style of interaction that requires a different kind of interpretive skill—but also a question of the physician's ability to relate to the long-suffering pain patient who shows poor judgment of surgical risk, denies anger, and rapidly alternates between idealizing and denigrating the medical caretaker. The fluctuations of both mood and cooperation often encountered in the clinical interview are symptomatic of the patient's damaged self-esteem or his or her injured narcissism. Patients with chronic pain invariably feel damaged not only in the body part afflicted with discomfort but also in self-image and spirit, a phenomenon known as narcissistic injury.[51] The techniques for interviewing the narcissistically injured pain patient are designed to establish a working relationship. They allow an accurate medical history to be elicited, mistrust between physician and patient to be avoided, an effective treatment plan to be developed, and the outcomes through compliance and education to be enhanced.

The interviewer should allow the patient to tell his or her own story. An initial degree of catharsis may be helpful in decreasing the patient's anxiety and in giving the physician a sense of the patient's character. The physician must actively facilitate an alliance with the patient while still maintaining neutrality and avoiding misplaced sympathy. The patient's underlying feelings of fear, anger, resentment, and mistrust are best uncovered by asking how others view the situation, essentially a counterprojective method. This approach sometimes bares unpleasant affects without the use of intrusive questions from the physician. Labeling overt and covert roles assigned by the patient to the physician is an important early intervention. Specifically, this means that the physician should point out when the patient is attributing unrealistic curative powers to him or her or appears to believe that the physician is indifferent to the patient's suffering. The longer one waits to confront these fantasies, the less effective any intervention will be. Expression of affect should be encouraged, and the physician should help the patient express the feelings he or she is having but does not want to acknowledge. The physician's assertive pursuit of the patient's true feelings avoids giving the appearance of unqualified support to feelings that need expression. Too much support not only bypasses psychological problems but also can actually increase conflicted feelings over control, dependence, and frail self-esteem. The physician's kindness should not be allowed to become a problem for the patient.

Optimal care for intractable pain requires the ability to process neurologic and psychiatric data while delineating and responding to the phrase-by-phrase manifestations of suffering and pain behavior. In essence, being able to get patients to talk about what they are angry about is just as important as discussing their insomnia or disk herniation. Progress occurs with these needy, angry patients only when there is clear processing and separation of the reality-based facts of the case from unrealistic expectations. In that way, every clarification of an unrealistic idea can be an introduction to a more-realistic alternative. The overall goal is to improve the patient's self-awareness and capacity for insight, thereby gaining control.

MEDICATION FOR PAIN: ANALGESIA AND ADJUVANTS

Judicious and effective use of medicine in patients with chronic pain rests on the concise evaluation of the four main components of the pain complaint: nociceptive pain, and the CNS mechanisms of pain, suffering, and pain behavior.

In its most elemental form, the medical management of these four components employs opioids, anticonvulsants, antidepressants, and behavioral treatment. Nonsteroidal antiinflammatory drugs (NSAIDs), aspirin, and nerve blocks are often helpful in the early stages of these illnesses. Opioids are, however, the most effective medicine for these pains when the severity increases.

Nonsteroidal Antiinflammatory Drugs

The World Health Organization (WHO) has established a three-step guideline for pain treatment (Figure 18–4). Step 1 involves the use of NSAIDs, aspirin, or acetaminophen. Step 2 adds codeine to the NSAID, with other adjuvants (e.g., TCAs, other antidepressants, antiepileptic medications, and stimulants). Step 3 employs narcotics with adjunctive medication. Conceived for cancer pain, and reported efficacious in 90% of cancer patients, the three steps are a useful template for many kinds of acute pain, adjusted for the particular pain mechanism being treated. NSAIDs are useful for acute and chronic pain (e.g., inflammation, muscle pain, vascular pain, and posttraumatic pain), or when the physician wants to use a potent nonnarcotic analgesic. NSAIDs are generally equally efficacious and have similar side effects.[52]

Side Effects

Most NSAIDs can cause bronchospasm in aspirin-sensitive patients, induce gastric ulcers, interact with angiotensin-converting enzyme (ACE) inhibitors (thereby contributing to renal failure), precipitate lithium toxicity, and impair renal function in the long term. NSAIDs can elevate blood pressure in patients treated with β-blockers and diuretics. The exception to this general rule is the nonacetylated (nonaspirin) salicylates that do not inhibit the synthesis of prostaglandins. These include choline magnesium trisalicylate and diflunisal; these agents do not cause bronchospasm in aspirin-sensitive patients, precipitate renal failure, or inhibit platelet aggregation. Certain NSAIDs, however, have features that make some preferable over others in particular situations. The discovery of the enzyme cyclooxygenase (COX) isoforms 1 and 2 led to the increased use of selective COX-2 inhibitors. COX-2 tends to facilitate the inflammatory response selectively, and it has been argued that the use of new agents (paracoxib, etoricoxib, lumiracoxib, and celecoxib) might increase GI safety.[53]

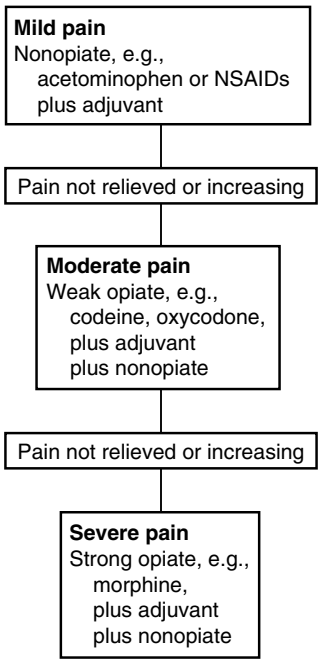

Figure 18–4. The analgesic ladder. *(From Borsook D, Lebel AA, McPeek B:* MGH handbook of pain management, *Boston, 1995, Little Brown).*

Based on currently available data, the U.S. Food and Drug Administration (FDA) has concluded that an increased risk of cardiovascularand cerebrovascular events has been demonstrated for all of the COX-2–selective NSAIDs (including rofecoxib, valdecoxib, and celecoxib).[53] Rofecoxib was voluntarily removed from the market in 2004 following the finding of increased cardiovascular events compared with placebo in a long-term study. Valdecoxib was voluntarily withdrawn from the market in 2005, after the FDA concluded that the overall risk-versus-benefit profile for the drug was unfavorable. Although an increased risk of cardiovascular events has also been demonstrated with celecoxib, the FDA has found that the benefits of celecoxib outweigh potential risks in properly selected and informed patients.

Special Features

Synergistic combinations of acetaminophen, aspirin, and caffeine (e.g., Excedrin) are the cornerstone for temporary relief of pain (e.g., headaches and muscle pain) and potentiation of the effects of narcotics. They do, however, have a limit on dosing and have only moderate potency; they are also not well tolerated by those who are very sick. NSAID variations then need to be considered. For a list of NSAIDs, see Table 18–6.

Choline magnesium trisalicylate (1000 to 1500 mg) is safe in aspirin-sensitive patients, and it does not prolong bleeding. Misoprostol can reduce GI erosions in patients on maintenance NSAIDs, but its use can be limited by diarrhea, pain, and flatulence in about one third of patients. Ibuprofen (800 mg) is a rapid-release agent that produces higher blood levels over the first half hour than the other preparations at equal dosage. Ketorolac (up to 30 mg every 6 hours) intramuscularly followed by oral dosing has a rapid onset and a high potency, enabling it to be substituted for morphine; 30 mg of ketorolac is equivalent to 10 mg of morphine. It should be used for no more than 5 days.

Extended-release preparations can be useful when long, steady analgesia and simple dose regimens are needed (e.g., nabumetone, oxaprozin, ketoprofen, piroxicam). Naproxen (375 to 500 mg twice a day with enteric-coated, delayed-release tablets) can be well tolerated over time. Ketoprofen (200 mg) extended-release tablets can be taken once a day, but they are not intended for patients with kidney disease or for those older than 75 years.

Ibuprofen works well as a narcotic adjuvant for bone pain. Naproxen (up to 1500 mg a day), but not flurbiprofen, has also had positive results for bone pain.

The newer COX-2 inhibitors may cause fewer GI problems compared to other NSAIDs. Celecoxib does not impair platelet function. Paracoxib, etoricoxib, and lumiracoxib are not currently available in the United States.

TABLE 18–6 Properties of Aspirin and Nonsteroidal Antiinflammatory Drugs

DRUG	DOSE (mg)	DOSAGE INTERVAL (h)	DAILY DOSE (mg/day)	PEAK EFFECT (hr)	HALF-LIFE (hr)
Aspirin	81–975	4	4500	0.5–1	0.25
Celecoxib	100–200	12	1200	1	11
Diclofenac	25–75	6–8	200	2	1–2
Diflunisal	250–500	12	1500	1	13
Etodolac acid	200–400	6–8	1600	1–2	7
Fenoprofen	200	4–6	3200	1–2	2–3
Flurbiprofen	50–100	6–8	300	1.5–3	3–4
Ibuprofen	200–400	6–8	3200	1–2	2
Indomethacin	25–75	6–8	200	0.5–1	2–3
Ketoprofen	25–75	6–8	300	1–2	1.5–2.0
Ketorolac, oral*	10	6–8	40	0.5–1	6
Ketorolac, parenteral*	60 load, then 30	6–8	120	0.5	6
Meclofenamic acid	500 load, then 275	6–8	400	1	2–4
Mefanamic acid	500 load, then 250	6	1250	2–4	3–4
Nabumetone	1000–2000	12–24	2000	3–5	22–30
Naproxen	500 load, then 250	6–8	1250	2–4	12–15
Naproxen sodium	550 load, then 275	6–8	1375	1–2	13
Oxaprozin	60–1200	24	1800	2	3–3.5
Phenylbutazone	100	6–8	400	2	50–100
Piroxicam	40 load, then 20	24	20	2–4	36–45
Sulindac	150–200	12	400	1–2	7–18
Tolmetin	200–400	8	1800	4–6	2

Adapted from Borsook D, Lebel AA, McPeek B: *MGH Handbook of Pain Management*, Boston, 1995, Little, Brown.
*Use no longer than 5 days.

Opioids

Opioids help some cancer patients as well as those with non–cancer-related chronic pain.[54,55] Cancer pain is the most common indication for maintenance narcotics.[56] Acute, severe, and unremitting pain also requires opioid treatment, as outlined in the WHO analgesic ladder. At times, narcotics may be the only effective treatment for chronic, nonmalignant pain, such as the pain associated with postherpetic neuralgia, degenerative disorders, and vascular conditions.[57] Bouckoms and colleagues[58] demonstrated that long-term oral narcotics provide effective relief of nonmalignant pain in about two thirds of those treated. Nociceptive pain, absence of depression, and absence of any drug abuse were all significantly associated with efficacy of long-term narcotic treatment. Patients with neuropathic pain or major depression fared especially poorly; a bad outcome was four times more likely than a good outcome. Even when patients were carefully selected (i.e., with a lack of previous addiction or gross personality disorder), one third of patients developed abuse, tolerance, or addiction over a 3-year period. Even so, drug abusers with chronic pain can still benefit from physician-prescribed narcotics for their physical pain if it stops them from turning to illicit supplies. These patients might require specific nonnarcotic prescriptions for their neuropathy and depression if gains are to be made.

Narcotic Potencies

Codeine is a good narcotic for mild to moderate pain, but it has limited efficacy for severe pain. Morphine is the narcotic of choice for acute and chronic pain because it is well known and has a good safety profile. Beyond these starting points, the basic principles of narcotics are as outlined in Table 18–7.

Principles of Narcotics Administration

Potency and Administration

Potency and administration are consistent with the characteristics of the drug, its half-life, and absorption by different routes; such knowledge helps to ensure that the dosage schedule is consistent with these parameters.

Oral Potency

Oral potency must be high so that parenteral use can be avoided if possible. Methadone is a good first choice because of its oral potency and relatively slow clearance. Morphine, hydromorphone, and levorphanol may be useful alternatives for initial treatment. Once oral doses have been initiated and titrated to a satisfactory level (e.g., dosing of morphine or methadone every 4 hours), the analgesic effect needs to be sustained by minimizing fluctuations in blood levels and the variable effects of dosing schedules. Morphine sulfate controlled-release (MSC) is ideal for this homeostasis because it is released more slowly than conventional oral morphine. Furthermore, morphine's effect is not significantly affected by minor hepatic disease. Fifty percent of the morphine in MSC reaches the CNS after 1.5 hours, three times longer than it takes conventional oral morphine to reach the CNS. Steady state is reached with MSC in about 1 day. A steady state with MSC at any fixed dose and dosing interval has a lower maximum blood concentration than does conventional morphine, thereby reducing fluctuations in blood levels. MSC does not release morphine continuously and evenly, so that a dosing schedule of every 12 hours has more peaks and troughs than conventional oral morphine given every 4 hours. Chewing or crushing MSC further increases erratic release. MSC should not be given less than every 12 hours.

TABLE 18–7 Potencies and Special Features of Narcotics

DRUG	PARENTERAL (mg EQUIVALENT)	ORAL (mg)	DURATION (hr)	SPECIAL FEATURES
Morphine	10	30	4	Morphine sulfate controlled release has 12-hr duration
Codeine	120	200	4	Ceiling effect as dose increases, low lipophilic
Oxycodone	4.5	30	4	Oxycodone controlled release has 8-12-hr duration (10, 20, 40 slow release mg)
Hydromorphone	2	8	5	Suppository 6 mg = 10 mg parenteral morphine
Levorphanol	2	4	4	Low nausea and vomiting, low lipophilic
Methadone	5	10	2	Cumulative effect; day 3–5 decrease respiration
Meperidine	100	300	3	κ, proconvulsant metabolite, peristaltic slowing and sphincter of Oddi dysfunction
Fentanyl	0.1	25 μg SL	1 (patch 72 hr)	50 μg patch = 60 mg/day morphine IM/IV
Sufentanil	Not recommended	15 μg SL	1	High potency with low volume of fluid
Propoxyphene	Not available	325	4	High dose leads to psychosis
Pentazocine	60	150	3	κ, σ agonist-antagonist, nasal 1 mg q1–2h
Butorphanol	2	N/A	3 (IM), 2 (NS)	μ, κ, σ, agonist- antagonist, nasal 1 mg q1–2h
Buprenorphine	0.3	0.3	4–6	μ-partial agonism; κ-antagonism; can precipitate withdrawal in patients already on chronic opioids
Tramadol	Not available	150	4	μ-agonist, decreased reuptake 5-HT and NE, CYP metabolism
Nalbuphine	10	N/A	3	Agonist–antagonist

CYP, Cytochrome P450; *5-HT*, serotonin; *N/A*, not available; *NE*, norepinephrine; *NS*, nasal; *SL*, sublingual.

Avoid As-Needed Dosing

A steady state of narcotic blood level requires approximately four half-lives to achieve consistency, and a steep dose–response curve makes pain relief erratic (e.g., if one dose is missed, it can take 23 hours to return to therapeutic analgesia). Dosing on an as-needed basis makes steady relief impossible. It also predisposes the patient to drug-respondent conditioning and to subsequent behavior problems.

Toxicity

Morphine and dihydromorphone uncommonly cause toxicity and hence are prescriptions of choice. Even so, when glomerular filtration rate is poor and morphine or hydromorphone doses are high, toxicity can occur, even when equivalent doses of morphine are used without signs of toxicity. Meperidine hydrochloride should be avoided in difficult cases because of its short duration of action (2 to 4 hours) and because even at normal doses its principal metabolite (normeperidine) can cause irritability, auditory and visual hallucinations, agitation, confused thinking, disorientation, hypomania, paranoia, and muscle twitches, in addition to partial and generalized seizures.[59,60] This CNS excitement is more likely to occur in patients with malignancy or renal impairment or when the drug is given intravenously and the dose exceeds 300 mg/day for more than 3 days—all conditions in which there may be significant accumulation of the proconvulsant normeperidine with repeated dosing. Methadone, safe and effective for analgesia on day 2, can accumulate and cause significant respiratory depression by day 5. Troubleshooting checklists for opioids may be required when the basic principles mentioned have not worked.[61]

Are Opioids the Drugs of Choice in This Case?

Unduly long clinical trials and ongoing suffering may be avoided by giving the patient 10 mg of IV morphine as a single-blinded test dose. This is a diagnostic procedure designed to determine if narcotics will relieve the pain. If there is a positive result with relief of pain, one concludes that morphine works well enough to continue its use. A negative outcome might result in a repeat dose of morphine at 20 mg to ensure that it was not just tolerance that failed to produce a benefit at 10 mg. In a doubtful case, one can give 0.4 mg of IV naloxone to confirm the lack of an opioid effect on pain. If there is neuropathic pain, for example, opioids might not produce a good enough response at normal doses. In about 50% of patients with intractable pain, opioids do not have a good enough analgesic effect. In a minority, it is the anxiolytic effect rather than the analgesic effect that is helpful.

Dosing

Prescriber fear and ignorance are the usual reasons that analgesics are given at inadequate dosages and frequencies. Appropriate dosing requires knowledge of the potency and half-life of the drug. Common errors that occur at critical moments include failure to adjust the dosage when switching from parenteral to oral use (e.g., not tripling the dose of morphine when switching from IM to oral dosing); failure to administer the drug at longer intervals than its half-life (e.g., methadone's analgesic half-life is 6 hours; consequently, methadone is needed at least four times a day when it is given for pain, not once a day as when it is given for opioid addiction); and underdosing when beginning MSC

or fentanyl patches because both require at least 24 hours to reach steady-state (supplementary opioids are required for the first 24 hours).

Drug Delivery

An important question to bear in mind is whether the method of administration and type of opioid have been optimized. The most common problem in severe pain is the threefold to eightfold variability of IM absorption. This can be decreased by using agents that are hydrophilic (e.g., morphine, hydromorphone) rather than lipophilic (e.g., fentanyl, methadone, meperidine). When more-lipophilic agents, such as methadone, are used intramuscularly, injections into the deltoid rather than the gluteus muscle are preferable. If an erratic response occurs, it might be due to inconsistent drug delivery. Alternative methods include delivery of the drug intravenously, sublingually, intrathecally, ventricularly, or transdermally. For example, Kunz and colleagues described the innovative use of sublingual sufentanil, 25 mg every 3 minutes (for three doses) for severe but episodic pain.[62] The drug and route were preferable to patient-controlled analgesia (PCA), fentanyl sublingually, or MSC because the volume of fluid was small, speed of onset was within 1 minute, and the half-life was short (and therefore not sedating the rest of the day); in addition, the cost was comparable to PCA, albeit more expensive than sublingual fentanyl. The patient could get out of bed and remain alert and comfortable with a low-tech intervention that is ideal for hospice or for home care.

Tolerance or Excessive Sedation

The age of the patient is an important factor in the efficacy of the drug. The duration of effect can double as age increases; as it does, so does the analgesic effect in a 70-year-old versus a 20-year-old. Opioid adjuvants (e.g., methylphenidate) can decrease or increase (e.g., with antidepressants) sedation.

Mixed Agonists and Antagonists

Pentazocine and butorphanol are commonly used opioids because of their mixed antagonist–agonist properties. Not only are they less potent than standard opioids, but also, if combined with standard opioids during a period of transition, they can cause the patient to develop withdrawal symptoms, an acute confusional state, or even psychosis. Older people are particularly susceptible. Avoidance of mixing agonist opioid drugs with agonist–antagonist agents obviates this problem.

Addiction

The risk of opioid addiction in a general population of medically ill patients is approximately 0.3%. Therefore, considering the patient as an addict on the basis of difficulties with managing narcotics should be done cautiously. Acute sympathetic symptoms from drug withdrawal are more likely to be problematic than addiction per se. Rather than addiction, unrecognized depression alone or co-morbid with anxiety is a more common, immediate explanation for the excessive need for opiates.

Oxycodone has attracted significant attention in the media due to its addiction potential. Clinical practice and research trials show that it is a good medication for pain due to its efficacy, fairly good side-effect profile, and short onset of action. In patients who cannot tolerate or respond to other opioids it remains a good option.[63]

Opioid Adjuvants

Opioid adjuvants are indicated when toxic or pharmacokinetic factors limit further increases in the patient's opioid dosage or when pain remains uncontrolled by opioids in combination with other secondary treatments, such as decompression surgery, nerve blocks, or use of anxiolytic drugs. The choice of adjuvant should be individualized; one should aim for the simplest and most potent combination of drugs. The selection of the adjuvant depends on the symptoms associated with the pain; the character of the pain; and the physician's knowledge of any special issues, risks, drug interactions, or special mechanisms.

Guidelines for Narcotic Maintenance Adjuvants

Maintenance narcotics should be considered only after other methods of pain control have proven unsuccessful. Alternative methods vary from case to case but typically include NSAIDs; oral, transdermal, IV, intrathecal, or epidural opioids; membrane-stabilizing drugs; monoaminergic agents and local nerve blocks; nerve stimulation; and physical therapy.

Narcotics should not be prescribed for addicts unless there is a new major medical illness with severe pain (e.g., cancer or trauma). In such cases, a second opinion from another physician is suggested for all narcotics used for longer than 2 months. If narcotics are prescribed for longer than 3 months, the patient should have a second-opinion consultation, plus a follow-up consultation at least once per year. There should be one pharmacy and one prescriber designated as exclusive agents.

Narcotic dosage should be defined, as should expectations of what will happen if there are deviations from it. For example, abuse leads to rapid tapering of the drug and a detoxification program, if necessary. There should be no doubt that the physician will stop the drug.

Informed consent as to the rationale, risks, benefits, and alternatives should be documented. The course of treatment (in particular, the ongoing indications, changes in the disease process, efficacy, and the presence of abuse, tolerance, or addictive behavior) should be documented.

Justification for maintenance narcotics, given the mixed benefits and risks, involves humanitarian and public health principles. If narcotics are the only effective treatment for intractable suffering, they should be used for humanitarian reasons. The risk of episodic abuse may be justified in marginally reliable people with drug abuse histories and chronic pain if use of narcotics lessens disability and illicit drug use. For example, an IV drug addict with chronic pain might benefit from a methadone maintenance program for pain; furthermore, it may be an effective public health means of reducing the risk of acquired immunodeficiency syndrome (AIDS).

ANALGESIC ADJUVANTS

Pain may be refractory despite the most judicious application of traditional anti-nociceptive measures (such as surgery, nerve blocks, and use of opioids). Stimulants, neuroleptics, TCAs, benzodiazepines, anticonvulsants, antihistamines, peptides, and prostaglandin inhibitors also have roles as nonnarcotic pain treatment adjuvants[64] (Table 18–8).

TABLE 18–8 Analgesic Adjuvants

AGENT	DOSAGE	INDICATIONS	SPECIAL ISSUES
Prostaglandin Inhibitors			
	Variable, limited by side effects and medical co-morbidity	Metastatic bone pain Inflammation Vascular pain	NSAID risks: GI bleeding, kidney impairment
Neuroleptics			
Phenothiazines Butyrophenones	Antipsychotic D_2 receptor–blocking doses	Postherpetic pain Cancer pain Diabetic neuropathy Adjunct to TCAs Co-morbid anxiety or delirium	Haloperidol binds to opioid receptors Membrane stabilizing
Stimulants			
Methylphenidate Dextroamphetamine Pergolide	5–50 mg/day (t½:2–7 hr) 5–20 mg/day (t½:4–21 hr) 0.05 mg tid (t½:6–72 hr)	Postoperative pain and pain in pediatric and cancer patients respond well to combination of analgesic and stimulant	Stimulants decrease pain and sedation Appetite and cognition improve Methylphenidate shows better long-term efficacy than does amphetamine
Steroids			
Prednisone Methylprednisolone	15 + mg/day PO 15 mg/kg IV boluses	Bone metastases Brain swelling Spinal cord compression Anorexia and pain Sickle cell pain	Risks: mood lability, withdrawal, anxiety, insomnia, GI upset
Peptides			
Calcitonin	100–200 IU SC bid Nasal 200 IC/day	Paget's, metastatic, and myeloma pain	Intrathecal, nasal, and SC are used
Somatostatin	500 µg	Vascular headaches	Somatostatin inhibits SP
Capsaicin cream	.075%	Neuralgia, cancer pain Hyperalgesia, postherpetic neuralgia, cluster headache, CRPS, inflammatory dermatoses, itching secondary to dialysis, psoriasis	Capsaicin effect peaks 4–6 wk, for diabetes, postmastectomy, and arthritis pain
Antihistamines			
Diphenhydramine	150 mg	Narcotic adjunct	Decreased inflammation, 5-HT, NE, dopamine, muscle spasm, opiate clearance
Hydroxyzine	100 mg		Increased opiate binding
Benzodiazepines			
Clonazepam Lorazepam	1–4 mg/day 2–16 mg/day	Adjuvant tricyclics Allodynia	Not a substitute for diagnosis of depression or substance abuse
Antiepileptics			
Phenytoin	300-450 mg/day	Cancer pain	Paroxysmal pain responds best to antiepileptic drugs
Carbamazepine	400–1600 mg/day	Headaches, neuralgia	
Valproate	500–2000 mg/day	Central pain	
Gabapentin	900–1800 mg/day	Neuropathy	
Lamotrigine	100–300 mg/day	Migraine headaches	
Oxcarbazepine	300-1600 mg/day	Neuropathy	
Pregabalin	600-1200 mg/day	Neuropathy; PHN	
Topiramate	200-400 mg/day	Neuropathy	
Antidepressants			
Tricyclics			
Desipramine Imipramine	25–300 mg/day 25–300 mg/day	Neuropathy Postherpetic neuralgia	Burning Deafferentation pains respond best to the tricyclic drugs Increased side effects with amitriptyline

Continued

TABLE 18–8 Analgesic Adjuvants—*cont'd*

AGENT	DOSAGE	INDICATIONS	SPECIAL ISSUES
Selective Serotonin Reuptake Innibitors			
Paroxetine	20-60 mg/day	Diabetic neuropathy	
Citalopram	20-60 mg/day	Diabetic neuropathy	
Serotonin–Norephrinine Reuptake Inhibitors			
Duloxetine	60-120 mg/day	Diabetic neuropathy, fibromyalgia	
Venlafaxine	75-375 mg/day	Fibromyalgia	

CRPS, Complex regional pain syndrome; *5-HT*, serotonin; *GI*, gastrointestinal; *NE*, norepinephrine; *NSAID*, nonsteroidal antiinflammatory drug; *PHN*, postherpetic neuralgia; *SP*, substance P; *TCAs*, tricyclic antidepressants.

The type of pain is as important as its cause in guiding the choice of an adjuvant. The pain may be characterized as a constant aching somatic pain, as in a fracture, or as a paroxysmal burning deafferentation sensation, as in phantom limb pain. The primary cause of the pain, however, does not necessarily determine its type or character. For example, the pain of metastatic cancer may be either neuropathic or somatic (and might or might not respond well to NSAIDs). Neuropathic pain is often refractory to opioids, and it covers a diverse group of conditions, which range from herpetic neuralgia to atypical facial pain. Patients suffering from this type of pain might respond to anticonvulsants or TCAs. In the most difficult or ambiguous cases, a valuable technique is to use an IV dose of the drug to gain a rapid and accurate assessment of its effectiveness for the long term. IV morphine, lidocaine, and lorazepam can be used in this way to see whether or not any of these classes of drugs are worth pursuing.

Antidepressants for Pain

The mechanisms of action of TCAs are multiple and probably co-modulate the pain-relieving effect.[65] First, they have an effect in augmenting the descending periaqueductal spinal inhibitory control of pain mediated by serotonin and norepinephrine. In the spinal cord, the dorsolateral funiculus is a serotoninergic inhibitory descending spinal pain pathway that modulates 80% of the spinal analgesic effect of opiates. Second, they potentiate naturally occurring or administered opiates. For example, desipramine, 8-OH-amoxapine, and imipramine are twice as potent as amitriptyline and four times as potent as trazodone and clomipramine at binding to opiate receptors. Third, antihistamine and α-receptor effects may be important with regard to potentiation. Fourth, there may be membrane-stabilizing anesthetic, anti-kindling anticonvulsant effects, which can also give secondary symptom relief of insomnia or anxiety.

The pain relief obtained from antidepressants is often independent of their effects on mood or their alleviation of major depression.[66,67] In fact, the greatest response to antidepressants in patients with pain can occur in those who are not depressed.[68] Antidepressants as analgesics are best thought of as monoaminergic cell stabilizers rather than just antidepressants. Serotonin, norepinephrine, and dopamine all modulate pain via their actions in the periphery to the CNS.

Serotonin presents a paradox because more serotonin is not necessarily better, yet function must be intact for pain to be inhibited. One type of peripheral serotonin receptor, 5-HT_{1D}, is found in cerebral blood vessels. Sumatriptan, a selective 5-HT_{1D} antagonist, acts to produce vasoconstriction and migraine headache relief. The raphe and mesolimbic structures are important sites of subcortical serotonin receptors, mainly types 1A, 2A, and B. These areas modulate pain and mood—the neurobehavioral sites of action. Despite the important role serotonin plays in pain, there are a number of exceptions to the simplistic notion of more serotonin, less pain.[69] For example, buspirone, fluoxetine, and trazodone have all been shown to be ineffective in attenuating certain pain syndromes.[70–72]

Norepinephrine-modulating medications also have value in treating chronic pain. Desipramine (at an average dose of 200 mg daily) relieved pain in diabetic neuropathy, in both nondepressed and depressed patients,[73] and it also relieved postherpetic neuralgia.[74] Duloxetine, a serotonin–noradrenergic reuptake inhibitor (SNRI), has become the first antidepressant to have a specific pain indication for the treatment of painful diabetic neuropathy.[75] Duloxetine has also been studied in a number of large trials for the treatment of fibromyalgia and found to be efficacious not only in reducing pain but also in reducing tender points and stiffness scores, while also increasing the tender-point pain threshold when compared with placebo.[76] These results have also been reproduced by other SNRIs; milnacipran and venlafaxine also have been shown to be efficacious for the treatment of pain associated with fibromyalgia.[77,78]

Reviews of Efficacy

Earlier reports of Lindsay and Wycoff showed an efficacy of 70% to 80% for antidepressants for the treatment of chronic pain in patients with depression.[79] Stein and associates reported that amitriptyline (150 mg/day) was more effective than acetaminophen (2 g/day) in a controlled, double-blind study, with mild depression being one of the predictors of pain relief at the end of the 5-week study.[80] Blumer and Heilbronn showed twice the improvement (60%) in outcome and a halving of the dropout rate (25%) in pain patients treated with antidepressants.[81]

Pain syndromes that may be responsive to antidepressants include those associated with cancer, postherpetic neuralgia, arthritis, vascular and tension headaches, and facial pain. The literature reports a wide range of generally positive, but poorly designed, studies. Feinmann reviewed the 11 largest and best-designed studies on pain relief from antidepressants when depressive symptoms were present.[82] TCAs (e.g., amitriptyline hydrochloride) and monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine sulfate) were used, and the results demonstrated that these antidepressant drugs were beneficial in treating chronic pain associated with depression.

A review by Goodkin and co-workers found that 37 of 53 trials (70%) of heterocyclic antidepressant drugs for chronic pain syndromes failed to meet minimum criteria for adequate design.[83] Of the remaining 16 trials that met design and protocol criteria, 7 evaluated headache pain and documented positive effects with low-dose regimens. Complicating these findings was that smaller than typical antidepressant doses were used in many studies. In this same review, another nonrandom series of 17 studies was selected, of which 5 (29%) met minimum design and protocol criteria (i.e., clear protocol, placebo-controlled, and defined outcome measurements); only two of the five trials showed positive results. One study was for low-dose amitriptyline in mixed pain syndromes, and the other study was for desipramine in postherpetic neuralgia. Max found that in 13 well-designed, randomized trials, antidepressants reduced pain in diabetic neuropathy and postherpetic neuralgia, particularly the SNRIs (e.g., imipramine, desipramine, and amitriptyline).[84]

Saarto and Wiffen, in a Cochrane-based review, reviewed available randomized clinical trials of antidepressants in neuropathic pain.[25] Sixty-one trials were included; they found that TCAs were effective. There was limited evidence for the effectiveness of the SSRIs based on current available data.

In a meta-analysis conducted to assess the efficacy of antidepressants in treating back pain in adults, antidepressants were more effective than placebo in reducing severity of pain, but not functional status in chronic back pain.[85] TCAs have been an option for patients with chronic back pain, but SSRIs have shown limited effectiveness. To date, SNRIs have not been studied for the treatment of chronic back pain.[26]

When is it worth trying a monoaminergic agent? A trial of an antidepressant medication is useful in any intractable pain condition, whether or not depression is present, because analgesic effects are at least partly independent from antidepressant effects. Furthermore, the size of the analgesic effect does not differ significantly in the face of depression.

There is no clear evidence for the superiority of any one antidepressant over any other. Amitriptyline, desipramine, and doxepin hydrochloride have been used most often in the clinical studies. Even though sedating and nonsedating properties of drugs have no significant association with analgesic effect, the antihistaminic profile of an antidepressant correlates with effect.[86] Potent serotonin reuptake blockade is not essential to pain relief; moreover, there is doubt about the efficacy of purely serotoninergic drugs for neuropathic pain (e.g., fluoxetine, zimeldine, and trazodone).[87,88] Buspirone does not appear to relieve pain. With the exception of paroxetine, all antidepressant drugs studied in placebo-controlled trials of neuropathic pain have some inhibition of norepinephrine reuptake (i.e., amitriptyline, desipramine, nortriptyline, imipramine, and maprotiline).[73] Venlafaxine has some agonist–antagonist opiate activity as well as norepinephrine, 5-hydroxytryptamine, and dopamine-reuptake effects, but it has yet to be rigorously proven as an analgesic.

Monoamine oxidase inhibitors may be particularly helpful in the attenuation of atypical pain associated with atypical depression. MAOIs and TCAs, however, can require a trial of at least 6 weeks for the full benefit to be evident.

Dopamine agonists can also augment analgesia. Dopamine has been associated with pain in clinical and experimental trials and has also been shown to comodulate opioid and substance P effects in the CNS. Psychostimulants can potentiate the effects of opioid analgesics.[89,90] Methylphenidate has been studied as adjuvant therapy for cancer patients receiving narcotics. In a randomized, double-blind, placebo-controlled crossover trial of 32 patients with advanced cancer receiving chronic opiate therapy, a statistically significant reduction in pain intensity and sedation was seen with the use of methylphenidate.[91] In another study of 50 patients with advanced cancer and opiate-induced sedation, 44 had a decrease in sedation after initiation of methylphenidate.[92] Patients with incident cancer pain (mild or no pain at rest, severe pain during movements) showed better pain control, and they tolerated higher doses of narcotics when narcotics were supplemented with methylphenidate.[93] A placebo-controlled trial demonstrated that the addition of oral methylphenidate resulted in improved cognitive function in 20 patients receiving continuous subcutaneous narcotics for cancer pain,[94] and similarly, 5 of 11 adolescent cancer patients receiving opiates exhibited improved interaction with family or decreased somnolence when methylphenidate was added to their medication regimen.[95]

Although it is classified as a dopamine reuptake inhibitor, bupropion also has noradrenergic activity. Evidence of its analgesic effect is still very limited, although in one double-blind, placebo controlled, crossover trial, 73% of 41 subjects with neuropathic pain obtained pain relief with bupropion treatment.

Monoaminergic agents in combination with clonazepam, valproate, or narcotics (for cancer pain) are often safe and desirable.

Although some patients respond to low doses of antidepressants for pain, a complete trial of an antidepressant in a pain patient requires a full dose of an antidepressant, the same as used in major depression. The placebo-controlled study of McQuay and associates found that low doses of antidepressants (amitriptyline 25 mg) did not have the efficacy of higher doses.[96] The best results in the largest number of people are obtained, however, when the usual antidepressant dosage of drug is used (e.g., 300 mg/day of imipramine hydrochloride or its equivalent). Other pointers include:

- Depression should not be rationalized as appropriate.
- Treatment of the depressed pain patient is no different from treatment of any other depressed patient.
- Education of the patient as to the rationale for antidepressant treatment is advised for good compliance.
- Maintenance treatment for 3 to 6 months is usually necessary for the best results.

Antiepileptic Drugs

Antiepileptic drugs (AEDs) have a long history of efficacy in the treatment of pain, especially neuropathic in origin, dating back to case reports for the treatment of trigeminal neuralgia with phenytoin in 1942 and carbamazepine in 1962.[97] Blocking abnormally high-frequency and spontaneous firing in afferent neurons, in the dorsal horn, and in the thalamus are the putative mechanisms for the efficacy of anticonvulsants with regard to pain. The consequence of blocking the hyperexcitability of low-threshold mechanoreceptive neurons in the brain lead to pain relief.[98]

Phenytoin, carbamazepine, valproic acid (VPA), benzodiazepines, and some of the newer AEDs including gabapentin, pregabalin, lamotrigine, topiramate, and oxcarbazepine are agents used to treat pain. These drugs have a number of shared cellular effects, which include antagonism of excitatory amino acids, gamma-aminobutyric acid (GABA)-receptor agonism, sodium and calcium pump stabilization, and antagonism of adenosine. Indirectly, they all antagonize the effects of excitatory amino acids, which are believed to kindle hyperexcitability of CNS neurons.

Phenytoin has been shown effective in alleviating pain associated with various neuropathies, particularly trigeminal, diabetic, and poststroke pain. Sharp, shooting, lancinating pain has been shown to respond especially well to this drug. It has more behavioral toxicity, however, and is less effective than carbamazepine, thus making it a second choice for analgesia.

Carbamazepine is generally superior to phenytoin for pain. The effect of carbamazepine on pain suppression is likely mediated by central and peripheral mechanisms. The ability of carbamazepine to block ionic conductance appears to depend on dosing frequency, which enables the drug to suppress the spontaneously active Aδ and C fibers responsible for pain without affecting normal nerve conduction. Since Blom reported the analgesic properties of carbamazepine for patients with trigeminal neuralgia in 1962, carbamazepine has been shown to be effective also for postherpetic pain, postsympathetic pain, diabetic neuropathy, multiple sclerosis, and assorted neuralgias.[99] Higher levels (8 to 12 μg/L) are typically necessary for optimal efficacy.

The first reports of VPA used in neuropathic pain appeared in the early 1980s. VPA prolongs the repolarization of voltage-activated Na^+ channels and also increases the amount of GABA in the brain, enhancing the activity of glutamic acid decarboxylase and inhibiting GABA degradation enzymes. VPA has been shown to decrease postherpetic neuralgia, episodic and chronic cluster headaches, migraine, and postoperative pain, as well as various neuralgias. It has also been demonstrated that VPA is effective in treating migraine headaches in two double-blind, placebo-controlled trials.[100,101] These demonstrations of efficacy in pain reduction are in addition to the traditional place for VPA in treating psychiatric disorders (bipolar and schizoaffective disorders). VPA sprinkles, in particular, are well tolerated and can substitute for carbamazepine and lithium in pain states, although no head-to-head comparisons have been completed.

Benzodiazepines have been controversial in the alleviation of pain, but they do have a definite place as safe and effective agents.[102] Combinations of benzodiazepines with antidepressants or opiates may be particularly useful clinically. IV lorazepam was superior to morphine, lidocaine, and placebo in a single-blind study of neuropathic pain[103]; however, these results were not reproduced in a randomized, double-blind trial in which lorazepam was less effective than amitriptyline in patients with postherpetic neuralgia.[104] Orally, clonazepam is the drug of choice. It binds more slowly to central than to peripheral benzodiazepine receptors, and it is synergistic with serotoninergic pain mechanisms, a factor that distinguishes it from other benzodiazepines. A useful diagnostic test for benzodiazepine-sensitive pain is to administer lorazepam 2 mg IV in a single-blind manner evaluated by visual analogue scale (VAS) monitoring. Positive results (greater than 3-cm decrease in VAS) signify relief of ongoing pain. If positive results are achieved, it is recommended to give sequential IV lorazepam doses to break the pain cycle (in severe cases) or clonazepam (e.g., 2 to 4 mg orally at bedtime, and 1 mg twice a day).

Of the new generation of AEDs used to treat neuropathic pain, gabapentin is perhaps the best studied. Developed as a structural GABA analogue, it has no direct GABAergic action. It is believed that gabapentin acts on the $\alpha_2\delta$ calcium channels. Gabapentin has relieved pain and associated symptoms in patients with peripheral diabetic neuropathy, postherpetic neuralgia, HIV-related neuropathy, and cancer-related neuropathic pain.[105–108] The dosages used in these studies typically ranged from 900 to 3600 mg daily in three divided doses. Additional studies are required to evaluate if gabapentin is efficacious in other pain states.

Topiramate works via multiple mechanisms, including prolongation of voltage-sensitive sodium channel inactivation, $GABA_A$ agonism, and non–*N*-methyl-D-aspartate (NMDA) glutamate receptor antagonism. Topiramate is useful in the treatment of trigeminal neuralgia, along with diabetic neuropathy. Like any of the newer AEDs, continued studies will be required to determine overall efficacy.

Oxcarbazepine is a keto-analogue of carbamazepine, with the analgesic mechanism likely due to inhibition of voltage-dependent sodium channels and also, to a lesser extent, potassium channels. Studies seem to show mixed results for the use of oxcarbazepine for diabetic neuropathy, but its efficacy seems to be similar to carbamazepine's in the treatment of trigeminal neuralgia. However, there are limited data regarding the efficacy and safety of this drug in the treatment of other neuropathic pain syndromes.

Pregabalin is a GABA analogue believed to exert its analgesic effect by binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels on primary afferent nerves and reducing the release of neurotransmitters from their central terminals. Evidence seems to show that pregabalin is effective for reducing the intensity of pain associated with diabetic polyneuropathy and postherpetic neuralgia.[109,110]

Lamotrigine is a direct glutamate antagonist that also inhibits sodium channels. Although initial case reports seemed to show some promise for use of lamotrigine in neuropathic pain states, most randomized, double-blind studies to date have not shown any significant efficacy.[111–115]

Sympathetic Blockade

Sympathetically maintained pain (SMP)—regardless of whether it is due to CRPS, opiate tolerance, hyperalgesia, inflammation, vascular headache, postherpetic neuralgia, trauma, facial pain, or arthritis—might respond to sympathetic blockade.[116] Sympathetic efferent fibers release norepinephrine, which in turn activates α-adrenergic receptors. Activation of these receptors, either directly or indirectly, excites nociceptors. Activity in the nociceptors then evokes pain and causes further discharge of nociceptors. α-Adrenergic receptor supersensitivity has been postulated as a likely mechanism for both the hyperalgesia and the autonomic disturbances associated with SMP.[117]

The clinician may consider the early use of sympathetic blockade in any chronic pain syndrome with features

of sympathetic dysfunction. SMP is diagnosed and treated using the method of injecting or transdermally applying an α-adrenergic blocking agent selected from the group consisting of an α_1-adrenergic antagonist, α_2-adrenergic agonist, or other drug that depletes sympathetic norepineprhine. One method to assess for SMP is to infuse 500 mL of half-normal saline before putting phentolamine into an ischemic regional block, and then administer phentolamine (10 mg IV over a 10-minute period). A positive test result is marked by relief of evoked pain stimulated by light touch or a tuning fork.[118] α-Blocking drugs (e.g., phentolamine and α-blocking antidepressants) and α_2-agonists (such as clonidine), given with or without opiates, are all potentially useful in patients with chronic pain. Intrathecal, epidural, and systemic administration of clonidine also produce analgesia, and clonidine is often useful in patients who have developed tolerance to opiates and who have some types of vascular or neuropathic pain.[119,120] Transdermal clonidine (0.1 to 0.3 mg/day) is sometimes useful in neuropathy, although the results of the treatment are mixed.

The mechanism of action of dexmedetomidine resembles that of clonidine, although its affinity for the α_2-adrenoceptor is approximately eight times that of clonidine[121] and it has a significantly higher α_2/α_1 selectivity ratio than does clonidine.[122,123] Besides its analgesic effects, its sedative effects are thought to be secondary to action on α_2-adrenoreceptors located in the locus ceruleus. Similar to clonidine, dexmedetomidine decreases the requirement for opioids in patients undergoing a variety of surgical procedures,[124] and in a clinical trial where it was administered as a single agent for sedation, it reduced by approximately 60% the number of patients who needed opioids to control pain.[125] Dexmedetomidine was approved in the United States in 2000 for up to 24 hours of pain treatment in surgical patients, and it is currently in clinical trials for the control of postoperative pain in thoracotomy patients.

β-Blockers are not efficacious in the treatment of sympathetically maintained pain except in their use for alleviating migraine headaches. Guanethidine, bretylium, reserpine, and phentolamine have been used successfully to produce a chemical sympathectomy.[126,127]

ADDITIONAL ASPECTS OF TREATMENT

Central Neuropathic Pain States

The clinical hallmark of central pain is that it persists without an obvious nociceptive stimulus; the physiologic goal of treatment is to stabilize hyperexcitable neurons. Table 18–9 outlines some clinical approaches to central pain.

TABLE 18–9 Pain Treatment

PAIN CHARACTERISTICS	WHAT TREATMENT IS NEXT?	COMMENTS
Nociceptive element present?	Nerve block for diagnostic and therapeutic reasons Imaging; MRI, looking for lesion	Even in pain that appears central (e.g., trigeminal neuralgia), nociceptive triggers can initiate pain and peripheral deafferentation
Allodynia present? (vibration, cold, or light touch)	Low-dose clonazepam (1–4 mg/day), if the person can tolerate benzodiazepines, alone or in combination with desipramine 50 mg at bedtime (up to 300 mg eventually, if necessary) Mexelitine 150–400 mg tid	Allodynia predicts response to clonazepam Clonazepam relaxes muscles and improves sleep and anxiety Membrane stabilizers are useful, but cardiotoxicity needs to be checked Peptides useful
Paroxysmal attacks? (lightning-like)	Antiepileptic drugs (AEDs) Carbamazepine 400–1600 mg/day (serum level 8–12 mcg/L) Valproate 500–2000 mg/day Gabapentin 300–1200 mg tid Lamotrigine 100–300 mg/day	Clonazepam should usually be tried first, but it works well synergistically with the AEDs listed Valproate for vascular headache Gabapentin: few drug interactions
Central pain? Allodynia Paroxysmal attacks Sharp perceived as light touch Decreased pain threshold Nondermatomal distribution of pain Hyperpathia	Definitive trial is a single-blind random assignment of IV lorazepam (2–4 mg) vs lidocaine (100 mg) vs morphine 10 mg, rated on a VAS IV amitriptyline 25 mg infusion as a test dose with VAS	Careful physical examination is essential Is sharp perceived as light touch? Light touch is painful, sustained, and has a delayed crescendo Tuning fork/moving a hair examination is best for allodynia
Co-morbid central pain? Vascular and myofascial pain	Valproate 250–2000 mg/day Physical therapy Monoaminergic prescription antidepressants Nasal calcitonin 200 IU/day Capsaicin 4–6 week trial Topical preparation (Zostrix)	Common in head, neck, and face pain Mixed results with SSRIs Rule out sympathetically maintained pain

Continued

TABLE 18–9 Pain Treatment—*cont'd*

PAIN CHARACTERISTICS	WHAT TREATMENT IS NEXT?	COMMENTS
DSM-IV psychiatric diagnosis? Rule out or treat	Co-morbid psychiatric and CNS pain: consider prescription with dual effects for pain and psychiatric diagnosis Benzodiazepine for allodynia and anxiety Antidepressants for neuropathy, depression, and anxiety Neuroleptics for neuralgia, anxiety, psychosis, and nausea Anticonvulsants and mood stabilizers for lancinating pain	Rule out depression and anxiety, consider mimics of central pain, such as somatoform, factitious, or psychotic disorders Pain drawing by the patient is a good tool to uncover psychosis and myofascial pain Rule out akathisia, restless legs syndrome

AEDs, Antiepileptic drugs; *CNS*, central nervous system; *MRI*, magnetic resonance imaging; *SSRIs*, selective serotonin reuptake inhibitors; *VAS*, visual analogue scale.

Carbamazepine has been shown to be among the most effective agents for some facial neuralgias, which can be so agonizing that some patients actually look forward to death. Within 24 hours of attaining steady state, it is effective in 80% of patients with trigeminal neuralgia, making it clinically superior to phenytoin. Other types of lancinating pain, such as postherpetic neuralgia, postsympathectomy pain, and posttraumatic pain, might also respond to AEDs. IV trials offer a quick, definitive way of identifying drug responders in complex or pressured situations.

For routine CNS pain, clonazepam is the best-tolerated anticonvulsant for pain syndromes, especially when allodynia is present. It facilitates both presynaptic and postsynaptic inhibition, increases recurrent inhibition, and decreases the firing rate of normal and epileptic neurons in the brain; it also enhances sleep, relaxes muscles and blood vessels, and treats panic. It is the drug that exemplifies the need to select prescriptions based not only on their efficacy and tolerability but also on their mechanisms of action for disease processes that have multiple pathophysiologies.

ECT has been used in long-standing pain accompanied by depression. The rationale is that treating the depression eases the suffering associated with pain. Unfortunately, ECT is effective for major depression, but it does not relieve pain. The assumption that there must be chronic depression with chronic pain and that it will be amenable to ECT is usually untenable.

Pain Behavior and the Use of Multidisciplinary Pain Clinics

Guidelines

Medicare guidelines offer one set of standards for multidisciplinary management of pain. The pain must be at least 6 months in duration (resulting in significant life disturbance and limited functioning), it must be attributable to a physical cause, and it must be intractable to the usual methods of treatment. Desirable characteristics for pain treatment facilities and standards of care in pain management have now been published in response to skepticism about cost, quality, control, and diversity of pain treatment facilities.[118] Quality-control guidelines developed by the Commission on Accreditation of Rehabilitation Facilities (CARF), under the umbrella of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), have led to the certification of more than 100 chronic pain-management programs nationwide. Behavioral treatments, however, are not primarily for pain relief; they merely extinguish the behavior associated with pain.[128] Furthermore, proof of the cost-effectiveness of inpatient multidisciplinary treatment is nascent and consequently still ill defined.

Reasons for Referral to an Inpatient Multidisciplinary Pain Clinic

Inpatient multidisciplinary pain clinics should be considered in the following circumstances:

- When the diagnosis of the physical and psychiatric pathology is already complete or is so obscure that intensive observation is necessary (e.g., malingering)
- When consultation from an independent physician who is an expert in the treatment of chronic pain is necessary to confirm that no single modality of outpatient treatment is likely to work
- When the patient has already obtained maximum benefit from outpatient treatments such as NSAIDs, nerve blocks, antidepressants, and simple physical and behavioral rehabilitation
- When intensive daily interventions are required, usually with multiple concurrent types of therapy, such as nerve blocks, physical therapy, and behavior modification
- When the patient exhibits abnormal pain behavior and agrees to the goals of improved coping, work rehabilitation, and psychiatric assessment
- When medications for pain relief are so complex or compliance management is so difficult that direct supervision of medical therapy is necessary
- When a self-medication program is required, typically with a written schedule of medications, a contract, and strategies mutually acceptable for patient and physician

Hypnosis

The use of hypnosis in chronic pain syndromes is well known. Self-hypnosis is particularly helpful, but only about one in four subjects is able to achieve a state of concentration of sufficient magnitude for lasting pain control. Hypnosis is a method worth considering, provided that the physician knows its limitations and how to apply it to the individual patient's needs.

Rehabilitation

Rehabilitation of patients who have chronic pain syndromes can require some combination of psychiatry, physical therapy, physiatry, behavioral psychology, and neurology. No special therapy, including exercise therapy, spinal manipulation, bed rest, orthoses, acupuncture, traction therapy, back schools, and epidural steroids, works well. Successful rehabilitation aims to decrease symptoms, increase independence, and allow the patient to return to work. A positive, rapid return to light-normal activities and work is essential if disability is to be minimized. Psychologically, this is the key to coping with acute trauma. Even with patients who experience low back pain, 50% of whom have a recurrence within 3 years of the initial episode, there is no evidence that a return to work adversely affects the course of the pain syndrome.[129]

Treatment of myofascial pain syndromes may be challenging. It involves restoration of stage 4 sleep, aerobic conditioning (which could include physical therapy or yoga), and avoidance of drugs, including caffeine and alcohol. Trigger point analgesia, behavioral modification of maladaptive sleep habits, and treatment of anxiety and depression may be necessary if chronic muscle pain is to be relieved. MAOIs are often effective. TCAs (e.g., desipramine and imipramine) can also be effective and are easier to use than MAOIs because dietary restrictions are not needed. Response to SSRIs has been unpredictable for myofascial pain; at times they provoke muscle spasms and do not help the myofascial pain.[130] Cyclobenzaprine and *S*-adenosylmethionine (SAMe), however, have resulted in some modest adjunctive efficacy.[131] Eight weeks is the duration of an optimal trial for any of these agents.

Education

Education is needed for the caregivers as well as the patient. In the past, medical professionals, be they physicians or nurses, viewed the patient who is in constant need of pain medication with suspicion. Physicians often underestimated the medication's effective dose, overestimated the medication's duration of action, and had an exaggerated notion of the danger of addiction. Rarely were physicians told to vary the amount of drug prescribed based on the patient's body weight, kidney function, and previous tolerance for the drug. The physician's ennui with failure, suffering, and death could also have led to flight from pain. When the amount of medication a patient requires for the management of pain becomes a cause célèbre on the ward, the consulting psychiatrist should call a meeting of the house staff, attending physicians, and nurses so that all biases and suspicions can be brought into the open. Medical personnel are far more apt to underestimate the amount of narcotic required for a given pain than to overestimate it. In either case, their opinions are usually based more on misinformation or folklore than on fact. Once these judgments are aired, the patient usually benefits.

Cognitive-Behavioral Therapies

Hypnosis and imagery conditioning to induce relaxation and pain control are consistently found to be more effective than cognitive-behavioral training.[132,133] Traditional hypnosis, autogenic exercises, yoga methods, and meditation are all useful paths to achieve those goals.

Coping and Psychotherapy

Coping with chronic pain always threatens two fundamentals of survival: attachment behaviors and intrapsychic defenses. To cope means to have people of quality around to fortify one's courage and to have adaptive defense mechanisms to negotiate the thoughts and feelings that arise in one's head. Helping the patient develop cognitive and behavioral coping skills is more effective for decreasing pain and psychological disability than is education alone.[134] Coping is also context dependent and is most effective when the focus includes the couple or family.[135,136]

The psychodynamic aspects of coping involve conflicts over autonomy and care. Old conflicts about nurturance suggest there may be mixed feelings about recovery. Shame can mimic depression, trigger conservation and withdrawal, and produce counterdependent behavior. Regression, some of which is normal, can be manifested as noncompliance, help-rejecting behavior, complaining, and behaviors akin to the metaphorical "cutting off your nose to spite your face." The hateful patient and the hateful physician are often compatriots in partnership with chronic pain, and a task of the psychiatrist is to clarify how these problems become played out in the physician–patient relationship. One should understand that the physician is a protective figure who is the recipient of both idealized and angry feelings when a cure is not forthcoming. Modern health care, with its fragmentation, multiple caregivers, and bureaucracies, guarantees rifts in the physician–patient relationship. To help the patient cope, the psychiatrist must be sensitive to the unconscious feelings of the patient and be prepared to manage denial and to employ family counseling, relaxation, exercise, physical rehabilitation, and pharmacotherapy, while still functioning as a teacher and physician. Wisdom, medicine, time, and hope are the professional's charge.

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19

Patients with Neurologic Conditions I. Seizure Disorders (Including Nonepileptic Seizures), Cerebrovascular Disease, and Traumatic Brain Injury

Jeff C. Huffman, M.D.
Megan Moore Brennan, M.D.
Felicia A. Smith, M.D.
Theodore A. Stern, M.D.

The structure and function of the central nervous system (CNS) is altered by many neurologic disorders. Because the CNS controls affect, behavior, and cognition, neurologic disorders can lead to neuropsychiatric symptoms that resemble those found in primary psychiatric conditions. Therefore the general hospital psychiatrist is frequently called on to assess patients who have classic psychiatric symptoms caused by an underlying neurologic disease

In this chapter we will review the management of patients with neurologic conditions that are commonly associated with neuropsychiatric phenomena. We will discuss seizure disorders and describe the diagnosis and management of nonepileptic seizures (also known as *pseudoseizures*). Furthermore, we will outline the treatment of neuropsychiatric symptoms in patients with cerebrovascular disease and traumatic brain injury (TBI). Chapter 20 will discuss the management of neuropsychiatric conditions associated with movement disorders, demyelinating disease, and CNS neoplasm or infection.

THE MANAGEMENT OF PSYCHIATRIC SYMPTOMS IN PATIENTS WITH SEIZURE DISORDERS

Approximately half of all patients with seizure disorders have co-morbid psychiatric syndromes[1]; therefore the general hospital psychiatrist should have a working knowledge of seizure disorders and the neuropsychiatric syndromes that are commonly associated with these disorders. Patients with seizures may have psychiatric symptoms that occur during a seizure (*ictal* symptoms), immediately before or after a seizure (*periictal* symptoms), or between seizures (*interictal* symptoms).

It may be useful to begin with some definitions. A *seizure*, as defined by Schwartz and Marsh,[2] is an abnormal paroxysmal discharge of cerebral neurons sufficient to cause clinically detectable events that are apparent to the patient or an observer. Seizures can be *partial* (focal) or *generalized*; partial seizures are localized in one area of the brain, whereas generalized seizures result in abnormal electrical activity throughout the cortex. Patients with a chronic course of repeated, unprovoked seizures are said to have *epilepsy*.

Generalized seizures are subclassified into a number of subtypes.[3,4] *Tonic–clonic* (grand mal) seizures are the most common form of generalized seizure; they are characterized by a sudden loss of consciousness, followed by a brief tonic phase with contraction of skeletal muscles and an upward deviation of the eyes. A more prolonged clonic phase follows; this stage is characterized by rhythmic and symmetric jerking of the extremities. *Absence* (petit mal) seizures are characterized by brief (usually 5 to 10 seconds) lapses in consciousness and by motionless staring; these seizures occur primarily in children and are rare after puberty. *Myoclonic* seizures are characterized by brief and sudden muscle contractions that may occur unilaterally or bilaterally, singly or repeatedly; these are more commonly seen in children but may also occur in adults. Finally, *atonic* seizures ("drop attacks" or akinetic seizures) are characterized by sudden loss of muscle tone in the neck, upper extremities, or lower extremities.

Partial seizures are classified as *simple partial seizures* when consciousness is unaffected or as *complex partial seizures* when consciousness is altered. Partial seizures may secondarily progress to become generalized seizures. An aura before a generalized seizure (e.g., an unusual sensation before the onset of a convulsive seizure) is essentially a partial seizure that secondarily generalizes. Complex partial seizures (CPSs) deserve special mention, insofar as they are the most common type of seizure in adults[4] and are commonly associated with neuropsychiatric phenomena (especially when the seizures have a temporal lobe focus; in this case the syndrome is often called *temporal lobe epilepsy [TLE]).*

CPSs may involve sensory, affective, perceptual, behavioral, or cognitive symptoms. CPSs may include hallucinations of any sensory modality; they can be olfactory (e.g., a noxious odor, like burning rubber), gustatory (metallic or

other tastes), auditory, visual, or tactile in nature. The most common affective symptoms are fear and anxiety, although depression may also occur; rage is uncommon. Such affective symptoms usually have a sudden onset and offset.

Behavior during CPSs may also be abnormal; automatisms are common and may include oral or buccal movements (e.g., lip smacking or chewing), picking behaviors, or prolonged staring. Cognitive symptoms associated with CPS include *déjà vu* (a feeling of familiarity), *jamais vu* (a feeling of unfamiliarity), macropsia, micropsia, and dissociative, or "out-of-body," experiences. Patients with neuropsychiatric symptoms secondary to CPS may be mistakenly diagnosed with a primary psychiatric disorder because the symptoms of a CPS are often similar to those of psychiatric disorders, because CPSs are generally not associated with classic tonic–clonic seizure activity, and because the interictal (and even ictal) scalp electroencephalogram (EEG) may appear normal. Therefore the general hospital psychiatrist must be particularly astute in differentiating patients with CPS from those with primary psychiatric disorders.

In the following discussion, we outline the phenomenology and treatment of neuropsychiatric symptoms among patients with seizure disorders. We discuss ictal, periictal, and interictal neuropsychiatric symptoms and delineate how these symptoms differ from those seen in patients without seizure disorders. In addition, we discuss practical approaches to treatment.

Ictal Neuropsychiatric Phenomena

Ictal psychiatric symptoms are most commonly associated with partial seizures, although they can also occur with generalized seizures.[1] Anxiety, fear, and psychosis are the most common psychiatric symptoms experienced during a seizure. Anxiety or fear is a component of the aura in one third of patients with partial seizures[5]; the anxiety is often intense and may last throughout the course of the seizure. It may be most common in patients with right temporal foci.[6]

Such symptoms may resemble those of panic attacks, with autonomic symptoms, nausea, intense anxiety, and depersonalization. The clinical situation may be further confused by the fact that patients with epilepsy have high rates (approximately 20%) of co-morbid panic attacks[7]; therefore patients with epilepsy may have both ictal anxiety and interictal panic attacks that can be difficult to distinguish. The more circumscribed the symptoms are to associated seizure phenomena (e.g., automatisms or hallucinations during an episode, or confusion or severe lethargy after the event), the more likely it is that the anxiety is ictal.

Ictal psychosis is also common in patients with partial seizures. Ictal psychotic symptoms are most often associated with temporal lobe foci, but nearly one third of patients have nontemporal lobe foci.[8] Hallucinations during a seizure are much more likely to be olfactory or gustatory; auditory hallucinations (common in primary psychotic disorders) are less common. Paranoia is uncommon and usually short-lived. In contrast to patients with primary psychosis, consciousness is usually impaired during ictal psychosis, and affected patients are usually amnestic for the episode.[9]

Ictal depression is uncommon; it occurs as part of the aura in approximately 1% of patients with epilepsy.[10] Such depressive symptoms, as with other ictal symptoms, appear abruptly and without obvious psychosocial precipitants. Although depressive symptoms often disappear abruptly, some authors have noted that ictal depressed mood may extend beyond other ictal or postictal symptoms.[10,11]

Ictal aggression has also been reported, but it appears to be exceedingly rare (fewer than 0.5% of patients in one large series[12]). Furthermore, ictal aggression is poorly directed and does not involve significant interactive behavior; stereotyped shouting and pushing are among the most common manifestations. Patients rarely perform intricate, directed acts of violence during a seizure.

Determining whether anxiety, depression, or other psychiatric symptoms are ictal events or part of primary psychiatric conditions can be difficult. Table 19–1 describes some distinguishing characteristics of ictal and nonictal symptoms. In general, ictal symptoms are more often abrupt in onset and offset, occur in concert with other stereotyped manifestations of seizures (e.g., automatisms and jerking), and are frequently short-lived, usually lasting less than 3 minutes.[1] Furthermore, ictal symptoms are usually stereotyped; that is, a patient will not experience fear with one seizure and depressive symptoms with another—the pattern of symptoms will generally be the same.

In most cases, these factors should help the clinician to distinguish ictal psychiatric symptoms from primary psychiatric phenomena. However, complicating factors may be present, and partial status epilepticus may result in prolonged ictal psychiatric symptoms. Therefore the EEG remains a key tool for establishing whether symptoms are ictal.

Treatment of ictal psychiatric symptoms requires a careful evaluation. Primary psychiatric symptoms and ictal psychiatric symptoms are similar, frequently co-morbid, and have different treatment. Therefore careful clinical evaluation; EEG monitoring; and, when indicated, other diagnostic procedures (e.g., determination of prolactin levels) should be performed to distinguish these phenomena. Once symptoms have been identified as ictal, treatment of the associated psychiatric symptoms requires treatment of the seizure with anticonvulsants. Treatment of ictal psychosis with antipsychotics or ictal anxiety with non-anticonvulsant anxiolytics is generally not indicated. Nonpharmacological strategies, including close observation and measures to reduce the risk of falls or other injury, are crucial for patients whose seizure disorders remain active.

Periictal Neuropsychiatric Phenomena

The majority of periictal neuropsychiatric disturbances are postictal; they usually occur several hours after a seizure. Preictal symptoms can occur and include psychosis, mood changes, or aggression in the hours or minutes before a seizure.[13] These symptoms tend to increase until the onset of ictus[14] and, depending on the time course and nature of the symptoms, may be conceptualized as prodromes separate from the ictus or as ictal events (i.e., as a partial seizure).

Postictal symptoms are relatively common. Approximately 8% to 10% of patients with seizures have postictal psychiatric disturbances.[15] These psychiatric symptoms may occur in the context of a postictal delirium

TABLE 19–1 Differences Between Ictal and Nonictal Neuropsychiatric Symptoms

APPEARANCE OF SYMPTOMS	LENGTH OF SYMPTOMS	ASSOCIATED SYMPTOMS	PSYCHOTIC SYMPTOMS	CONSCIOUSNESS DURING EVENT	RECALL FOR EVENT	EEG DURING EPISODES	EEG BETWEEN EPISODES	POSTEVENT PROLACTIN LEVEL
Ictal Symptoms								
Sudden onset and offset	Usually < 3 minutes	Stereotyped ictal symptoms: rhythmic blinking, abnormal movements, unusual sensations, automatisms	Usually olfactory, gustatory, or tactile hallucinations	May be altered	Frequently none or limited	Almost always abnormal	Frequently normal	Often elevated
Nonictal Symptoms								
More often gradual in nature	Usually 20-30 minutes (panic attack); usually days-weeks (depression, psychosis)	Absence of blinking, jerking, automatisms	Usually auditory hallucinations; paranoia; common	Generally intact	Usually intact	Usually normal	Normal	Normal

or in the setting of clear consciousness. In general, postictal symptoms remit spontaneously and are often short-lived; in one study, symptoms lasted approximately 72 hours.[16] However, such symptoms may persist for days or even weeks, and patients with well-defined, prolonged postictal neuropsychiatric syndromes may be more likely to develop persistent interictal symptoms.

Psychosis is the most common postictal neuropsychiatric symptom, occurring in up to 7.8% of epilepsy patients[17]; such psychosis generally appears after a nonpsychotic postictal period of hours to days. It most commonly occurs in patients with CPSs that become secondarily generalized,[9] especially in those with temporal lobe or bilateral foci. Psychotic symptoms vary widely, and affective symptoms (depressive or manic) may also be present. Symptoms can include paranoid or grandiose delusions and hallucinations in a variety of sensory modalities; Schneiderian first-rank symptoms of schizophrenia are rare.[16] Symptoms tend to resolve spontaneously but recur an average of two to three times per year.[18] In a minority of patients, such symptoms become chronic.

Postictal depression is also associated with CPS but is less common than postictal psychosis.[19] Patients with postictal depression may have flattened affect and anhedonia more often than sadness, and postictal depression is commonly associated with delirium and other postictal cognitive disturbances.[20] Kanner and colleagues[19] found that symptoms last an average of 24 hours, although symptoms may be more prolonged.[11] In most cases, postictal depressive symptoms do not just represent a reactive response to the stress of having a seizure.

Other postictal symptoms are less common. Acute postictal anxiety is relatively infrequent and is usually associated with postictal depression.[19] Postictal mania and hypomania occur infrequently. Postictal aggression can also occur; it is generally associated with delirium, psychotic symptoms, or abnormal mood states.

The management of patients with postictal neuropsychiatric symptoms has a number of tenets. First, enhanced treatment of the seizure disorder is crucial; patients whose seizure disorders are poorly controlled appear to have a greater tendency toward postictal affective and psychotic symptoms. In addition to anticonvulsants for seizure prophylaxis, other psychotropic medications may be indicated, especially if symptoms are prolonged, present a risk to the patient or to others, or adversely affect the patient's ability to receive appropriate treatment. Such situations occur most commonly with psychosis; low doses of antipsychotics can reduce agitation and diminish psychotic symptoms. If such symptoms are limited to the postictal period, these medications can be discontinued once symptoms resolve, because the best prophylaxis against recurrence of psychosis is treatment with anticonvulsants to prevent seizures. Antidepressants are uncommonly indicated for depressive symptoms limited to the postictal period.

In addition to medications, behavioral treatments can be instituted to facilitate coping and to maintain the patient's safety. Such interventions may include the use of restraints or sitters, frequent reorientation, or the presence of familiar family members. Finally, it is important to know the patient's postictal pattern of symptoms to prepare caregivers and family members for what lies ahead. Seizures and their neuropsychiatric sequelae are commonly stereotyped; that is, patients tend to have the same postictal symptomatology from seizure to seizure. If a patient is known to become psychotic or dangerous after a seizure, the treatment team can be prepared with antipsychotic treatments or other safety-enhancing measures.

Interictal (Chronic) Neuropsychiatric Phenomena

Psychiatric syndromes are also common in the period between seizures; patients with seizure disorders have chronic psychiatric disorders at substantially higher rates than do those in the general population. Depression, anxiety, and psychosis are all common, with depressive disorders being the most prevalent. In contrast, interictal hypomanic or manic symptoms are uncommon.

Interictal depression is common and can be disabling. Rates of depression and suicide among patients with epilepsy are four to five times greater than those in the general population,[1,21,22] and up to 80% of patients with epilepsy report having some feelings of depression.[23,24] A constellation of biological and psychosocial factors likely coalesce to result in these elevated rates of depression, but risk factors for depression that are specific to seizure disorders include poor seizure control and CPS,[25,26] especially with left-sided temporal lobe seizure foci. In fact, suicide may be 25 times more likely among patients with TLE than among those in the general population.[27]

Furthermore, this relationship between depression and seizures may be bidirectional. History of depression has been associated with the onset of seizures, given that a history of depression increases (by threefold) the risk of developing a seizure disorder.[20,28] Some have hypothesized that depression and epilepsy share neurotransmitter abnormalities (e.g., reduced noradrenergic, dopaminergic, and serotonergic activity), and that these shared abnormalities may explain the link between the two conditions.

The symptoms of interictal depression are often distinctive. Atypical features are common,[23] and many patients have depressive symptoms that are more consistent with dysthymia than with major depression. Furthermore, these dysthymic symptoms are often interrupted by symptom-free periods that can last for hours or days.[29] Blumer and associates[30] have described a clinical syndrome called *interictal dysphoric disorder*, which is characterized by interictal dysthymic symptoms with intermittent irritability, impulsivity, anxiety, and somatic symptoms.

Interictal anxiety disorders vary in frequency. Anxiety symptoms are more common in patients with epilepsy than those in the general population, and, of the anxiety disorders, panic disorder appears to be the most common. Interictal panic disorder is present in approximately 20% of patients with epilepsy,[7] with symptoms that differentiate the panic attacks from the feelings of panic that occur during a seizure. Other anxiety disorders, such as generalized anxiety disorder (GAD) or obsessive–compulsive disorder (OCD), are less common.[1]

Interictal psychosis can be intermittent (with brief, recurrent episodes), but more commonly it is continuous and chronic. Psychotic symptoms are approximately 10 times more likely to occur in patients with epilepsy.[31]

Psychosis is more common in patients with CPS (especially those with TLE) and in those with multiple seizure types, a poor response to treatment, or a history of status epilepticus.[32] Clinically, interictal psychotic symptoms most often consist of paranoid delusions with associated visual or auditory hallucinations. Affective blunting, a lack of motivation, and catatonia are also common.[32] Compared with patients with primary schizophrenia, patients with interictal psychosis have a greater preservation of affect and more visual hallucinations.

Finally, some evidence supports an interictal personality change among patients with TLE. The TLE personality syndrome, described primarily by Gastaut and co-workers[31] and by Geshwind,[33] has features that include moral rigidity, hyperreligiosity, hypergraphia, hyposexuality, and hyperviscosity ("a sticky personality"). However, this concept remains controversial, with other authors[34] refuting the existence of such a syndrome.

The management of interictal psychiatric phenomena is similar to the treatment of primary psychiatric disorders. However, there are a number of special considerations in this population. Given that most interictal psychiatric symptoms are more common when seizures are poorly controlled, effective treatment with anticonvulsants is of vital importance. Treatment of psychiatric symptoms associated with epilepsy should also include behavioral and educational interventions that reduce the risk related to their seizure disorder (e.g., having family ensure that depressed patients take their anticonvulsants or keeping manic or psychotic patients from driving when this is unsafe).

Treatment of psychiatric symptoms with psychotropics is frequently indicated, but the effects of these agents on the seizure threshold should be considered. Treatment of epileptic patients with antidepressants has been controversial, given the propensity of some antidepressants to increase the risk of seizure. However, the risk of seizure with most antidepressant agents is quite small when these agents are used at standard doses.[35] Citalopram,[36] sertraline,[35,36] venlafaxine,[20] and tricyclic antidepressants (TCAs)[30] have all been used successfully in patients with epilepsy without significantly exacerbating the underlying seizure disorder.

Given their relative safety with regard to seizure exacerbation and their overall safety and tolerability, selective serotonin reuptake inhibitors (SSRIs) should be considered as first-line treatment for patients with interictal depression. In general, starting with a low dose and increasing the dose gradually should minimize the risk of seizure in these patients. In general, bupropion and maprotiline should be avoided because these agents are more strongly associated with the development of seizures. Among the TCAs, clomipramine may be associated with a greater risk of seizure and should probably be avoided as well.[37] Monoamine oxidase inhibitors (MAOIs) have not been associated with an elevated risk of seizure, although they have not been studied in patients with seizure disorders. Finally, electroconvulsive therapy (ECT) can be used to treat patients with epilepsy and severe depression[38]; ECT appears to increase the seizure threshold,[39] and it has been used safely in patients with epilepsy.[40]

Patients with anxiety disorders can be treated with antidepressants or with benzodiazepines; buspirone, sometimes used for the treatment of GAD, can lower the seizure threshold and generally is not recommended for this population.[41] Interictal psychosis can be treated with antipsychotics. It appears that all antipsychotics may modestly lower the seizure threshold; however, low-potency antipsychotics, such as chlorpromazine, may have greater effects on the seizure threshold than higher-potency agents.[42,43] Furthermore, clozapine has been associated with an elevated seizure risk and, in general, should be avoided. Therefore atypical antipsychotics, such as risperidone, or high-potency typical antipsychotics, should be used when needed. Again, titrating the dosage slowly and using the lowest effective dose should minimize the risk of seizure in this population.

In sum, virtually any psychiatric symptom can occur with any type of seizure at any time before, during, or after the seizure. However, anxiety is most common during a seizure, psychosis is most common postictally, and depression is the most common chronic symptom between seizures. Virtually all symptoms are more common in patients with CPS than with other types of seizure disorders. Treatment of ictal phenomena involves treatment of the seizure, whereas postictal and interictal phenomena may require the use of antipsychotics, anxiolytics, or antidepressants for optimal symptomatic relief. Careful attention to the patient's safety is always an important consideration (whether from seizure or suicidality), and a knowledge of the patient's pattern of symptoms associated with their seizures helps caregivers and family members prepare for sequelae.

NONEPILEPTIC SEIZURES

Patients who appear to be having epileptic seizures may, in fact, be having abnormal movements as the result of another medical or neurologic problem or, most often, as a consequence of psychological factors (e.g., a conversion reaction). These events, called *nonepileptic seizures (NESs)* and also referred to as *psychogenic seizures* or *pseudoseizures*, pose a common and important problem. Patients with NESs have convulsive events more frequently and are more significantly disabled by these events than are those with true seizure disorders.[44] Even after a diagnosis of NESs has been made, affected patients continue to be disabled by recurrent convulsive events.[45]

The general hospital psychiatrist is frequently called on to assess patients suspected of having NESs. Knowledge of the epidemiology, differential diagnosis, clinical features, and relevant diagnostic studies that may suggest the presence of NESs can significantly facilitate making the diagnosis. Once the diagnosis of NESs is suspected, it is just as important for the psychiatrist to be able to discuss the diagnosis of NESs with the patient in a way that is validating, reassuring, and supportive.

NESs are common; they are seen in approximately 10% of outpatients with intractable seizure disorders and in approximately 20% of patients with intractable seizures referred to epilepsy monitoring units.[46,47] About three quarters of those with NESs are women, and they most often exhibit symptoms when they are between the ages of 15 and 35.[45] A history of sexual abuse is common among patients with NESs, occurring in at least 25% of those with the condition.[48–51] Further complicating the picture is the fact that patients with NESs often have true seizure disorders as well, with roughly 25% of patients with NESs also having true seizures.[52]

TABLE 19–2 Differential Diagnosis of Nonepileptic Events

General Medical Conditions
Transient ischemic attack (TIA)
Complicated migraine
Syncope
Hypoglycemia
Parasomnia (e.g., rapid eye movement [REM] behavior disorder or night terrors)
Narcolepsy
Myoclonus (from metabolic disturbance)
Psychiatric Causes
Conversion disorder
Somatization disorder
Dissociative disorder
Panic disorder (simulating partial seizures)
Volitional Deception
Factitious disorder (goal is to maintain the sick role)
Malingering (goal is to obtain secondary gain, e.g., disability income)

NESs are associated with general medical conditions, deceptive acts, and unconscious productions of symptoms that appear to be epileptic seizures. Table 19–2 displays a number of conditions that can be mistaken for epilepsy. Of these conditions, unconscious, psychologically mediated convulsive activity (essentially conversion seizures) are the most common,[46] and we will focus on this etiology of NESs. Other causes of functional somatic symptoms, such as factitious disorder and malingering, are more extensively covered in Chapter 16.

Clinical Considerations

In this section, we discuss methods for making a clinical diagnosis of NESs. For the purposes of this discussion, we will assume that medical and neurologic causes of NESs have been ruled out and that the etiology of the NESs is psychogenic (i.e., conversion disorder).

Although all features suggestive of NESs (discussed later) can also occur in true seizure disorders, certain clinical features of the periictal and convulsive phases are more suggestive of NESs. That said, a single clinical feature taken in isolation should not be used to confirm a diagnosis of NESs. Most NESs simulate generalized tonic–clonic (GTC) seizures. The more features that deviate from the usual characteristics of a GTC seizure, the more likely it is that the event is a NESs. Therefore it is useful to know the usual characteristics of GTC seizures. Careful observation throughout the seizure can be very useful in the diagnostic assessment.

GTC seizures usually are sudden in onset; although there may be an aura before the seizure, there is usually a sudden loss of consciousness, followed by a brief tonic period of less than 30 seconds. A more prolonged period of convulsive, clonic activity follows. This activity is characterized by bilateral, symmetrical, and rhythmic jerking of the upper and lower extremities; trunk activity and pelvic thrusting are uncommon. Loss of continence, tongue-biting, and other injuries may occur. The patient remains unconscious and unresponsive throughout the event and is amnestic for the episode. After the event the patient may be confused or drowsy or complain of headache; the patient is rarely completely lucid in the immediate postictal period. Most GTC seizures are quite brief, lasting less than 3 minutes, and they have a stereotyped pattern in a given individual.

Table 19–3 lists the clinical features that suggest NESs. The gradual onset of a seizure, responsiveness during the seizure, pelvic thrusting, asymmetrical clonic activity, and lucidity immediately after the event indicate that the event may not be epileptic. It should be emphasized again that certain types of seizure are marked by symptoms that appear to suggest NESs. For example, simple partial seizures may involve asymmetrical jerking with preserved consciousness. CPS can manifest with only behavioral or psychiatric symptoms. Frontal lobe seizures may cause pelvic thrusting. Automatisms during partial seizures may result in acts that appear volitional. However, combinations of atypical features suggest that NESs are the more likely diagnosis.

A number of diagnostic procedures can be performed to aid in the diagnosis of NESs. The two most useful of these are video-EEG monitoring and so-called provocative testing. The use of video-EEG monitoring allows one to correlate EEG changes (or the lack thereof) during a convulsive event. If a patient experiences a typical event and the EEG remains normal, this suggests NESs, especially when there are other clinical features that are inconsistent with epilepsy. However, it should be noted that both complex and simple partial seizures may give rise to normal EEGs in 10% to 40% of cases.[46,53] The EEG capture of multiple events reduces the likelihood of such false-negative EEG findings.

TABLE 19–3 Features that Suggest Nonepileptic (Conversion) Seizures

Historical Features
History of sexual abuse
History of other unexplained neurologic symptoms occurring during stress
Seizures despite multiple adequate trials of anticonvulsants at therapeutic levels
Features of Event
Events occur with suggestion/provocation
Gradual onset and offset of symptoms
Responsiveness during event
Weeping, speaking, or yelling during the event
Asymmetrical clonic activity
Head bobbing or pelvic thrusting
Rapid kicking or thrashing
Prolonged duration of symptoms (> 3 minutes)
No EEG abnormalities during the event
Postevent Features
Lucid during immediate postictal period
Able to recall event
Lack of incontinence, tongue biting, or physical injury despite numerous events
Postictal prolactin is normal
Neuropsychological testing suggestive of conversion symptoms

In addition to using video-EEG monitoring, use of suggestion or provocative stimuli can induce a seizurelike event during EEG monitoring. Provocative stimuli include injection of normal saline or placement of a tuning fork on the head after a suggestion has been given that the procedure will likely cause a seizure. It is crucial that EEG monitoring be done during these procedures because true epileptic seizures can also be more frequent during periods of stress and patients may have both epileptic and nonepileptic events. Much discussion has ensued about the ethics of deception under these circumstances; researchers have found that such provocative testing can be approached honestly with the patient with high rates of suggestibility and little adverse effect on the patient–physician alliance.[54,55]

In addition, a number of other ancillary studies can be used when considering a diagnosis of NESs; prolactin levels have been measured, given that prolactin levels typically rise during seizures, possibly due to disruption of hypothalamic inhibition of prolactin release during a seizure. This rise is maximal within the first 30 minutes after a seizure. However, in more than 10% of patients with GTC seizures, 30% of patients with temporal lobe seizures, and 60% of patients with frontal lobe seizures, prolactin is not elevated.[56] Cragar and colleagues,[56] in their review of the literature, found that a rise in prolactin is suggestive of epilepsy but that a failure of prolactin to rise is less predictive of NESs. Other diagnostic laboratory values, such as creatine phosphokinase (CPK), may be even less sensitive and specific, especially when taken in isolation.

Neuropsychological testing can be a useful adjunct to a clinical and laboratory evaluation. Such testing can provide information about co-morbid psychiatric diagnoses, personality styles, and tendency toward conversion reactions. Some studies demonstrate that patients with NESs, when compared with patients with epilepsy, exhibit less objective evidence of cognitive impairment and are more likely to show impairments that are a function of poor effort rather than real deficits.[57,58] Also, some studies of patients with NESs using the Minnesota Multiphasic Personality Inventory (MMPI) report an association with the "conversion V" profile with elevations in scales 1 (Hs, hypochondriasis), 3 (Hy, hysteria), and 2 (D, depression).[56] However, such testing cannot definitively make or exclude a diagnosis of NESs, and there is significant overlap of results, particularly on cognitive testing, between patients with NESs and those with epilepsy.[59]

In short, making a definitive diagnosis of NESs can be difficult. There are characteristic features of epidemiology, clinical events, laboratory values, and EEG monitoring that may suggest NESs, but for each individual thought to have NESs, there are others in whom true epilepsy can result in a diagnosis of NESs. However, a thorough evaluation using each of these domains—with EEG-video monitoring being perhaps the best diagnostic test—can help the psychiatrist determine whether NESs are more or less likely.

It is important to allow for the possibility that one's diagnosis of NESs may be incorrect. Patients with NESs typically have symptoms that are quite convincing for epileptic seizures; conversely, patients diagnosed with conversion symptoms are found to have an organic syndrome related to the supposed conversion symptom roughly 20% of the time.[60] This should not prevent clinicians from moving forward on the basis of their clinical findings but should simply serve as a reminder to maintain an open mind about the diagnosis.

General medical providers often feel that once the diagnosis of NESs has been made, treatment is over. However, fortunately *and* unfortunately, treatment is truly just beginning. After the diagnosis is made, patients with NESs continue to have frequent and disabling NESs events; only about 30% will stop having convulsive events.[45,61] However, early diagnosis is associated with better outcome,[61] and presentation of the diagnosis and a treatment plan in a way that is acceptable to the patient is critical.

Table 19–4 lists the important features of NESs diagnosis and the treatment plan for patients with the disorder. In general, the tenets of revealing the diagnosis are similar to those outlined for conversion disorder in Chapter 16. First of all, the diagnosis should be framed in a positive way: It is tremendously reassuring that these events are not due to abnormal electrical discharges in the brain, and there is no need to take anticonvulsant medications and deal with their side effects.

If a patient feels as if he or she is being told that there is nothing wrong, it can be useful to emphasize that although there is not a *structural* or *electrical* abnormality present, it is clear that there is an abnormality of *function* of their nervous system that will require integrated treatment. Furthermore, the physician should make it clear that he or she understands that these events are having a significant impact on the patient's life and obviously require ongoing efforts to reduce their negative impact.

Next, the physician should describe the impact of mood, anxiety, and stress on these symptoms and inform the patient that reduction of these symptoms is absolutely imperative to help the patient improve his or her function and quality of life. However, rather than simply making a referral to a psychiatrist, the physician should also emphasize that the patient will continue to see his or her neurologist or primary care physician on a regular basis as a crucial part of the treatment. The regularity of this follow-up is important: The patient should have an appointment with the caregiver regardless of whether he or she is having active symptoms, thus disconnecting the link between symptoms and medical attention.

Finally, suggesting to the patient that his or her symptoms are likely to improve gradually over time can be helpful. As with pain management, the goal of treatment should be to optimize function and quality of life rather than focusing on the total absence of symptoms.

CEREBROVASCULAR DISEASE

Given that cerebrovascular accidents (CVAs) result in brain areas with reduced or absent function, it is not surprising that abnormalities of affect, behavior, and cognition are common after a CVA. This section discusses the prevalence, diagnosis, and management of patients with psychiatric symptoms after a CVA.

Each year 795,000 people suffer new or recurrent stroke[62]; more than half of them suffer from significant poststroke neuropsychiatric sequelae.[63] Such neuropsychiatric sequelae of strokes have been recognized for decades. More than 50 years ago, both Kraeplin[64] and Bleuler[65]

TABLE 19–4 Guidelines for Presenting a Diagnosis of Nonepileptic Seizures and Developing a Treatment Plan

Presentation of the Diagnosis

1. Frame the diagnosis in a positive way: Symptoms are not due to abnormal electrical activity, and risks of anticonvulsants need not be undertaken.
2. Explain that symptoms are likely due to a problem with the *function* of the nervous system, rather than electrical or structural abnormalities.
3. Explain that these symptoms are common and are likely to improve gradually over time. Give specific suggestions regarding how they will improve (e.g., episodes will become less prolonged, then become less frequent, then have fewer symptoms during each episode, and so forth).
4. Acknowledge the disability that such symptoms have caused and the importance of developing a treatment plan that will improve the function of the nervous system and reduce disability.
5. Introduce the idea that anxiety, stress, and mood significantly affect the frequency and severity of these events and that reduction of these symptoms is crucial in the patient's treatment.
6. Describe a treatment plan that includes integrated, consistent treatment from providers in psychiatry, neurology, and primary care.

Treatment Plan

1. The treatment plan should include as much psychiatric care as the patient will allow. Weekly psychotherapy to assess unconscious motivation, to allow psychoeducation, and to provide support is ideal.
2. Psychotropic medications should be used to treat co-morbid psychiatric symptoms (e.g., associated with major depression).
3. Regular follow-up from other caregivers is a key component of the treatment plan. Appointments should be scheduled at regular intervals, whether or not the patient is symptomatic, and patients should receive positive reinforcement (and not a decrease in frequency of follow-up) when symptoms subside.
4. Physical examinations should be done regularly, but diagnostic studies should be avoided unless clearly indicated.
5. Despite the diagnosis of nonepileptic seizures, all caregivers should remain vigilant for the possibility that an organic diagnosis has been missed or that nonepileptic seizures and epilepsy are both present.

noted an association between cerebrovascular disease and depressive illness. Ironside,[66] in 1956, was the first to describe pathologic crying and laughing associated with cerebral infarction, now a well-described poststroke syndrome termed *pseudobulbar affect*. Despite the high incidence of these disorders and their frequent description in the literature, acute emotional and behavioral sequelae of stroke go largely unrecognized and untreated.[67]

Neuropsychiatric syndromes caused by stroke can be conceptualized on the basis of lesion location. Whereas our understanding of brain circuitry has become much more sophisticated than prior models postulating that certain cortical lobes performed specific cognitive functions, it remains true that lesions in specific cortical areas are more likely to cause characteristic cognitive and neuropsychiatric deficits. For example, strokes in the left frontal lobe are more likely to result in a nonfluent aphasia, and strokes affecting the right parietal lobe most frequently cause anosognosia, an unawareness of illness or of neurologic deficits. Table 19–5 provides a list of some correlations between neuropsychiatric deficits and lesion locations.

Neuropsychiatric syndromes caused by strokes can also be discussed with regard to symptomatology. The following section discusses poststroke depression, mania, psychosis, anxiety, and other common neuropsychiatric sequelae of stroke.

Poststroke Depression

Poststroke depression (PSD) is the prototypical acute psychiatric manifestation of stroke. It is common; approximately 20% of patients meet criteria for major depression in the poststroke period, and another 20% meet criteria for minor depression.[68–70] Stroke-associated depression may reduce survival and increase the risk of recurrent vascular events.[71,72] Risk factors for PSD include a history of depression, prestroke functional impairment, living alone, poststroke social isolation, and possibly female gender.[73]

Both biological and psychological theories of etiology have been studied. Biological hypotheses include lesion location (e.g., of the left frontal region and left basal ganglia),[69,74,75] neurotransmitter mechanisms (decreased serotonin and norepinephrine), inflammatory cytokine-mediated (increased interleukin [IL] 1-β, IL-18, and tumor necrosis factor [TNF] -α), and gene polymorphism mechanisms (e.g., short variant of serotonin transporter gene–linked promotor region).[76] Psychological factors, largely related to the various functional and personal losses associated with stroke, also contribute to the development of PSD. The correlation between location of stroke and the likelihood of developing PSD has been controversial; some studies have demonstrated positive correlations, and a large meta-analysis of 143 studies by Carson and co-workers[77] found no correlation between lesion location and the risk of PSD.

PSD is associated with significant long-term negative effects on social function, motor abilities, and quality of life.[78–80] Moreover, the negative effect of depression on functional impairment continues well beyond the period of abnormal mood symptoms.[81] Such extended functional disability may be due to poor initial rehabilitation efforts by patients with PSD that limit the recovery of strength and mobility.

Diagnosis of PSD is straightforward in many cases, although certain situations can make diagnosis quite challenging. A number of nondepressive neurologic stroke sequelae may resemble symptoms of depression. Patients with expressive aprosodias have monotonous speech that may make them appear sad or withdrawn, and their affect

TABLE 19–5 Correlations Between Cortical Lesion Location and Neuropsychiatric Symptoms

CORTICAL AREA	POTENTIAL NEUROPSYCHIATRIC SYMPTOMS
Frontal Lobes	
Orbitofrontal region	Disinhibition, personality change, and irritability
Dorsolateral region	Executive dysfunction: poor planning, organizing, and sequencing
Medial region	Apathy and abulia
Left frontal lobe	Nonfluent (Broca's) aphasia, poststroke depression (possibly)
Right frontal lobe	Motor dysprosody
Temporal Lobes	
Either side	Hallucinations (olfactory, gustatory, tactile, visual, or auditory), episodic fear, or mood changes
Left temporal lobe	Short-term memory impairment (to verbal or written stimuli), fluent (Wernicke's) aphasia (left temporoparietal region)
Right temporal lobe	Short-term memory impairment (nonverbal stimuli; e.g., music), sensory dysprosody (right temporoparietal region)
Left parietal lobe	Gerstmann's syndrome (finger agnosia, right/left disorientation, acalculia, and agraphia)
Right parietal lobe	Anosognosia, constructional apraxia, prosopagnosia, and hemineglect
Occipital lobes	Anton's syndrome (cortical blindness with unawareness of visual disturbance)

may appear blunted. The presence of anosognosia (neurologically mediated unawareness of illness usually associated with right parietal lesions) may look like denial associated with depression, and this symptom can itself lead to frustration and anger when others insist that the patient has a problem that he or she simply cannot recognize. Finally, aphasias can make the diagnosis of depression—or any diagnosis—more difficult because of the difficulty of communicating with such patients. By being aware of these potential neurologic sequelae and by carefully using criteria from *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[82] with particular attention paid to depressive symptoms that overlap less with concurrent medical and neurologic symptoms (e.g., feelings of guilt, worthlessness, hopelessness, and suicidality), in most cases the psychiatrist can verify the presence or absence of PSD.

Despite the significant consequences of PSD (both because of underdiagnosis[67] and the fear of intolerable side effects from antidepressant medications), it is often undertreated. However, early and effective treatment of depression is perhaps even more crucial in this patient population than it is in other populations, given the need for full mobilization for occupational and physical therapy and other functional retraining early in the course of recovery.

A number of placebo-controlled trials have demonstrated that antidepressants are effective in the treatment of PSD. SSRIs[83–86] and nortriptyline[87] have been shown to relieve symptoms of PSD; another study of nortriptyline found that treatment of depression resulted in improved cognitive outcome.[88] A study by Robinson and associates[89] found that nortriptyline was more effective than either fluoxetine or placebo in treating PSD and improving functional outcomes.

Studies of PSD have found disruptions of both noradrenergic and serotonergic pathways[85]; the effectiveness of venlafaxine was demonstrated in a case series by Kucukalic and colleagues,[90] and only 2 of 30 patients studied had mild elevations in blood pressure, which would be a side effect of concern with venlafaxine in poststroke patients. Psychostimulants have also been used in the treatment of PSD. Retrospective studies using psychostimulants (methylphenidate and dextroamphetamine) to treat PSD found these medications to be effective, with response rates of 47% to 80%.[91,92] Response to psychostimulants was rapid (usually within 48 hours), and adverse events were rare. However, unlike SSRIs and TCAs, psychostimulants have not been studied under placebo-controlled, double-blind conditions for the treatment of PSD.

ECT also appears to be an effective treatment for PSD, with high rates of response and low rates of medical complications.[93] ECT is more extensively discussed in Chapter 33. In addition to the somatic treatments of PSD, group and family psychotherapy have also been reported to safely and effectively treat PSD.[94,95] There are few randomized and controlled trials of individual psychotherapies for PSD. One study found that problem-solving therapy reduced the incidence of depression and also delayed the time to onset, compared to placebo, for poststroke patients.[96] Another study found no significant difference between cognitive-behavioral therapy, attention placebo, and standard care.[97] More studies are needed in this area.

Administration of psychiatric medications to at-risk populations to prevent the onset of psychiatric illness is an increasingly popular area of study. Several recent studies have evaluated whether antidepressant medication can prevent PSD.[96,98–100] Although initial studies demonstrated differences in rates of depression in poststroke patients who received medication compared to placebo, they were not statistically significant and were underpowered.[98,99] A more recent and methodologically sound study by Robinson and associates[96] evaluated 176 nondepressed patients within 3 months of stroke and randomized them to three groups, a double-blinded escitalopram and placebo group and a nonblinded problem-solving therapy group. Rates of major and minor depression were statistically significantly lower for both escitalopram and problem-solving therapy, though escitalopram remained significant only with an intention-to-treat analysis. The potential clinical impact of these studies is impressive, but more studies are needed to definitely direct clinical care.

For most patients with mild to moderate PSD, SSRIs are the treatment of choice, given their proven efficacy, favorable side effect profile, and cardiovascular safety. However, TCAs, despite higher rates of side effects than SSRIs, might also be considered first-line agents for PSD because of their potentially superior efficacy. For more severe depression

that impairs decision-making capacity, nutritional intake, or ability to participate in rehabilitation, psychostimulants should be strongly considered; methylphenidate or dextroamphetamine can be started at 2.5 to 5 mg in the morning, and a protocol for dosing and patient monitoring can be followed (Table 19–6). ECT can also be considered in patients with incapacitating depression. Prophylactic treatment with antidepressants to prevent depression is supported by preliminary studies and may be prudent in patients with numerous risk factors; careful analysis of risks and benefits for the individual patient is still required.

Other Poststroke Psychiatric Phenomena

Other psychiatric syndromes than occur in the poststroke period include anxiety, mania, and psychosis. Poststroke anxiety is common, and usually arises in concert with PSD. Approximately one fourth of patients meet criteria for GAD (except for duration criteria) in the acute poststroke period; at least three fourths of these patients with poststroke GAD symptoms have co-morbid depression.[101,102] Poststroke anxiety has a negative impact on the functional recovery of stroke victims and has been associated with impairment in activities of daily living (ADL) up to 3 years after the event.[102] The functional impairment of PSD and poststroke GAD appear to be additive, insofar as patients with both GAD and PSD have greater ADL impairment at follow-up than those with isolated PSD.[103]

Poststroke mania occurs in fewer than 1% of patients.[3] Symptoms of poststroke mania are similar to those of primary mania (with flight of ideas, pressured speech, a decreased need for sleep, grandiosity, and associated psychotic symptoms). Lesions in the right orbitofrontal cortex, right basotemporal cortices, dorsomedial thalamus, and head of caudate appear to be associated most often with poststroke mania.[104–109] Stroke in the right hemisphere, compared with the left, has led to increased serotonin binding, and it is hypothesized that this may result in poststroke mania.[110]

Poststroke psychosis is also uncommon, occurring at a rate of approximately 1% to 2%.[111] Such patients usually have right temporoparietal lesions and a high rate of associated seizures.[111,112] This suggests that temporal lobe damage that leads to CPS and to associated psychosis may account for symptoms in a significant percentage of these patients.

Finally, there are two other clinical neuropsychiatric syndromes that are common in the poststroke period. The first is termed *catastrophic reaction*, a collection of symptoms involving patient desperation and frustration. This syndrome is relatively common; rates of poststroke catastrophic reaction are 3% to 20%.[113,114] Catastrophic reactions are strongly associated with PSD, with roughly three quarters of patients with catastrophic reaction having PSD.[114] Catastrophic reactions are also associated with a personal and family history of psychiatric disorders.[113]

Catastrophic reactions also appear to be associated with anterior subcortical lesions and with left cortical lesions.[113–115] Given the strong association of catastrophic reactions and depression, some feel that such a reaction is a behavioral symptom of depression (provoked by anterior subcortical damage) rather than a discrete syndrome. Others feel that catastrophic reactions result from damage to left hemispheric areas involved in the regulation of emotions related to social communication.[114]

The second of these clinical syndromes is *pseudobulbar affect*, also termed *pseudobulbar palsy*. This syndrome (which consists of frequent and easily provoked spells of laughing or crying) occurs to some degree in approximately 15% of poststroke patients.[116,117] The pathophysiology is unknown but is thought to involve frontal release of brainstem emotional centers.[118] It is usually seen in a mild form, with brief fits of crying or laughing linked with appropriate changes in mood; however, in more serious cases it may involve frequent and spontaneous fits of laughing and crying inappropriate to the context. It can cause embarrassment, curtailment of social activities, and a decreased quality of life.[119]

Treatment of these poststroke phenomena generally parallels the treatment of primary psychiatric syndromes. Poststroke anxiety can be treated like any primary anxiety syndrome. SSRIs are effective in the treatment of a variety of anxiety disorders, including GAD, and, given that most patients with poststroke anxiety have co-morbid PSD, these agents are often the treatments of choice. Benzodiazepines can also be given for isolated anxiety, but they can lead to ataxia, sedation, and paradoxical disinhibition; therefore they must be used with caution in this population. Furthermore, these agents do not treat co-morbid depression.

Treatment of poststroke mania follows the same rules as does the treatment of primary mania: Mood stabilizers and adjunctive antipsychotic medications or benzodiazepines are used to control symptoms. Treatment studies of poststroke

TABLE 19–6 Guidelines for the Use of Psychostimulants to Treat Depression

1. Consider possible (relative) contraindications to psychostimulant use:
   (a) history of ventricular arrhythmia
   (b) recent myocardial infarction
   (c) congestive heart failure with reduced ejection fraction
   (d) poorly controlled hypertension
   (e) tachycardia
   (f) concurrent treatment with MAOIs
2. Initiate treatment with morning dose of 5 mg methylphenidate or dextroamphetamine (2.5 mg in frail elderly or medically tenuous patients).
3. Check vital signs and response to treatment in 2-4 hours (the period of peak effect).
4. If the initial dose is well tolerated and effective throughout the day, continue with a single daily morning dose.
5. If the initial dose is well tolerated and effective for several hours, with a loss of effect in the afternoon, give the same dose twice per day (in the morning and the early afternoon).
6. If the initial dose is well tolerated but is without significant clinical effect, increase dose by 5 mg per day until a clinical response is achieved, intolerable side effects arise, or 20 mg dose is ineffective (i.e., a failed trial).
7. Continue treatment throughout the hospitalization; stimulants can usually be discontinued at discharge.

mania have found lithium, valproic acid, carbamazepine, neuroleptics, and clonidine variably efficacious, though none of these treatments has been examined in placebo-controlled, double-blind trials for this condition.[105,110,120–122] Poststroke psychosis can be treated symptomatically with antipsychotics. However, anticonvulsants (especially valproic acid and carbamazepine) should be used when psychotic symptoms are the result of CPS, because psychotic symptoms should improve with better seizure control.

Finally, pseudobulbar affect and catastrophic reaction may respond well to antidepressants. A few trials of TCAs and SSRIs, some of which were placebo-controlled, have demonstrated efficacy in reducing symptoms of pseudobulbar affect.[123–126] Symptoms of catastrophic reaction may also improve with antidepressant treatment of co-morbid PSD.

In short, psychiatric symptoms after stroke are common and have a significant impact on the long-term outcome of poststroke patients. Awareness of neurologic symptoms that may mimic psychiatric illness (e.g., anosognosia) and careful diagnostic interviews can allow accurate diagnosis and prompt treatment. In general, psychiatric symptoms secondary to stroke are treated in the same way as are nonstroke-related psychiatric syndromes with similar symptoms.

THE MANAGEMENT OF PATIENTS WITH TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States; nearly 1.4 million head injuries occur every year.[127] Of these, approximately 235,000 result in hospital admission, and between 50,000 and 60,000 result in death.[127,128] Permanent neuropsychiatric disabilities affect an estimated 80,000 to 90,000 patients who suffer a TBI.[128] Of this group, psychosocial and psychological impairments lead to substantial disability and cause significant stress to their families.[129] The consulting psychiatrist plays an important role in the evaluation and treatment of these patients. In this section the epidemiology and pathophysiology of TBI will be addressed; this will be followed by a discussion of the clinical features and treatment of the affective, behavioral, and cognitive aspects of TBI.

Epidemiology

Disorders that result from TBI are more common than are any other neurologic disease except for headache.[129] Falls cause 28% of TBIs, and motor vehicle accidents (20%), assaults (11%), having one's head struck against an object (19%), other trauma (13%), and unknown trauma (9%) account for the remaining TBIs.[127] Among adults, alcohol is a contributing factor in 40% to 56% of cases.[127,129,130] The highest rates of hospitalization and death after TBI are found in persons older than 75 years.[127] Individuals who have had one brain injury are three times as likely, compared with the general population, to sustain a second, and after a second TBI the risk of another is 10 times higher.[128] It should be noted, however, that even more mild TBIs (i.e., without an associated hospital stay) may result in neuropsychiatric sequelae.

Pathophysiology

TBI can be divided into primary and secondary brain injuries. Primary injury consists of focal and diffuse lesions. Focal TBI generally results from a blow to the head that produces cerebral contusions or hematomas. Epidural hematomas, subdural hematomas, and cerebral contusions are all types of focal lesions. The location, size, and progression of the injury determine resultant morbidity and mortality.[130] Most injuries occur in the polar temporal lobes and on the inferior surface of the frontal lobes as a result of contact with the bony prominences along the base of the skull, often a result of a coup–contrecoup mechanism of injury.[129,131] All are diagnosed by computed tomography (CT) scanning or magnetic resonance imaging (MRI) of the brain. An epidural hematoma is usually caused by head trauma that is associated with a lateral skull fracture and with tearing of the middle meningeal artery and vein and therefore is most often located in the temporal or temporoparietal region.[130,132] There is often loss of consciousness followed by a period of lucency, and then neurologic deterioration. Prompt surgical evacuation of the hematoma is essential. Subdural hematoma is more common than epidural hematoma and generally results from tearing of a bridging vein between the cortex and a venous sinus. Much of the force of an impact is often transmitted to the brain, and the underlying brain injury actually determines the outcome in approximately 80% of cases.[130] Treatment also involves surgical evacuation. Finally, traumatic cerebral contusion is often associated with an initial bout of unconsciousness, generally followed by recovery. Edema may cause fluctuations in the level of consciousness, seizures, or focal neurologic signs.[132] Surgery is rarely undertaken for cerebral contusions.

Diffuse lesions, or *diffuse axonal injury*, is seen more commonly in injuries that involve rapid acceleration, deceleration, or rotational forces.[133] The sites most prone to such injury are the reticular formation, basal ganglia, superior cerebellar peduncles, limbic fornices, hypothalamus, and corpus callosum.[129] Patients who suffer diffuse axonal injury have high rates of morbidity and mortality. The diagnosis, often missed on CT, may be made by use of diffusion-weighted MRI, which is sensitive to the axonal swelling seen after injury. Lack of radiographic evidence of injury does not translate into an absence of damage. Deficits in arousal, attention, and cognition (i.e., processing speed) often result from diffuse axonal injury.

Whereas primary brain injury (focal and diffuse) results from mechanical injury at the time of the trauma, secondary brain injury is caused by the physiologic responses to the initial injury. This is thought to involve a cascade of events, with edema and hematomas leading to increased intracranial pressure, which leads to compression and deformation of surrounding brain tissue and further damage. Neuronal damage is also mediated by release of neurotoxic substances. Although a full discussion of each of these is beyond the scope of this chapter, each substance must be considered when evaluating the status of a brain-injured individual in the acute care setting.

Clinical Presentation

TBI is often divided into three categories according to the severity and the duration of altered mental status; however, there is no definitive breakdown of specific types of sequelae that may be affiliated with each. Whereas more severe injuries are often thought to have more persistent and pervasive consequences, there are certainly instances of significant morbidity even with mild TBI. The severity of the injury is classified by the Glasgow Coma Scale (GCS; Table 19–7). Mild head injury correlates with a GCS score of 13 to 15, moderate injury with a GCS score of 9 to 12, and severe head injury corresponds to a GCS score of less than 8. Lower scores are associated with more severe injury and poorer recovery outcomes.[128]

Other factors that may increase morbidity include the following: lower intelligence quotient (IQ), a concomitant substance abuse disorder, older age, and a history of brain injury.[129] Moreover, the DSM-IV[82] suggests the following criteria to establish the severity of injury significant enough to cause postconcussional disorder, a diagnosis under research (two of the following): (1) a period of unconsciousness lasting more than 5 minutes; (2) a period of posttraumatic amnesia that lasts longer than 12 hours after the closed head injury; or (3) new seizures (or a marked worsening of a preexisting seizure disorder) that occurs within the first 6 months after the closed head injury. Diagnostic criteria for this disorder also include cognitive disturbances and three or more of the following[80]: fatigue; disordered sleep; headache; vertigo or dizziness; irritability or aggressivity; anxiety, depression, or affective lability; changes in personality; and apathy or lack of spontaneity.

These features are representative of the three major categories of neuropsychiatric sequelae that may be seen with TBI: cognitive impairment, changes in personality and behavior, and Axis I psychiatric disorders (e.g., mood, anxiety, and psychotic disorders). Each of these is outlined briefly.

Cognitive Impairment

Cognitive difficulties in acute care settings following TBI may be due to the brain injury itself, delirium, or other factors.[134] As recovery progresses, deficits related to the TBI (e.g., attentional impairment, associated with the reticular activitating system and prefrontal white matter) become more apparent.[135] Impairments in language and executive function (those skills necessary for independence in the world) as well as memory often follow TBI.[135] Examples of executive dysfunction include poor planning, impaired abstraction, and difficulties with calculations.[129,131] Neurocognitive testing is essential to further specify and quantify deficits. Moreover, neuropsychological testing is invaluable in designing an individualized rehabilitation program to meet the specific needs of each patient.

TABLE 19–7 Glasgow Coma Scale

Eye Opening	
Spontaneous	4
To voice	3
To painful stimulus	2
None	1
Verbal Response	
Oriented	5
Confused	4
Inappropriate words	3
Unintelligible sounds	2
None	1
Motor Response	
Follows commands	6
Localizes pain	5
Withdraws from pain	4
Flexor response	3
Extensor response	2
None	1

Personality Changes

Personality change due to TBI is a DSM-IV[82] diagnosis characterized by a persistent personality disturbance that represents a change from the individual's prior personality; it is a direct consequence of the injury and is not better explained by delirium, dementia, or another Axis I disorder. The disturbance must also cause clinically significant distress or impairment in occupational or social function.[82] The terms *frontal lobe syndrome* and *organic personality syndrome* are often used to describe these personality changes.[136] Personality changes and behavioral manifestations often include labile affect, disinhibition, poor social judgment, apathy, lewdness, loss of social graces, perseveration, aggressive behavior, paranoia, and inattention to personal hygiene. In a 30-year follow-up study of patients with TBI, Koponen and colleagues[137] found that 23% of injured adults manifested an Axis II diagnosis. These changes may be a direct result of the TBI but also may be exacerbated or caused by delirium, seizures, or use of medications or substances. When evaluating personality changes, the physician should note that the patient may have little insight into the change, so including supportive family members in the evaluation and planning of treatment is essential. Additionally, families may need significant support to cope with changes present in their loved ones.

Mood and Anxiety Disorders

As many as 40% of patients with TBI will develop an Axis I disorder, most commonly major depression, an alcohol-use disorder, panic disorder, a specific phobia, or a psychotic disorder.[137] Depression occurs in 26% to 77% of those with mild TBI, whereas higher rates of depression are associated with more severe injuries.[138–141] These individuals have higher risk because of the neuroanatomic and physiologic changes that occur and because of lost capabilities, changes in roles, and financial and other losses that have occurred.[142] Premorbid substance abuse, poor functioning, lower education, and an unstable work history predict depression after TBI.[143,144] Because there may be significant overlap with cognitive impairment and personality changes, the diagnosis must be made with care. Major depression is associated with poor outcome across multiple domains[139]; this makes its early diagnosis and treatment particularly important. Prominent signs and symptoms include fatigue, distractibility, anger, irritability, and rumination.[138] Neuropsychological testing may be helpful in these individuals. Finally, there is an increased risk of suicide after TBI; up to 15% of individuals make a suicide attempt in the 5 years after TBI.[129] In this population, intense despair, hopelessness, worthlessness, and loss of sense of integrity,

as well as relationship breakdown and isolation, contribute to the risk for suicide.[142,145] The combination of depression and disinhibition associated with frontal lobe injury is also thought to contribute to higher rates of suicide.[129]

Mania has also been shown to occur more often after TBI than it does in the general population.[141] Predisposing factors may include a family history of affective illness, right temporal lobe lesions, and right orbitofrontal cortex injuries; unfortunately, consensus is lacking.[129,141] Furthermore, seizures seem to be more common in this group[141]; this makes the EEG an important diagnostic tool following TBI. For this reason, anticonvulsant medications are the preferred mood stabilizers after TBI (see treatment section).

Regarding anxiety disorders after TBI, GAD and posttraumatic stress disorder (PTSD) appear to be the most common.[141–147] OCD, specific phobias, and panic disorder have also been reported.[140,148] GAD is co-morbid with depression in approximately 11% of patients.[129] There is some evidence that early intervention with cognitive-behavioral therapy for acute stress disorder may prevent PTSD after mild TBI.[146] Other investigators have shown a relationship between impaired memory of the traumatic event and lower rates of PTSD[147]; however, more research is needed in this area.

Psychosis

Psychosis as a consequence of TBI is thought to be relatively rare. Although some authors doubt that a correlation exists,[141] others argue that psychosis may appear immediately after brain injury or years later (with rates between 0.7% and 9.8%).[149] Frontal and temporal lobe injuries are associated with psychosis, as are posttraumatic seizures.[150] Cognitive impairment and behavioral changes (already described) may mimic the symptoms of schizophrenia. Because individuals with schizophrenia have also been found to have a higher incidence of brain injury than those in the general population,[150] it may be true that head injury predisposes these individuals to schizophrenia. Alternatively, it may be that individuals who are already predisposed to schizophrenia have a higher incidence of brain injury for other reasons. More research is needed in this area.

Treatment

Treatment of neuropsychiatric sequelae of TBI is best accomplished with a comprehensive, multidisciplinary, rehabilitative approach. This may include psychiatric, neurologic, psychological, behavioral, occupational, and vocational evaluations.[129] Specific brain-injury centers are best equipped to undertake this; however, not all communities have such resources. Psychiatric evaluation and consultation generally focus on several areas of intervention: pharmacological, behavioral, cognitive, and social (family support). These are discussed in the following section.

Pharmacology

Generally, medications effective for primary psychiatric disorders in non-TBI patients are similarly effective in TBI patients. Because brain-injured patients are often more sensitive to certain medications and their side effects, several guidelines should be considered. The principle of "start low, and go slow" is wise; being overly cautious may lead to inadequate medication trials if therapeutic doses are not achieved or medications are not given sufficient time to work. Slow titration as tolerated by side effects and an adequate duration of trials should be the goal.

Although treatment of depression and anxiety in patients with TBI follows the same principles as those for the treatment of depression and anxiety in the general population, careful attention should be paid to medication side effects. Medications with a high potential for lowering the seizure threshold, causing sedation (typically mediated by antihistamine effects), and inducing anticholinergic side effects and hypotension (usually mediated by peripheral alpha antagonism) should be avoided or used with great care if no better alternative exists. TCAs and bupropion, which both lower seizure threshold, are generally avoided. SSRIs are usually well tolerated. Several studies (only one of which was a randomized controlled trial) with citalopram, fluoxetine, and sertraline have demonstrated improvements in mood and aggression.[151–154] Psychostimulants may be employed for depressive symptoms (irritability, apathy, and depressed mood), cognitive symptoms (arousal, processing speed, and attention), and fatigue,[155,156] although paradoxical dysphoria, agitation, and paranoia may be seen in the brain-injured patient.[129] Improvements have also been seen in depression, anxiety, irritability, and aggression with buspirone; it has a more favorable side effect profile and less abuse potential than benzodiazepines.[157–159] Propranolol (a β-blocker) has been shown to reduce the intensity of agitation and aggression following TBI.[149] ECT remains a good option and is often underutilized. Care should be taken to assess memory and cognitive dysfunction before recommending ECT, given the potential side effects of this treatment.

Mania should be treated using standard agents. However, neurotoxicity from lithium may develop at higher rates in patients with TBI[129]; anticonvulsant mood stabilizers, such as valproic acid or carbamazepine, may be preferable. For patients with co-morbid seizures, anticonvulsants are the treatment of choice.

Neuroleptics are frequently used for agitation and aggression in TBI patients, as well as psychosis. The use of neuroleptics in this population is controversial given research, largely conducted on animals, that indicates they interfere with neural plasticity and are associated with longer posttraumatic amnesia and worse outcomes.[155,160,161] That said, there is also evidence that antipsychotics may be effective for the management of agitation and aggressive behavior.[162] Because brain-injured patients are at increased risk for extrapyramidal symptoms (dystonias, akathisias, and parkinsonian side effects),[129] high-potency agents should be used with care and atypical antipsychotics are generally preferred over typical antipsychotics. Antipsychotics with significant anticholinergic side effects (e.g., clozapine and low-potency typical agents) and antipsychotics that lower the seizure threshold, such as clozapine, should be monitored carefully.

Finally, benzodiazepines and barbiturates should be used sparingly in patients with TBI on account of their potential for causing paradoxical disinhibition, sedation, and worsening of cognitive and motor impairments.[155] If rapid sedation is desired in an agitated patient, low doses may be used with caution.

Behavioral, Cognitive, and Social Interventions

Once deficits related to TBI have been delineated, a comprehensive plan of treatment can be instituted. Behavioral treatments are helpful for the management of maladaptive social behaviors (including aggression) and personality disorders. For patients with prominent mood or anxiety symptoms, who are easily agitated, or who have low thresholds to anger and aggression, environmental modification (e.g., increasing structure, simplifying tasks, reducing or increasing stimulation, and removing triggers and irritations) helps reduce symptoms.[163] Specific cognitive rehabilitation programs may be helpful, depending on individual deficits. These deficits are best assessed by administration of neuropsychiatric testing. Teaching about stress management and coping skills may also be particularly useful. Finally, psychotherapeutic and social interventions, including family education and supportive therapy, may prove useful given the sense of loss and distress often felt by family members and by loved ones.

CONCLUSION

Traumatic brain injury is an important cause of neuropsychiatric disability in the United States. A thorough assessment of mood, anxiety, personality change, and cognition should be a routine part of postinjury screening. The consulting psychiatrist plays an important role in the evaluation and treatment of these patients. Prompt diagnosis and treatment, as well as appropriate referral using a multidisciplinary approach, greatly benefit patients and their families.

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20

Patients with Neurologic Conditions II. Movement Disorders, Multiple Sclerosis, and Other Neurologic Conditions

Shamim H. Nejad, M.D.
Joshua L. Roffman, M.D.
Karsten Kueppenbender, M.D.
Felicia A. Smith, M.D.
Jeff C. Huffman, M.D.
Theodore A. Stern, M.D.

Chapter 19 discussed the epidemiology, diagnosis, and management of neuropsychiatric symptoms associated with seizures, strokes, and traumatic brain injuries (TBI). In this chapter, we extend such discussion to other neurologic conditions. We discuss neuropsychiatric symptoms associated with movement disorders, multiple sclerosis, connective tissue diseases, brain neoplasms, and central nervous system (CNS) infections; as in the last chapter, the focus will be on phenomenology, diagnosis, and the practical management of patients with such symptoms.

MOVEMENT DISORDERS

Movement disorders are characterized by abnormalities in the extrapyramidal motor system that result in progressively impaired regulation of voluntary motor activity in the setting of normal strength. Depending on the particular illness, as well as on the stage of the disease, a patient can exhibit hyperkinetic, involuntary movement or hypokinetic, impoverished motor activity. These clinical features reflect dysfunction or degeneration of subcortical gray matter structures, known as the *basal ganglia*. Three movement disorders discussed in the following sections—Parkinson's disease, Huntington's disease, and Wilson's disease—are associated with particularly high psychiatric co-morbidity, ranging from mood and thought disorders to dementia. These disorders pose a particular diagnostic challenge for psychiatrists, for in each case, behavioral symptoms can reflect the primary pathophysiology of the disease, psychologic reactions to debilitating illness, or both. Treatment can be equally challenging, for although medications used to treat the underlying neurologic process can also induce psychiatric symptoms, certain treatments directed at psychiatric symptoms can worsen the movement disorder.

Parkinson's Disease

Parkinson's disease (PD), a neurodegenerative disorder characterized by the clinical triad of resting tremor, rigidity, and bradykinesia/akinesia, affects up to 2.5% of the geriatric population, although its onset in young adults has also been reported.[1] The pathophysiology of PD likely reflects both genetic and environmental influences; it involves loss of dopamine neurons in the midbrain substantia nigra, with subsequent downstream effects in striatal, frontal, and cingulate regions and disruption of cortical–basal ganglia–thalamic circuitry. Postmortem examination can reveal the presence of Lewy bodies as well as the degeneration of noradrenergic neurons in the locus ceruleus, cholinergic neurons in the nucleus basalis, and serotonergic neurons in the dorsal raphe nucleus.[2] Antiparkinsonian medications potentiate dopamine transmission as well as modulate the dopamine–acetylcholine balance in the basal ganglia. The mainstay of treatment is the dopamine precursor levodopa, usually given with carbidopa (which inhibits peripheral metabolism of dopamine). Other useful agents include dopamine agonists (e.g., bromocriptine, pramipexole, and ropinirole), inhibitors of dopamine metabolism (e.g., monoamine oxidase B inhibitors, such as deprenyl and selegiline, and the catecholamine transferase inhibitor tolcapone), anticholinergics (e.g., trihexyphenidyl and benztropine), and amantadine.

Psychiatric disturbances in PD are common and multifactorial. These complications, which encompass dysregulated mood, psychosis, and cognitive impairment, can be primary to the underlying neurodegenerative process or secondary to its pharmacological treatment; in some cases, they may be engendered or exacerbated by the psychologic stress of experiencing a severe, progressive illness. The following sections will discuss the more common psychiatric

sequelae of PD and review approaches to management, bearing in mind that in most cases, well-controlled clinical trials establishing safety and efficacy have yet to be conducted.

Depression in Parkinson's Disease

The reported occurrence of depression in PD ranges widely, possibly because of variations among diagnostic instruments and disease-defining criteria, but in many studies, incidence of clinically relevant depressive symptoms is approximately 35%.[3] Indeed, early PD is often mistaken for depression, given the sizable overlap in clinical phenomenology between the two disorders. Features common to both disorders are summarized in Table 20–1. According to the Global Parkinson's Disease Survey conducted by the World Health Organization, even among patients with established diagnoses of PD, depression was recognized by clinicians in only 1% of cases.[4] The same study indicated that among all measured factors, including severity of motor disability, depression accounted for the greatest impairment in quality of life (QoL).

Given the mixture of potential neurobiological, pharmacological and psychosocial substrates that could account for mood disorders in patients with known PD, careful consideration should be given to differential diagnosis. Depressive features thought to be related to the underlying neuropathology of PD have been well characterized and likely reflect altered monoamine transmission in the brain regions described earlier. In contrast to primary major depressive disorder, patients with parkinsonian depression primarily exhibit anhedonia, anxiety, and sleep disturbance, with far less prominent guilt, irritation, and psychotic features. Although suicide attempts are rare, suicidal ideation is common.[5] Alterations in mood can parallel the "on–off" phenomenon related to abrupt changes in motor activation[6]; depression associated with the "off" period can be reversed with acute administration of levodopa.[5] However, the degree of depression does not usually correlate with either severity of motor symptoms or duration of PD.[2] Caregivers should also bear in mind the possibility that depressive symptoms in PD might alternatively reflect dysthymia, an adjustment disorder, or (rarely) bipolar disorder.[7]

TABLE 20–1 Symptoms Common to Parkinson's Disease and Major Depression

Motor
Bradykinesia/psychomotor retardation
Masked facies/restricted affect
Stooped posture
Cognitive
Impaired memory
Impaired concentration
Indecisiveness
Vegetative
Decreased energy
Fatigue
Impaired sleep
Appetite changes
Somatic
Physical complaints

From Damier P: The role of dopamine, serotonin, and noradrenaline in Parkinson's disease. In Wolters ECH, Scheltens PH, Berendse HW, editors: *Mental dysfunction in Parkinson's disease II*, Utrecht, 1999, Academic Pharmaceutical Productions.

Few controlled studies have examined the safety and efficacy of antidepressant medications in patients with PD and depression. Several reports suggest some benefit from use of dopamine agonists. The D_2 and D_3 receptor agonist pramipexole, which appears to provide significant antidepressant effect when used as an adjuvant in refractory major depressive disorder (MDD) and bipolar disorder,[8–10] has also shown some promise in treating depression among patients with PD.[11–14] Selegiline, a selective type B monoamine oxidase inhibitor (MAOI) originally developed as an antidepressant, has been used to slow the progression of motor decline in PD. Limited studies have not consistently demonstrated an antidepressant effect for selegiline in PD.[15,16] The most widely used treatments for depression in PD are tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). A single double-blind study indicated a greater effect of nortriptyline (up to 150 mg per day) than placebo in improving depressive symptoms in PD patients[17]; similar results have been obtained with imipramine and desipramine in smaller studies.[18,19] Given their particular efficacy in improving sleep as well as their mild anticholinergic action, TCAs can be especially useful in the PD population; at the same time, though, elderly PD patients are at greater risk for TCA-induced adverse effects, including delirium, cardiac arrhythmias, orthostatic hypotension, and urinary retention.[5] Several SSRIs, which exhibit an improved safety profile compared to TCAs, ameliorated depression among PD patients in open-label trials and case reports.[20] To date, there have been two randomized comparison studies looking at the treatment of depression in PD with use of SSRIs and TCAs. One study conducted by Antonini and associates[21] assessed the effect of 3 months of treatment with low-dose sertraline (50 mg daily) and low-dose amitriptyline (25 mg daily). Patients taking both medications had significantly reduced Hamilton Depression Rating Scale scores, however only sertraline accounted for a significant benefit in QoL. In another study, a randomized, placebo-controlled trial was conducted evaluating the efficacy of citalopram and desipramine.[22] After 14 days, patients taking desipramine showed an improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) when compared with citalopram and placebo, and after 30 days, both medications showed significantly improved MADRS scores when compared with placebo. Mild adverse side effects were twice as frequent in the desipramine group than in the groups receiving citalopram and placebo.

There are also conflicting reports about SSRI-induced exacerbations of motor symptoms in PD.[23] Caution must also be exercised when prescribing both an MAOI and an SSRI or (especially) a TCA, given the risk of serotonin syndrome.[24] Efficacy of newer antidepressants in PD (including norepinephrine and combined serotonin and norepinephrine reuptake inhibitors) is plausible but remains to be studied.[25–27]

Although not supported by well-controlled studies, electroconvulsive therapy (ECT) appears to be effective in improving depression among PD patients.[28] One

retrospective study described a similar benefit of ECT among 25 patients with parkinsonism and 25 age- and gender-matched patients without neurologic co-morbidity.[29] Two studies have also indicated a transient improvement in motor symptoms among PD patients receiving ECT for depression.[29,30] However, the same studies also reported that PD patients demonstrate an increased vulnerability to ECT-related mental status changes, including delirium. There is increasing evidence that transcranial magnetic stimulation (TMS) may improve both the depressive and motor symptoms in PD, via effects on brain monoamine levels.[31–33]

Psychosis in PD

Psychotic features are also common, occurring in as many as 20% to 30% of cases, and are multifactorial in PD patients.[34,35] Especially prominent in patients with dementia, psychotic symptoms are often manifest initially as illusions or as "friendly" visual hallucinations (e.g., beloved relatives or animals). With time, hallucinations typically progress to include frightening or threatening images (e.g., insects or snakes) and paranoid delusions, often involving persecution or spousal infidelity.[34–36] As in depressive syndromes among patients with PD, consideration should be given to several potential etiologies. Psychotic features were recognized as part of the natural course of PD in up to 10% of patients before the advent of antiparkinsonian medications,[35] potentially related to altered subcortical dopamine transmission and to diffuse Lewy body pathology.[37] Both dopamimetic and anticholinergic medications given to alleviate motor symptoms can induce psychosis in PD. Dopaminergic agents can provoke a subacute psychotic disorder (perhaps akin to the putative role of dopamine in primary psychoses); there is no apparent relationship between dose, duration, or plasma levels of dopamine agonists and the incidence or severity of psychosis.[38,39] Anticholinergic agents can induce a toxic delirium with associated autonomic dysfunction (e.g., tachycardia, mydriasis, and priapism). Other factors predisposing PD patients to psychosis include cognitive deterioration, preexisting psychiatric diseases, infection or other medical illness, and dehydration.[35] Of note, virtually all patients with PD eventually exhibit cognitive impairment,[40] with the presence of Lewy bodies being the most consistent pathological correlate of dementia in this population.[3]

Optimal management of psychosis in PD is highly dependent on consideration of differential diagnosis, as detailed in Table 20–2. Once other causes of mental status alteration have been ruled out, the next step is to reduce or eliminate anti-PD medications in order of their most psychotogenic and least antiparkinsonian effects (i.e., anticholinergic and other agents) followed by dopamine antagonists, and finally levodopa/carbidopa. Nighttime psychosis can often be alleviated by reduction or discontinuation of bedtime medications.[34] Finally, treatment with antipsychotics can be attempted. The best-studied antipsychotic for use in PD is clozapine, an atypical antipsychotic associated with virtually no extrapyramidal symptoms (EPS).[41,42] Poewe and Seppi[20] reviewed several case reports with a total of 432 patients receiving clozapine for psychotic symptoms in PD and found significant benefit in approximately 85% of patients; similar results were obtained in two recent placebo-controlled trials, which also yielded no evidence of motor decline attributable to clozapine.[41,43] In most cases, the dose of clozapine used (e.g., 50 mg) was much lower than the dose typically used in schizophrenia. The use of clozapine is associated with life-threatening agranulocytosis in 1% to 2% of cases, necessitating weekly white blood cell count monitoring; no leukopenia-related deaths have been reported in PD patients.[20] Of the second-generation antipsychotics, quetiapine has the closest structural resemblance to clozapine. Numerous open-label studies of quetiapine for the treatment of psychosis in PD have been reported, two of which were retrospective studies. One study found that 35 of 43 PD patients showed significant improvement in their psychotic symptoms when treated with quetiapine, and only five patients experienced a mild deterioration in motor function.[44] In another study, 78 of 106 PD patients treated with quetiapine at a movement disorders center took quetiapine for a mean duration of 15 months, with 82% experiencing partial or complete resolution of psychosis.[45] Mild motor worsening was reported over 15 months by 32% of patients, and these patients tended to have more advanced dementia. Several double-blind trials of quetiapine in PD have been conducted, with mixed results.[46–48] Overall, quetiapine appears to be less effective than clozapine for the treatment of psychosis in PD. However, unlike olanzapine and risperidone, no declines in motor function reported in PD patients have required hospitalizations. In addition, quetiapine does not carry an increased risk of agranulocytosis, and does not mandate the monitoring required with use of clozapine. Therefore, despite

TABLE 20–2 Stepwise Management of Psychosis in Parkinson's Disease

I.	**Consider etiologies unrelated to PD or anti-PD medications and treat accordingly**
	Medications: antihistamines, anticholinergics, benzodiazepines, antispasmodics, narcotics, and corticosteroids
	Metabolic, electrolyte, or fluid-related abnormalities
	Infection
	Alcohol, benzodiazepine, or opiate withdrawal; Wernicke's encephalopathy
	Hypoxia
	Stroke or intracranial hemorrhage
	Hypertensive encephalopathy
	Seizure
II.	**Reduce anti-PD medications**
	Reduce or discontinue anticholinergic medications, amantadine, or MAOIs; then
	Reduce or discontinue dopamine agonists; then
	Reduce levodopa
III.	**Consider a trial of antipsychotics**
	Treatment of choice: clozapine
	Next line: quetiapine, olanzapine
	Last resort: risperidone, low-potency typical antipsychotics

From Cantello R, Gill M, Riccio A et al: Mood changes associated with "end-of-dose deterioration" in Parkinson's disease, *J Neurol Neurosurg Psychiatr* 49:1182–1190, 1986; Kuzuhara S: Drug-induced psychotic symptoms in Parkinson's disease. Problems, management and dilemma, *J Neurol* 248(suppl 3):11128–11131, 2001.

the lack of efficacy of the medication in randomized, placebo-controlled trials, because of its tolerability, efficacy in several open label studies, clinicians still use quetiapine as one of the first-line treatments for psychosis in PD. A randomized, controlled trial (RCT) that assessed the use of the atypical antipsychotic, olanzapine, in PD patients with psychosis was stopped prematurely because of exacerbation of motor symptoms in the olanzapine group[49]; although no improvement in psychosis was observed in this study, several open-label and case studies have documented amelioration of psychotic symptoms with olanzapine.[50,51] With regard to risperidone and the typical antipsychotics, given their propensity toward inducing EPS and parkinsonian symptoms in patients with primary psychosis, these medications should only be used as a last resort in PD.

Other Neuropsychiatric Aspects of PD

Patients with PD suffer from a variety of other neuropsychiatric problems, including dementia, behavioral disorders, sleep pathology, and anxiety. As previously mentioned, there is significant clinical and neuropathologic overlap between PD and dementia with Lewy bodies (DLB), although it remains to be determined whether one or several concurrent etiologies are at work.[3] Whether as a function of age or primary disease progression, the frequency of dementia and cognitive impairment increases with PD duration.[52] PD patients, especially men, can exhibit a marked increase in libido and hypersexual behavior as a result of levodopa treatment.[53] Excessive daytime sleepiness, sleep attacks, and parasomnias also occur with increased frequency in PD patients; these symptoms can be treated effectively with sleep hygiene, intermittent use of nonbenzodiazepine hypnotics, and occasionally with a reduction in dopamimetics.[54] Finally, especially in PD patients with co-existing depression, anxiety disorders can significantly detract from quality of life[55]; although no randomized studies have been conducted to assess pharmacological intervention, citalopram has demonstrated good anxiolytic effect in an open-label study of depressed PD patients.[56]

Huntington's Disease

An autosomal dominant disorder occurring with a frequency of 4 to 8 per 100,000, Huntington's disease (HD) is characterized by progressive choreiform movements, dementia, and neuropsychiatric symptoms. The usual course involves initial presentation in the fourth and fifth decades of life, with gradual deterioration and death occurring within 10 to 15 years.[57,58] Although expression of neurologic and psychiatric symptoms is variable, the underlying disease process reflects a single mutation on chromosome 4p16.3.[59] Expansion of CAG repeats beyond the usual number (wild type, approximately <37) and results in an elongated huntingtin protein, which (because of a variety of putative mechanisms) induces neuronal death.[60] The neuronal population most severely affected includes gamma-aminobutyric acid (GABA)-ergic medium spiny striatal neurons, causing decreased inhibitory output to the substantia nigra and globus pallidus; some cortical neurons in layers III and VI also appear to be directly affected.[61] Accordingly, disruptions in dorsolateral prefrontal–subcortical, orbitofrontal, and medial prefrontal–thalamic circuitry may underlie respective alterations in executive function, mood, and response inhibition.[62]

In his description of the disorder, Huntington himself noted a "tendency to insanity and suicide."[63] Indeed, HD appears to incorporate a spectrum of psychopathologies, including mood, anxiety, and psychotic symptoms. In a prospective study of 52 HD patients, Paulsen and coworkers[64] described neuropsychiatric symptoms in 98% of subjects, with dysphoria, agitation, and irritability occurring most frequently (65% to 69%); 52% exhibited anxiety symptoms, whereas 13% demonstrated hallucinations or delusions. Symptoms did not correlate with dementia or chorea-scale ratings or with disease duration. Notably, suicide risk in HD was as high as 12.7%, and findings showed that frequency of suicidal ideation doubled from 9.1% in at-risk persons with a normal neurologic examination to 19.8% in at-risk persons with soft neurologic signs. Suicidal ideation increased to 23.5% in persons with "possible" Huntington's disease.[64,65] Of 102 HD patients evaluated by Dewhurst and associates,[66] 42 exhibited depressive symptoms, and 50% were described as delusional (12 had hallucinations). Another large study indicated the presence of MDD in 28 of 88 HD patients, with bipolar disorder diagnosed in an additional 8 cases.[67] Although in the latter study the onset of affective symptoms preceded chorea and dementia by an average of 5.1 years, De Marchi and Mennella[68] similarly concluded that psychotic symptoms often emerged significantly earlier than motor dysfunction in HD. These studies, as well as others that described clustering of psychiatric symptoms in specific HD families, suggested that affective and psychotic symptoms in HD may be primary expressions of the disease process.[68] As always, though, medical causes of new-onset psychiatric symptoms in HD patients should first be ruled out; particular consideration should be given to alcohol withdrawal, because ethanol abuse has been reported in up to 24% of men with HD.[69]

As in PD, there are few well-controlled trials that establish the efficacy of treatment strategies for psychiatric problems in HD. The observations of Rosenblatt and LeRoi[70] suggested that SSRIs are well-tolerated in HD patients with depression and perhaps are safer than TCAs, given the vulnerability of HD patients to anticholinergic delirium, sedation, and falls. They also reported that SSRIs are useful in managing the irritability, aggression, apathy, and obsessiveness often seen in those with HD. ECT can be useful to treat severe or psychotic depression in HD, although again the risk of ECT-induced delirium must be weighed.[71] For treatment of psychotic symptoms in early HD, small doses of high-potency neuroleptics (e.g., haloperidol) should be considered; these medications are also useful for management of chorea and motor tics. However, in more advanced HD, when parkinsonism and dystonia are more likely to occur, atypical antipsychotics (e.g., quetiapine and clozapine) are preferable.[70,72]

Wilson's Disease

Wilson's disease (WD) is a rare, autosomal recessive disorder of copper metabolism with an incidence of 12 to 30 per 1 million.[73] Mutations on chromosome 13q14 result in altered function of apoceruloplasmin, a copper-transporting

protein[74]; subsequent toxic accumulations of copper in the liver, brain, and other organs lead to progressive hepatic and neuropsychiatric dysfunction. Onset usually occurs in the first four decades of life, with a mean onset at age 17.[75] Low serum ceruloplasmin and high urinary copper levels are diagnostic; associated neuroimaging findings include increased signals in the putamen, lenticular nuclei, ventral or lateral thalamic nuclei, subcortical white matter, lamina tecti, and caudate nuclei.[76] Atrophy of the hemispheres or brainstem was evident in 68% of patients with neurologic symptoms, but in only 6% of neurologically-asymptomatic patients.[76] Functional neuroimaging often shows reduced striatal glucose metabolism and reduced *N*-acetylaspartate levels in the globus pallidus.[77,78]

Initial clinical presentation can be divided among predominantly hepatic, neurologic, or psychiatric symptoms with roughly equal frequency. Liver-related presentations include hepatitis and cirrhosis, whereas neurologic presentations most commonly involve dysdiadochokinesia and dysarthria[79]; tremor, spasticity, rigidity, or chorea in the absence of sensory changes can also occur. Psychiatric symptoms are varied, but personality change and incongruous behavior are the most frequently described.[80] A prospective study of MDD in WD indicated an incidence of 27%, although it remains unclear whether this reflects primarily a reactive or biological process.[79] Case reports of secondary mania have also been reported with WD.[81–83] Psychotic symptoms are seen infrequently, but catatonia can occur in 8% of patients with other neurologic manifestations of WD.[84] Kayser-Fleischer rings, which reflect copper deposition in the corneal limbus, occur much more frequently with neuropsychiatric than with hepatic presentations.[79]

Given the clinical heterogeneity with which WD can present, a high degree of clinical suspicion is important in making the diagnosis and therefore in establishing treatment. Moreover, treatment with copper-chelating and depleting agents (e.g., penicillamine and zinc) is only effective during the first few years of illness, so early intervention is essential.[75] Improvement in psychiatric symptoms has been less well studied than neurologic recovery, but incongruous behavior and psychosis appear to respond better than irritability and depression.[85] There have been no controlled evaluations of adjunctive psychotropic medications in WD, although there are reports of increased sensitivity to neuroleptic-induced EPS.[86]

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disorder of white matter in the brain and spinal cord, characterized pathologically by inflammatory demyelination of axonal sheaths and by gliosis. The illness is disseminated in space and time (i.e., it affects different locations within the CNS and is manifested by separate symptomatic attacks). Neurologic dysfunction frequently involves changes in vision (e.g., blurred vision, alteration of color perception, and diplopia), spastic paresis, hypoesthesia and paresthesia, ataxia, and bladder or bowel dysfunction.

Epidemiology

Multiple sclerosis affects approximately 300,000 to 350,000 people in the United States.[87] The disease usually becomes manifest between the ages of 18 and 50 years. Most cases (80%) are of the relapsing–remitting type; episodes of dysfunction last for several weeks and they are followed by substantial or complete improvement. Some patients remain well for decades. The prevalence of the relapsing–remitting type of MS is roughly twice as high in women than in men. Primary progressive MS, which is characterized by a steady neurologic decline, more often affects men.[88]

Etiology

The pathogenesis of MS remains enigmatic. Its inflammatory white matter changes are thought to be immune-mediated. The absolute risk of disease for a first-degree relative of an MS patient is less than 5%, but is still approximately 20 to 40 times higher than the rate in the general population. Several linkage studies have shown an association between major histocompatibility complex (MHC) alleles and other genes related to the immune system. Infectious agents and other environmental factors may also contribute; however, no causal link has yet been established.[89]

Psychiatric Changes

Cognition

Cognitive changes occur in 45% to 60% of patients with MS.[90] The impairment is often not readily apparent; it is frequently missed by bedside cognitive screening, such as with the Mini-Mental State Examination (MMSE).[91] Systematic psychologic testing has shown impaired memory function within the first 5 years of diagnosis in at least half of afflicted patients.[90,92] In most studies, cognitive decline was not significantly correlated with physical impairment or depressed mood, and there has been no association with the duration of disease.[90] However, cognitive deficits have been shown to be detrimental to the QoL and productivity in patients with MS, and in particular, neuropsychologic deficits having a large impact on QoL.[93] Dramatic worsening of cognitive function that occurs during an acute episode may remit completely over several months, as described in a case series by Franklin and colleagues.[94]

Mood and Behavior

MS greatly increases the risk for development of an underlying mood disorder. The lifetime prevalence of a major depressive episode for patients with MS is roughly 50%.[95–98] Several studies describe a higher incidence of depression in MS patients compared to those with other chronic neurologic disorders[99,100]; patients with prominent plaque formation in the cerebrum were more likely to be depressed than were patients with solely spinal involvement and comparative physical disability.[98] Furthermore, the risk of bipolar disorder is 2 to 13 times higher for MS patients than for those in the general population.[96,101] Population studies in Denmark and Canada showed a 2- and 7.5-fold increase of suicide risk, respectively, for patients with MS compared to the general population. The Danish investigators found that suicide was most likely during the first 5 years after diagnosis was made.[102,103] Fatigue is also a problem for 80% to 97% of MS patients.[104] Paradoxically, symptoms of fatigue are inversely proportional to the degree of brain injury as measured on MRI.[105]

Intermittent emotional expression disorder (IEED) is a neurologic phenomenon that occurs in the absence of

subjective emotional lability and has been reported in 10% to 20% of patients with MS.[106,107] Previously referred to as pseudobulbar affect (PBA) or pathologic crying (PLC) and laughing, case reports have implicated varied neuroanatomic regions in the development of IEED, including areas of the prefrontal cortex, cerebellum, and the brainstem.[108,109]

Psychosis

Although symptoms of psychosis in patients with MS tend to be rare, the belief that psychosis is not increased in MS was recently challenged in a study by Patten and colleagues.[110] They found rates of psychosis of 2% to 3% in MS compared with 0.5% to 1% in the general population. An MRI study of psychotic MS patients reported more extensive lesions in the temporal horns compared to other MS patients.[111,112]

Sexual Dysfunction

Up to 70% of MS patients experience sexual dysfunction.[113] Both genders experience decreased libido, orgasmic dysfunction, and decreased genital sensation. The incidence of these symptoms may be higher in men, who also describe difficulty with erection and ejaculatory dysfunction.[114] Women report decreased vaginal lubrication and decreased vaginal sensation.[115] Sexual dysfunction is a common contributor to marital problems for MS patients.

Iatrogenic Neuropsychiatric Changes

Corticosteroids, which are used in high doses to treat MS exacerbations, are known to induce insomnia, irritability, mood lability, and maniform psychosis.[116] Minden and colleagues[117] described a higher incidence of steroid-associated mania or hypomania in MS patients with a history of depression.

Concerns that interferon-beta may induce or exacerbate depression were raised after the first controlled clinical trial of interferon-beta-1b and follow-up data reported one completed suicide and four suicide attempts in the active treatment group.[118,119] This association, however, was not replicated in subsequent trials of interferon-beta-1a and interferon-beta-1b.[120,121] Prospective studies of MS patients during interferon-beta therapy suggest that patients with a recent depressive episode may experience a recurrence of their symptoms after initiation of interferon treatment; a family history of mood disorder by itself was not an independent risk factor for depression during interferon treatment.[122,123]

Treatment

Neuropsychiatric changes associated with MS are primarily treated in the same way as neuropsychiatric changes in other types of psychiatric patients.

Depression, which is the strongest predictor of poor quality of life in MS patients, responds well to treatment with antidepressants and psychotherapy.[124] Cognitive-behavioral therapy, and therapies focused on developing problem-solving skills, are more effective than are insight-oriented approaches.[122,125,126]

Fatigue may be improved by aerobic exercise, timed rest periods, improved sleep, and avoidance of heat. Often patients with MS-associated fatigue require pharmacologic treatment. Amantadine (100 to 200 mg/day) and modafinil (200 to 400 mg/day) have both been effective in controlled trials. If fatigue recurs despite continuing treatment with amantadine, drug holidays may restore its efficacy.[125,127,128]

Patients with a history of steroid-induced mania have been treated acutely and prophylactically with lithium, carbamazepine, olanzapine, quetiapine, risperidone, haloperidol, and chlorpromazine before and during the treatment with steroids to prevent the recurrence of a manic or psychotic episode.[129–133] IEED has also been shown to improve with use of TCAs, SSRIs, along with dextromethorphan/quinidine.[109]

Few studies have addressed the treatment of sexual dysfunction. Foley and colleagues[134] reported a successful pilot study involving couples counseling. Male patients with MS who have erectile dysfunction may benefit from sildenafil, 50 to 100 mg, administered 1 hour before intercourse. Because sildenafil can enhance the effect of nitrates, which produce severe hypotension, this combination should be avoided.[135] Often it is appropriate to refer patients with sexual dysfunction to a urologist or gynecologist with expertise in this area.

Cognitive dysfunction can be treated with rehabilitation, which focuses on retraining and developing compensatory strategies.[136] Acetylcholinesterase inhibitors have been evaluated in patients with MS, with most research attention focusing on donepezil. A double-blind, placebo-controlled RCT with 69 MS patients showed that donepezil improved objective memory performance on list learning, as well as subjective ratings and clinician ratings of memory abilities.[137,138] Amantadine, though commonly used to treat fatigue in MS, has not been shown to have any effect on treating the cognitive deficits in MS.[139] In another RCT of 38 patients with MS, no effect on cognition was appreciated with use of ginkgo biloba. However, a trend was noted for improved performance on the Stroop test, which measures resistance from interference and processing speed.[140]

CONNECTIVE TISSUE DISEASES

Connective tissue diseases (also known as collagen vascular diseases) are characterized by inflammation, small vessel damage, and serosal surface inflammation; they cause a constellation of symptoms ranging from arthritis to severe, multisystem illness. Although the etiology of many connective tissue diseases is unknown, autoimmune processes have been implicated in most cases. Neuropsychiatric presentations of connective tissue disease are variable and can reflect the primary disease process, psychologic stress related to the illness, or side effects of medications. The following sections will discuss neuropsychiatric manifestations and treatment approaches for common connective tissue diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, and other rheumatologic disorders.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease with multiorgan involvement primarily affecting adult women, in particular African American women in their third through fifth decades of life.[141] Non-CNS manifestations of the disease are varied and include malar or discoid rash, arthritis, proteinuria, hematologic disorders, photosensitivity, oral ulcers, and serositis. The diagnosis is made by satisfying minimal criteria as established by the

American Rheumatological Association, as well as by the presence of serum autoantibodies, including antinuclear antibodies (ANA), as well as anti-DNA, anti-Smith, and anti-RNP antibodies.[142]

Neuropsychiatric manifestations of SLE (NP-SLE) occur in reportedly 14% to 75% of patients and can be divided into focal and nonfocal signs (Table 20–3).[143] Not surprisingly, whereas focal signs have been correlated with macroscopic CNS pathology at autopsy (including infarction, hemorrhage, and thrombosis), patients with nonfocal signs exhibit more subtle findings, such as encephalomalacia, arteriolar infarction, and fatty infiltration. Clinically, there has been inconsistent evidence to support a relationship between emergence of NP-SLE symptoms and changes in biological markers, largely because it is unlikely that one pathogenic mechanism is exclusively causal in the variety of syndromes seen in NP-SLE. Primary mechanisms likely include vascular occlusion and hemorrhage, autoantibody-mediated effects (antineuronal antibodies), choroid plexus dysfunction, cytokine effects, neuroendocrine–immune imbalances, and direct neural tissue injury via oxidative stress, excitatory amino acid toxicity, and matrix metalloproteinase injury.[144] Antineuronal antibodies are felt to have a significant role in NP-SLE pathogenesis, and various antibodies have been found in the serum of SLE patients. A subset of anti–double-stranded DNA antibodies cross-react with a consensus sequence present in the ligand-binding region of the CNS *N*-methyl-D-aspartate (NMDA) receptor, NR2.[144] These receptors are responsible for the binding of glutamate, the primary excitatory amino acid of the brain. Furthermore, antibodies against ribosomal P proteins have been linked to psychiatric manifestations of SLE. Shoenfeld and colleagues[145,146] have reported experimental depression induced by anti–ribosomal P, pointing to limbic and olfactory areas in the pathogenesis of depression and CNS involvement in SLE. Anti–ribosomal P positivity and the titer of these antibodies have been correlated with clinical disease activity in both adults and children, although the validity of these results continue to be debated.[147]

Although many patients with CNS manifestations exhibit cerebrospinal fluid (CSF) abnormalities (e.g., elevated protein, immunoglobulin G [IgG], and immunoglobulin M [IgM]),[148] and most demonstrate electroencephalographic (EEG) abnormalities (e.g., diffuse slowing),[149] neither test appears to be sensitive or specific. MRI studies can be useful, but abnormal findings often do not correlate with clinical changes.[150]

Psychiatric symptoms in SLE are varied and occur with an unpredictable course. They can reflect primary effects of SLE, secondary metabolic abnormalities, side effects of treatment (steroid treatment or withdrawal in particular), or psychologic reactions to illness.[151] Depressed mood can occur in 41% to 70% of patients,[152] although the exact prevalence is difficult to determine because of a lack of standardized diagnostic criteria; other mood-related symptoms can include lability, irritability, and anger.[150] Although the prevalence of psychotic symptoms was initially reported at greater than 50%,[153] many of these patients may have in fact exhibited delirium; a more recent study employing a more standardized diagnosis indicated an incidence of 5%.[154] Cognitive impairment, with specific impairment in concentration and attention, occurs quite frequently, perhaps in as many as two thirds of SLE patients.[155]

Because of the heterogeneity of symptomatic presentations of NP-SLE, the general hospital psychiatrist will often face the problem of deciding whether symptoms are due to SLE itself, or secondary to another primary etiology (including a psychiatric one). It is essential to consider the timing of symptom emergence in relation to medication changes, and new physical or laboratory findings. If NP-SLE is suspected, the first priority is identification and treatment of exacerbating factors, such as hypertension, infection, and metabolic abnormalities. Immunosuppression is the cornerstone of the management of NP-SLE and may rely on high-dose glucocorticoids, cyclophosphamide, or azathioprine. Immunosuppressant agents are usually used in combination with glucocorticoid therapy, and often adjunctive medications (e.g., dopamine antagonists, antidepressants, and antiepileptic drugs) will be used for optimal clinical and symptomatic response.

TABLE 20–3 Presenting Features in Systemic Lupus Erythematosus

	CNS	
NON-CNS	**FOCAL**	**NONFOCAL**
Malar rash	Seizure (generalized, partial)	Headache
Discoid rash	Hemiplegia	Delirium
Photosensitivity	Cranial neuropathy	Psychosis
Oral ulcers	Transverse myelitis	Mood disorders
Arthritis	Peripheral neuropathy	Cognitive dysfunction
Serositis (pleuritis, pericarditis)	Abnormal movements	
Renal disorder (proteinuria, casts)		
Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia)		

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a common and debilitating disease of unknown etiology that causes symmetrical inflammation of the joint synovium. Symptoms usually begin in the hands, with sparing of the distal interphalangeal joints; morning stiffness is common. Extraarticular manifestations occur in more than three fourths of patients and can involve the heart (e.g., pericarditis, cardiomyopathy, and valvular lesions), lungs (e.g., pleurisy, fibrosis, and pneumoconiosis), eyes (e.g., scleritis and iridocyclitis), and peripheral nervous system. Rheumatoid factor is a sensitive, although nonspecific, diagnostic test.

Although there is a high (40% to 50%) prevalence of depressive symptoms in RA, it is unclear whether these reflect the underlying disorder or a secondary psychologic reaction to the disease[156]; treatment should include both analgesics and adjunctive antidepressants or psychotherapy.[151] Of particular concern, though, is the potential for psychiatric complications related to RA treatment. The rare ability of salicylates to cause delirium and psychosis has been known since 1965.[157] Nonsteroidal antiinflammatory drugs (NSAIDs) have been reported to cause paranoia, depression, hallucinations, and delirium,[158] and can also increase plasma lithium levels by decreasing its renal clearance.[157] Finally, as mentioned previously, the use of corticosteroids has been associated with manic and psychotic symptoms as well as delirium.

Sjögren's Syndrome

Sjögren's syndrome, a chronic inflammatory disorder characterized most commonly by keratoconjunctivitis sicca (dry eyes), xerostomia (dry mouth), and xerosis (dry skin), can also be associated with focal neurologic symptoms, movement disorders, spinal cord involvement, along with nonfocal symptoms that include encephalopathy, cognitive dysfunction, and neuropsychiatric abnormalities. Neuropyschiatric symptoms (anxiety, depression, hypochondriasis, cognitive dysfunction, and reduced concentration and attention) are common and may represent as early manifestation of the disease. Malinow and colleagues[159] reported psychiatric disturbances in up to 60% of patients examined. Drosos and co-workers[160] found a significantly higher level of introverted hostility and higher scores for paranoid ideation, somatization, and obsessive-compulsiveness when compared with healthy subjects. Psychiatric symptoms influencing QoL have been studied and have shown that patients with Sjögren's syndrome had a significantly higher scoring rate for possible clinical anxiety and for possible clinical depression versus controls.[161] When compared with patients affected by RA, patients with Sjögren's syndrome complained more commonly of low mood, irritability, headache, gastrointestinal symptoms, and impaired concentration and memory performance. In addition, patients with Sjögren's syndrome appear vulnerable to cognitive dysfunction (ranging from mild problems with attention and concentration to severe dementia).[159]

Treatment of Sjögren's symptoms, both glandular and extraglandular, is generally supportive, with use of steroids and other immunosuppressants reserved for severe, systemic cases.[162] Caution should be exercised when using anticholinergic medications, because these can exacerbate glandular symptoms.

Other Connective Tissue Diseases

Several other connective tissue diseases are sometimes associated with neuropsychiatric sequelae, but these phenomena have not been extensively described. End-stage scleroderma can cause delirium as a consequence of renal or hepatic failure.[163] Fibromyalgia has been associated with sleep disturbance, hypochondriasis, and depression.[164] Finally, vasculitides (e.g., temporal arteritis) can cause transient blindness, cerebral ischemia, delirium, and stroke.[165]

BRAIN TUMORS

Brain tumors may originate in the CNS, where they are derived from neuroepithelium, glia, or meninges (a *primary brain tumor*), or may be metastases from tumors in another locations in the body (a *secondary brain tumor*).

Epidemiology

Each year, roughly 16,500 patients in the United States are diagnosed with a primary brain tumor. In addition, approximately 120,000 individuals experience morbidity resulting from brain metastases of a systemic neoplasm. In adults, more than one half of the primary brain tumors are gliomas (i.e., tumors derived from the interstitial tissue of the nervous system). High-grade tumors, predominantly glioblastoma multiforme, constitute up to 80% of the gliomas. Unfortunately, the prognosis associated with glioblastomas remains poor; even with treatment, few patients survive longer than 1 year. Meningioma, a slow-growing tumor of the meninges, is the second most common CNS tumor; it accounts for about 20% of cases. Unlike glioblastomas, meningiomas can be cured with surgery or controlled by use of radiation. Although primary CNS lymphomas represent only 1% of adult brain tumors, their incidence has tripled during the past 20 years. Advances in high-dose chemotherapy, with or without radiation therapy, have increased the median survival of patients with these tumors to at least 40 months. In children, the two most common brain tumors are low-grade astrocytic or glial tumors and medulloblastomas. Meningiomas in children occur infrequently.[166–168]

Neuropsychiatric Changes Associated with Brain Tumors

All brain tumors can produce changes in affect, behavior, cognition, and perception. Upon initial presentation, mental status changes are most often seen in those with lymphoma (61%) and high-grade gliomas (40% to 60%) and less frequently seen with meningiomas (21%).[166] Most of these mental status changes are typically associated with infiltration of the tumor into the frontal and temporal lobes, and are rarely associated with occipital and parietal tumors.

Mood

Alterations in mood lead to anxiety, depression, fatigue, irritability, anger, and full-blown mania, especially with lesions of the ventral frontal and temporoparietal cortices.[169–171] Symptoms inconsistently correlate with lesion size and location. Prospective studies have shown both higher rates of depression with left-sided tumors[172] and no effect based upon hemisphere involvement.[173] One crucial distinction to make is between depression and abulia. *Abulia* or *akinetic mutism* (manifested by reduced spontaneity of speech, motion, and goal-directed behavior and by the absence of despair, sadness, or crying) is distinct from depression.[174] Tumors that cause abulia most frequently invade and affect the frontal lobes. Caplan and Ahmed[175] described bedside testing suggestive of abulia. This involves asking a patient to give lists of common objects, such as animals, fruits, or

vegetables. The abulic patient will often produce only two or three items. Another strategy is to ask the patient to count out loud from 1 to 20 and then backward from 20 to 1. Abulic patients often stop in the middle of the task, and then will either lose interest in the task, or take significantly longer than the normal (10 to 20 seconds) to complete the task. Patients with depression may also fail to pay full attention to these tasks, but with prodding their behavior changes. Delirious patients may be unable to respond appropriately; in contrast to abulic patients, they often exhibit other cognitive deficits, such as disorientation. Fluctuations in performance over time, a hallmark of delirium, is not anticipated in abulic patients, whose lack of persistence and effort is more stable.

Psychosis

Perceptual disturbances are caused by mass lesions that impinge directly on the auditory, visual, tactile, or olfactory pathways (located in the temporal and occipital cortices), the brainstem, and the base of the frontal lobes. Less frequently, brain tumors cause hallucinations indirectly through increased intracranial pressure. Paranoid ideation and other delusions are also associated with lesions of the temporal lobes.[169,170]

Cognition

When cognitive testing is performed on patients with frontal and temporal lobe tumors, measurement of memory, attention, language, and executive functions shows significant impairment in at least one area of function in most patients assessed immediately after the diagnosis. Verbal fluency and learning are most often impaired in patients with left-sided tumors.[172,176] Tucha and colleagues[177] found only a weak correlation between self-reports of cognitive dysfunction (of 139 brain tumor patients) and formal neuropsychologic assessment.

Iatrogenic Neuropsychiatric Changes

Neuropsychiatric changes are commonly caused by cancer treatments. Dexamethasone, which frequently relieves headaches and improves cognitive function by reducing brain edema, is known to induce insomnia, irritability, mood lability, and maniform psychosis.[116] Whole brain irradiation may cause sudden, transient cognitive changes. In addition, a delayed-onset subcortical dementia, thought to be related to delayed white matter necrosis, has been reported between 6 months and 20 years after radiotherapy.[178,179] Memory impairment also occurs more frequently in patients who receive high doses of radiation and in patients older than 60 years.[180,181] Combined radiotherapy and chemotherapy increase the risk of neurotoxicity. Reports of cognitive dysfunction in adults with primary brain tumors treated exclusively with chemotherapy are few and far between. Long-term follow-up studies of patients with primary CNS lymphoma suggest that chemotherapy alone does not contribute to cognitive impairment.[182,183]

Tumor resection or *debulking* often produces neuropsychiatric improvement, once the postsurgical edema has resolved; however, it carries the risk of creating lesions in functional brain areas. Careful preoperative mapping of target regions with the help of conventional and functional MRI reduces the morbidity surrounding eloquent brain areas.[184]

Treatment

The consulting psychiatrist may be called to help with the treatment of mood and behavior symptoms in patients with brain tumors. Such symptoms may be sequelae of tumor invasion into the patient's brain, tumor-related brain edema, or neurotoxic side effects of treatments. In addition, the psychiatrist can help the patient and family members to cope with and adapt to a devastating illness.

Psychopharmacologic Interventions

Clinical depression is best treated with SSRIs, such as citalopram, sertraline, paroxetine, or fluoxetine. Use of TCAs and bupropion may lower the seizure threshold and thus should be avoided (unless the patient has a therapeutic level of an anticonvulsant medication). Abulia and apathetic depression respond best to psychostimulants.[185] Methylphenidate or dextroamphetamine are usually given in the morning and around lunch time. Administration later in the day should be avoided because it may cause insomnia.

Anxiety, especially surrounding the initial diagnosis and before procedures or imaging studies, responds well to low doses of benzodiazepines (such as lorazepam or clonazepam), given two to four times per day. Acute psychosis, due to the tumor, postoperative delirium, or use of steroids, is treated best with high-potency dopamine antagonists (e.g., haloperidol) or second generation serotonin–dopamine antagonists (e.g., risperidone, olanzapine). Chlorpromazine and clozapine may lower the seizure threshold and create anticholinergic symptoms and are best avoided. Mania after initiation of dexamethasone treatment is often short-lived and quickly controlled with antipsychotic medications. If prolonged treatment with steroids is necessary and is accompanied by intolerable mood swings, lithium or valproic acid can help stabilize the patient. These medications can also be prescribed prophylactically to patients with a history of bipolar disorder, or with a previous episode of steroid-induced mania, before a future course of dexamethasone.[129,186]

Psychosocial Interventions

Supportive psychotherapy (conducted individually or in a group) may be helpful to both the patient and his or her family. Patients struggle with vulnerability and mortality; they wonder "Why me?" Patients may redefine the meaning and priorities of their life and ponder their legacy left behind. A patient with young children may want to make a recording or to leave a picture album or a letter, which can be addressed to his or her children for when they are older. Family members often struggle with the patient's decline in function and behavior that may be induced by the tumor. Studies have repeatedly shown that caregivers tend to give lower estimates of patient QoL and hope than do patients themselves.[187,188] Cognitive rehabilitation,

originally developed for patients with traumatic brain injuries, can help to improve function and dysphoric mood in patients with brain tumors.[189]

PARANEOPLASTIC LIMBIC ENCEPHALITIS

The description of limbic encephalitis is attributed to Brierley and co-workers,[190] who in 1960 reported 3 patients with "subacute encephalitis of later adult life, mainly affecting the limbic areas." Corsellis and colleagues[191] used the term "limbic encephalitis" to describe a series of patients with severe memory loss, and memory loss with dementia in association with bronchial carcinoma. The authors also reviewed previously reported cases and established for the first time a relationship between limbic encephalitis and systemic cancer.

The classic syndrome includes rapid development of irritability, depression, sleep disturbances, hallucinations, along with seizures and short-term memory deficits.[192] Patients may seem to be quietly confused, making repetitive statements, and sometimes with episodes of staring, along with psychomotor or partial seizures that predominate over generalized seizures. Encephalitis associated with *N*-methyl-D-aspartate receptors (NMDAR) typically occurs in young women, who for a few days after a flu-like illness develop anxiety and other mood disorders, which progress to severe behavioral and personality disturbances, delusions, or disorganized thinking, paranoid ideation, and hallucinations.[192] They may eventually also develop symptoms similar to catatonia and remain with eyes open, unresponsive to visual threats, mutism, increased muscle tone, or dystonic posturing.[193] These symptoms are generally associated with seizures, a decline of the level of consciousness, central hypoventilation, autonomic instability, and dyskinesias. Agitation is generally unresponsive to usual pharmacologic interventions, and may necessitate intubation.

After excluding a viral etiology, the next diagnostic question is whether the suspected limbic encephalitis is paraneoplastic or not. Sixty percent to 70% of paraneoplastic encephalitis cases present neuropsychiatrically, before the detection of the tumor.[194] Patients may have CSF inflammatory findings (e.g., pleocytosis, increased protein concentration, increased IgG index, and oligoclonal bands), EEG abnormalities (focal or generalized slowing, or foci of epileptic activity in one or both temporal lobes), MRI changes (hyperintense signal in the medial aspect of the temporal lobes), and antineuronal antibodies. These antibodies are directed against two broad categories of antigens: intracellular (Hu, Ma2, CV2/CRMP5, and amphiphysin) and cell membrane antigens (voltage-gated potassium channels [VGKC], NMDAR, along with others expressed in the neuropil of the hippocampus and cerebellum that have yet to be characterized).

In cases where a tumor is found in association with a possible paraneoplastic disorder, removal of the tumor is critical for neurologic improvement and stabilization.[195] Unfortunately, most limbic encephalitides related to intracellular antigens do not improve, and at best stabilize, after tumor removal and immunotherapy. There are anecdotal cases of patients that improve with tumor removal, coricosteroids, IV Ig, or plasma exchange. In contrast, limbic encephalitis associated with cell membrane antigens is significantly more responsive to immunotherapy (IV Ig, plasma exchange, coricosteroids, cyclophosphamide, rituximab).[196] Control and removal of the tumor for this group of patients seems to be required not only for more rapid response but to attain full recovery.[192]

CNS INFECTIONS

Infections of the CNS must be considered in the differential diagnosis of both acute and chronic neuropsychiatric symptoms. Manifestations of CNS infections may involve the entire gamut of neuropsychiatric disorders, including delirium, psychosis, mania, depression, dementia, catatonia, behavioral changes, agitation, or anxiety.[197–199] The consequence of missing a CNS infection may contribute to increased morbidity and a devastating outcome for the patient. The general hospital psychiatrist plays an important role in ensuring that such diagnoses are considered and evaluated. The following section will first describe the signs and symptoms that should prompt a more thorough medical evaluation in this regard. This will be followed by a discussion of specific types of CNS infection most likely to be seen by the psychiatric consultant. These include meningitis and encephalitis due to bacteria, viruses, and parasites.

Because CNS infections may present with such a wide array of neuropsychiatric symptoms, the diagnosis may not be readily apparent. However, certain clues suggest that neuropsychiatric symptoms are due to a medical illness rather than a primary psychiatric disease (Table 20–4).

Moreover, the presence of fever, nuchal rigidity, headache, visual changes, or focal neurologic signs puts CNS infection atop the list of possible etiologies. Work-up may then include serum laboratory tests, CSF analysis, CT scan or MRI scans of the head, and an EEG. These will be discussed in more detail later, with each of the specific types of infection.

Bacterial Meningitis

Bacterial meningitis often presents with a constellation of signs and symptoms, including fever, headache, lethargy, confusion, vomiting, irritability, and a stiff neck.[200,201] Focal neurologic abnormalities and seizures may also be observed. Although a complete discussion of etiological

TABLE 20–4 Factors Suggestive of Medical Illness

Sudden onset of symptoms
Absence of prior psychiatric history
Vital sign abnormalities
Disorientation
Younger or older age (younger than 12 years or older than 40 years)
Immunocompromised host
Concurrent physical symptoms
Focal neurologic signs
Nonauditory hallucinations

From Reeves RR, Pendarvis EJ, Kimble R: Unrecognized medical emergencies admitted to psychiatric units, *Am J Emerg Med* 18(4):390–393, 2000.

agents is beyond the scope of this chapter, the most common pathogens include *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. The propensity of infection with specific pathogens varies according to age of the patient and with the following factors: neurosurgical procedure, immunocompromised state, alcoholism, systemic illness, cancer, and head trauma.[201,202] Bacteria may enter the subarachnoid space via hematogenous spread, which generally begins in the nasopharynx. Alternatively, bacteria may invade the meninges directly through structural defects. Because of the diffuse nature of bacterial involvement, confusion and altered sensorium are typical manifestations. Focal findings often suggest a localized cerebritis or abscess.[201]

Bacterial meningitis is diagnosed by lumbar puncture, which should be performed at the earliest suspicion, given high rates of mortality. Table 20–5 illustrates typical CSF findings for different types of CNS infections. CSF should also be sent for culture to identify specific organisms involved. Other diagnostic measures include a complete blood count (CBC), which may show leukocytosis or leukopenia. An EEG is most commonly marked by generalized slowing. Brain imaging is most helpful in instances where an abscess or focal disease is suspected.

Intravenous antibiotics are the mainstay of treatment for bacterial meningitis. Although specific agents will not be discussed here, the standard practice involves starting broad coverage and then narrowing the range once an etiologic agent is discovered. Corticosteroids may also be used for patients with cerebral edema or with high levels of bacteria in the CSF.[202] Neuropsychiatric side effects of steroid treatment should be closely monitored. Early diagnosis of meningitis greatly improves outcome; however, despite intervention, bacterial meningitis may be fatal in an estimated 20% to 30% of cases.[200,201]

Viral Meningitis

Viral meningitis is commonly referred to as *aseptic meningitis* because of characteristic aseptic CSF. Diagnosis is made by lumbar puncture (see Table 20–5), and care must be taken to exclude fungal or mycobacterial etiologies, because these may take days or weeks to grow in culture medium. Viruses generally infect the subarachnoid space and leptomeninges with rare involvement of the brain parenchyma.[202,203] Clinical features most commonly include a triad of fever, meningismus, and vomiting. Irritability, clouding of consciousness, and lethargy are less frequent.[203] Focal neurologic signs, seizures, or more severe presentation suggests encephalitis.

Viral meningitis is most often caused by the enterovirus family; however, the most common single causal agent is mumps.[200] It often affects young adults in the late summer or early fall. Herpes viruses and human immunodeficiency virus (HIV) infection may also produce viral meningitis and is discussed separately. The course of aseptic meningitis is usually benign, and treatment involves supportive measures. Fatalities are extremely rare, as are long-term sequelae. However, at least one study suggests that viral meningitis in adults may result in underdiagnosed mild cognitive impairment, especially in areas of nonverbal learning and cognitive speed.[199] Neuropsychologic testing may prove to be beneficial in this regard.

Herpes Simplex Virus Encephalitis

Herpes simplex virus (HSV) is the most frequent and potentially dangerous cause of sporadic and focal encephalitis in the United States. Mortality rates are estimated at 10% to 40% with similar rates of significant sequelae.[200,202] HSV typically invades the inferior frontal and anterior temporal lobes via cell-to-cell spread along branches of the trigeminal nerve.[200,204] Because of its predisposition for these locations, typical presentations include behavioral disturbances, personality changes, aphasia, memory loss, and dementia. Fever and headache are also frequently present.

Definitive diagnosis of HSV encephalitis may be difficult, because brain biopsy is the gold standard, and CSF often does not reveal the presence of virus. However, brain imaging by CT or MRI may demonstrate inflammation and edema in characteristic temporal and frontal areas. An EEG with periodic sharp waves in the temporal regions should also raise concern for HSV infection. In cases in which there is a high index of suspicion, treatment with acyclovir is started empirically, because delay increases the risk of mortality.

Human Immunodeficiency Virus Infection

Central nervous system infections related to HIV may result from meningitis due to HIV itself, or from superimposed infections due to an immunocompromised state. Moreover, the differential diagnosis of neuropsychiatric disturbance in patients with HIV infection or AIDS may result from a variety of factors. These include primary psychiatric illness, primary effects of HIV infection of the CNS, opportunistic infections, and side effects of medications used to treat HIV-related illnesses.[205] Because HIV infection is described in detail elsewhere in this book, only a short overview is provided here.

TABLE 20–5 Typical CSF Findings with CNS Infections

	CELL TYPE PREDOMINANCE	GLUCOSE	PROTEIN (mg/dl)
Bacterial meningitis	Polymorphonuclear cells	Low	>150
Viral meningitis	Lymphocytes	Normal	<100
Tuberculous meningitis	Lymphocytes	Low	>150
Syphilitic meningitis	Lymphocytes	Low	<100
Herpes simplex encephalitis	Lymphocytes	Normal	<100

From Andreoli TE, Bennett JC, Carpenter CC et al: *Cecil essentials of medicine,* ed 4, Philadelphia, 1997, Saunders; Sagar SM, McGuire D: Infectious diseases. In Samuels MA, editor: *Manual of neurologic therapeutics,* ed 6, Philadelphia, 1999, Lippincott Williams & Wilkins.

In brief, of the two categories of CNS infection seen with HIV infection (meningitis due to HIV itself and CNS opportunistic infections), meningitis usually runs a more benign course. HIV meningitis is marked by a syndrome of fever, headache, acute confusional state, meningeal irritation, and cranial nerve palsies (especially cranial nerve VII).[201] This often occurs at the time of HIV seroconversion as a complication of the flu-like illness experienced by approximately one third of HIV-infected people.[205] The CSF generally reveals a mononuclear pleocytosis, and the symptoms generally resolve spontaneously. Meningitis, encephalitis, and abscesses caused by opportunistic infections are generally more serious, and they signify worsening of the immune status. Others include cryptococcal meningitis, HSV encephalitis, varicella-zoster encephalitis, cytomegalovirus encephalitis, and cerebral toxoplasmosis. In addition, progressive multifocal leukoencephalopathy (PML) occurs in up to 5% of patients with AIDS. It is caused by the reactivation of the polyomavirus JC (JCV) in immunocompromised individuals. The mortality rates for those with HIV PML have fallen dramatically from approximately 90% to between 30% and 50%.[206] Classically, patients with PML present with a subacute onset of neurologic deficits, corresponding to one or multiple CNS lesions on neuroimaging, which is restricted to white matter changes. Typical symptoms associated with PML can be diverse, and are related to the location and extent of CNS injury in the brain. The most prominent symptoms are clumsiness and progressive weakness, along with visual, speech, and behavioral changes. In HIV-positive patients, highly active antiretroviral treatment (HAART) is the only effective therapeutic option for PML. There have been several case reports suggesting that mirtazapine may be potentially useful in treating PML in HIV-infected patients receiving HAART. The efficacy of mirtazapine therapy may be through its antagonist properties at $5HT_{2A}$ receptors, the putative receptors for JCV infection of oligodendrocytes.[206] Mirtazapine likely acts by preventing the spread of JCV infection to additional glial cells rather than by direct antiviral properties.

In general, organic causes of psychiatric symptoms should be at the top of the list of possible causes in people with HIV infection or AIDS, especially at later stages of the illness.

Tuberculous Meningitis

Tuberculous meningitis is important to consider in patients who present with confusion, especially in those with a history of pulmonary tuberculosis, alcohol abuse, homelessness, HIV infection, or chronic steroid treatment.[201] It is caused by a rupture of latent parameningeal tubercles, which remain dormant in the subarachnoid space from earlier exposure. Tuberculous meningitis is characteristically subacute with symptoms generally present for up to 4 weeks at the time of presentation. Clinically, one sees headache, fever, meningismus, and delirium most frequently. Papilledema and ocular palsies are also notable. CSF usually reveals low glucose levels and mononuclear predominance (see Table 20–5). Acid-fast smears may be initially negative, though they are an aid in early diagnosis when positive. Definitive diagnosis may be delayed, given that *Mycobacterium tuberculosis* may take up to 4 weeks to be cultured, and only 50% to 65% of patients have a positive purified protein derivative (PPD) skin test or chest x-ray evidence of prior exposure to tuberculosis.[202,203] Treatment is therefore initiated with antituberculous medications when the level of suspicion is high while awaiting culture results. Once a diagnosis is established, treatment continues for 4 to 10 months. Recurrences may develop because of poor compliance. Even with treatment, mortality is significant, at about 30%.[201]

Syphilitic Meningitis

The incidence of syphilis is rising globally, partly because of the increased transmission in HIV patients and other high risk groups.[207] Neurosyphilis occurs when *Treponema pallidum* invades the CNS and is reactivated up to years later. Because neurologic symptoms rarely appear until at least the secondary stage of the disease, earlier detection of syphilis infection is essential to prevent long-term sequelae. The serologic test for syphilis (STS) or Venereal Disease Research Laboratory (VDRL) test is used for large screening programs, but the fluorescent treponemal antibody (FTA-ABS) is much more sensitive and should be used when suspicion is high. There are several categories of neurosyphilis that occur when *T. pallidum* enters the CNS (including meningeal and parenchymal). Patients may exhibit confabulation, dysarthria, impaired judgment, and psychosis.[199] *General paresis* refers to dementia associated with parenchymal neurosyphilis; it had been a common cause of admission to psychiatric facilities. *Tabes dorsalis*, also of the parenchymatous type, results from chronic infection, and it causes a progressive sensory neuropathy. Other complications of neurosyphilis include communicating hydrocephalus, lightning pains (associated with tabes dorsalis), Charcot joints, parenchymal or meningeal gummas, and spinal pachymeningitis.[202] Treatment is with penicillin; however, once later stages of neurosyphilis are reached, full recovery is not expected.

Lyme Meningitis

Lyme disease is caused by *Borrelia burgdorferi*, a spirochete transmitted by ticks primarily on the Atlantic coast of the United States and in parts of the West and Midwest, as well as parts of western Europe. Lyme is the major vector-borne infection in the United States, and in endemic areas (as listed earlier), the attack rate may be as high as 2% to 3%.[208] Initial presentation is marked by *erythema migrans*, an expanding skin lesion at the location of the tick bite. Because there is a typical central clear region, the lesion has been called the *bull's eye* lesion.[208] If untreated, Lyme disease may progress to a subacute or chronic meningitis marked by lymphocytic predominance in the CSF. Serological tests are generally positive for Lyme as well; however, during late neurologic disease, CSF serology may be negative. Of particular note, patients with Lyme disease may have a false-positive test for syphilis (and vice versa) because of cross reactivity.[202]

Particular neuropsychiatric sequelae from Lyme disease have been noted to include paranoia, dementia, psychosis, mania, panic attacks, depression, anorexia, obsessive–compulsive disorder, and cognitive impairment.[209,210] Depression has been reported to be as high as 26% to

66%.[209] Other studies suggest that impairment in verbal memory is significant.[210] However, more recent studies suggest that long-term sequelae may not be as common as initially suspected, and that the psychiatric sequelae (listed previously) may not be caused by Lyme disease in a majority of patients.[211,212] Nevertheless, prompt diagnosis and treatment with doxycycline is important to prevent long-term complications that may occur.

Parasitic Meningitis

Parasitic infections are an important cause of meningitis, especially in immunocompromised hosts and in certain areas of the world. Although the scope of such organisms is too large to discuss fully in this chapter, one organism is of particular note because of increasing reemergence in the United States and other developed areas of the world.

Neurocysticercosis is caused when the larval form of *Taenia solium* (pork tapeworm) infects the CNS. The parasite is typically ingested from undercooked pork, and later eggs from the tapeworm residing in the human gut make their way to the CNS. Though autoinfection is possible, more commonly eggs are passed on by fecal–oral transmission by food handlers and such. Cysticercosis is endemic in rural Latin America, Asia, and Africa, and immigration has recently caused a reemergence of the disease in the United States (California, Texas, and the Southwest United States are particularly affected).[212–214]

Neurocysticercosis may present in a number of ways depending on the part of the CNS involved. The main clinical manifestations are seizures, headache, and focal neurologic deficit. Hydrocephalus may contribute to acute presentations of psychosis and delirium. A more chronic picture of depression and dementia is also seen.[212,214] Definitive diagnosis is by brain biopsy; however, CT or MRI often shows the characteristic cysts. Treatment for neurocysticercosis depends on clinical presentation. Anticonvulsants are the mainstay for seizures. Steroids may be used for edema, whereas shunting is used to manage hydrocephalus. Standard antidepressants and neuroleptic medications are used for psychiatric manifestations. Anthelmintic medications are standard as well; however, no controlled trial has established definitive doses or durations of treatment.[214]

CONCLUSION

Infections of the CNS may cause both acute and chronic neuropsychiatric symptomatology. Presentation may be quite varied; it includes delirium, psychosis, dementia, depression, behavioral changes, and mania, among others. The general hospital psychiatrist plays an important role in safeguarding patients from medical diagnoses that may be missed because of psychiatric manifestations. This introduction to the more commonly seen CNS infections and their neuropsychiatric sequelae should provide a starting point for such consultations and evaluations.

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21 Catatonia, Neuroleptic Malignant Syndrome, and Serotonin Syndrome

Gregory L. Fricchione, M.D.
Anne F. Gross, M.D.
Jeff C. Huffman, M.D.
George Bush, M.D., M.M.Sc.
Theodore A. Stern, M.D.

Each of the syndromes described in this chapter involves a complex interaction of motor, behavioral, and systemic manifestations that are derived from mechanisms that are not fully clear. What *is* clear is that neurotransmitters, such as dopamine (DA), gamma-aminobutyric acid (GABA), and glutamate, are of major importance in catatonia and neuroleptic malignant syndrome (NMS), whereas serotonin (5-hydroxytryptamine [5-HT]) is a key to the serotonin syndrome (SS). Many now believe that NMS represents a catatonic state that results from the use of DA-blocking medications. These syndromes have symptoms and treatments that overlap.

As our psychopharmacologic armamentarium grows and as drugs with potent effects on modulation of monoamines proliferate, the diagnosis and management of these complex disorders becomes even more important. How can we approach such complicated clinical syndromes? Use of vignettes should help to clarify issues of diagnosis and treatment.

CATATONIA

CASE 1 Catatonia

A 42-year-old man with a long history of complex partial seizures and a history of a left temporal lobectomy had intermittent seizures despite the use of phenytoin and other antiepileptics. After admission to the hospital following a seizure, he developed catatonic withdrawal. After administration of IV lorazepam, he became alert, agitated, and aggressive; moreover, he was paranoid, and reported nihilistic and religious delusions. After several more doses of lorazepam, a higher dosage of phenytoin, and a dose of an atypical antipsychotic (risperidone), his psychosis gradually dissipated. At that point, he was able to state that he felt alone and dissociated, and he was unsure whether he even existed. "I feel separated from the human race, like I am on another planet," he said.

Definition

The catatonic syndrome comprises a constellation of motor and behavioral signs and symptoms that often occurs in relation to neuromedical insults. Structural brain disease, intrinsic brain disorders (e.g., epilepsy, toxic–metabolic derangements, infectious diseases), a variety of systemic disorders that affect the brain, and idiopathic psychiatric disorders (such as affective and schizophrenic psychoses) have all been associated with catatonia.[1–3] Catatonia was first defined by Karl Kahlbaum, who, in 1847, published a monograph that described 21 patients with a severe psychiatric disorder.[4] It was among the first studies in the area of mental illness to use the symptom-based approach of Sydenham to diagnose disorders without a known etiopathogenesis.[1]

Kahlbaum believed that patients with catatonia passed through several phases of illness: a short stage of immobility (with waxy flexibility and posturing), a second stage of stupor or melancholy, a third stage of mania (with pressured speech, hyperactivity, and hyperthymic behavior), and finally, after repeated cycles of stupor and excitement, a stage of dementia.[4]

Kraepelin,[5] who was influenced by Kahlbaum, included catatonia in the group of deteriorating psychotic disorders named dementia praecox. Bleuler[6] adopted Kraepelin's view that catatonia was subsumed under severe idiopathic deteriorating psychoses, which he renamed the schizophrenias.

Kraepelin and Bleuler both recognized that catatonic symptoms could emerge as part of a mood disorder (either mania or depression). It also was well known that catatonia developed secondary to neurologic, toxic–metabolic, and infectious etiologies. These states were considered phenomenologically indistinguishable from primary psychogenic catatonias.

Nevertheless, catatonia was overly associated with schizophrenia until the 1990s as a result of a nosological misconception. Thanks in large part to the work of Fink and Taylor,[7] the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), finally included new criteria for mood disorders with catatonic features, and for catatonic disorder secondary to a general medical condition, as well as the catatonic type of schizophrenia.[8] Catatonia, whether a consequence of medical illness, major depression, mania, a mixed affective disorder, or

schizophrenia, is diagnosed when the clinical picture includes at least two of the following:

- Motoric immobility, as evidenced by catalepsy (including waxy flexibility) or stupor
- Excessive motor activity, apparently purposeless and not influenced by external stimuli
- Extreme mutism or negativism, characterized by an apparently motiveless resistance to all instructions or by maintenance of a rigid posture against attempts to be moved
- Peculiarities of voluntary movement, such as the voluntary assumption of inappropriate or bizarre postures, stereotyped movements, prominent mannerisms, or grimacing
- Echolalia or echopraxia

Epidemiology and Risk Factors

The incidence of catatonia in the general psychiatric population varies according to study design and diagnostic criteria. Nevertheless, prospective studies on patients hospitalized with acute psychotic episodes place the incidence of catatonia in the range of 7% to 17%.[9] In patients who suffer from mood disorders, occurrence rates have ranged from 13% to 31% over the past century. Catatonia appears commonly in people with bipolar disorder.[10] Others at particular risk include patients with mixed manic episodes and those with severe mood disorders.[9] Some have contended that the incidence of catatonia has diminished in cases of schizophrenia, but here, too, diagnostic and study design variations over the decades make this interpretation problematic.

Catatonia is a nonspecific syndrome associated with a variety of etiologies.[9] Neuromedical "organic" etiologies account for 4% to 46% of cases in various series. This underscores the need for a thorough neuromedical workup when catatonic signs are present. Personality disorders or conversion disorder is cited as etiologic in 4% to 11% of cases of catatonia. Catatonia is idiopathic in 4% to 46% of cases in various case series.

Subtypes of Catatonia

Subtypes of catatonia include catatonic withdrawal (characterized by psychomotor hypoactivity) and catatonic excitement (characterized by psychomotor hyperactivity), and these may alternate during the course of a catatonic episode. Kraepelin identified a "periodic" catatonia with an onset in adolescence characterized by intermittent excited states, followed by catatonic stuporous stages and a remitting and relapsing course.[11] This disorder was further elaborated upon by Gjessing[12] in 1932. In 1934, Stauder[13] described lethal catatonia, distinguished by the rapid onset of a manic delirium, high temperatures, and catatonic stupor; it has a mortality rate of greater than 50%.

Although a genetic predisposition has not been clearly identified for catatonia, there appears to be a dominant gene effect for families with periodic catatonia.[14] The disease locus for periodic catatonia appears to map to chromosome 15q15.[14] However, in one family the locus was mapped to chromosome 22q13, affecting the gene *WKL1*. *WKL1* codes for a cation channel found in limbic and dorsal striatal tissues, suggesting that periodic catatonia may be associated with mesolimbic and nigrostriatal changes.[15] More recently, single-nucleotide polymorphisms for the gene *MLC1*, which was thought to be a risk gene for schizophrenia, also located on chromosome 22q13, has been associated with periodic catatonia, but not with general schizophrenia or bipolar disorder.[16] Interestingly, a recent study identified a shared-susceptibility chromosome region on chromosome 15 between catatonia, schizophrenia, and autism, and the authors argued that catatonia may represent an intermediate phenotype in schizophrenia and autism.[17]

In 1986, Mann and associates[18] reviewed the world's literature on lethal catatonia, dating back to the pre-neuroleptic era. Cases from the pre-neuroleptic era classically began with a period of intense motor excitement, which lasted uninterrupted for an average of 8 days. These patients often acted in a bizarre and violent fashion, refused to eat, and displayed intermittent mutism, posturing, catalepsy, and rigidity that alternated with their excitement. They manifested thought disorders with disorganized incoherent speech and experienced delusions and hallucinations. During the hyperactive stage, their fevers rose rapidly, and they were diaphoretic and tachycardic. This stage would be followed by exhaustion, characterized by stupor and high body temperatures.

Terminal rigidity and posturing were noted in Stauder's series of 27 lethal catatonia cases,[13] although others reported cases of flaccidity.[19] Some cases in the pre-neuroleptic era were characterized by catatonic stupor and rigidity in the absence of an early excitement phase. Pre-neuroleptic–era lethal catatonia was fatal in more than three out of four cases.

For Kraepelin, lethal catatonia was a syndrome with various neuromedical and psychiatric causes; the review by Mann and co-workers[18] of 292 cases since 1960 supports this concept. Most of the patients in this series received neuroleptics at some point during their treatment. Of those, 60% died. The classic hyperactive form of catatonia was found in 69% of the cases. Patients either presented with catatonic excitement or it developed early on. High fever, altered consciousness, autonomic instability, anorexia, electrolyte imbalance, cyanosis, and associated catatonic signs (e.g., posturing, stereotypies, and mutism) were present from the early stages. Stupor typically followed the early hyperactive state, but 31% of patients with lethal catatonia presented with stupor. Once stupor and rigidity emerge, patients with catatonic stupor act like those with NMS, which also has a substantial mortality rate.[19] Indeed, the symptoms of predominantly stuporous patients with catatonia were clinically indistinguishable from those with NMS.

Clinical Features and Diagnosis

Signs and symptoms of the catatonic syndrome are outlined in Table 21–1 (the Modified Bush–Francis Catatonia Rating Scale). A key is to differentiate catatonia from other syndromes with similar manifestations but with different etiologies (Table 21–2).[20–42] When assessing the etiology of the catatonia, the psychiatrist should consider secondary causes of catatonia related to underlying neurologic, toxic, or metabolic abnormalities, as well as primary psychiatric causes.

In addition to routine studies to identify neuromedical causes of catatonia, the clinician can obtain a metabolic panel; serum and urine toxicologies; an infectious-disease

TABLE 21–1 Modified Bush–Francis Catatonia Rating Scale*

Catatonia can be diagnosed by the presence of two or more of the first 14 signs listed below.

1. Excitement	Extreme hyperactivity, and constant motor unrest, which is apparently nonpurposeful; not to be attributed to akathisia or goal-directed agitation
2. Immobility/stupor	Extreme hypoactivity, immobility, and minimal response to stimuli
3. Mutism	Verbal unresponsiveness or minimal responsiveness
4. Staring	Fixed gaze, little or no visual scanning of environment, and decreased blinking
5. Posturing/catalepsy	Spontaneous maintenance of posture(s), including mundane (e.g., sitting/standing for long periods without reacting)
6. Grimacing	Maintenance of odd facial expressions
7. Echopraxia/echolalia	Mimicking of an examiner's movements/speech
8. Stereotypy	Repetitive, non–goal-directed motor activity (e.g., finger-play, or repeatedly touching, patting, or rubbing oneself); the act is not inherently abnormal but is repeated frequently
9. Mannerisms	Odd, purposeful movements (e.g., hopping or walking on tiptoe, saluting those passing by, or exaggerating caricatures of mundane movements); the act itself is inherently abnormal
10. Verbigeration	Repetition of phrases (like a scratched record)
11. Rigidity	Maintenance of a rigid position despite efforts to be moved; exclude if cogwheeling or tremor present
12. Negativism	Apparently motiveless resistance to instructions or attempts to move/examine the patient; contrary behavior; doing the exact opposite of the instruction.
13. Waxy flexibility	During reposturing of the patient, the patient offers initial resistance before allowing repositioning, similar to that of a bending candle
14. Withdrawal	Refusal to eat, drink, or make eye contact
15. Impulsivity	Sudden inappropriate behaviors (e.g., running down a hallway, screaming, or taking off clothes) without provocation; afterward, gives no or only facile explanations
16. Automatic obedience	Exaggerated cooperation with the examiner's request or spontaneous continuation of the movement requested
17. *Mitgehen*	"Anglepoise lamp": arm raising in response to light pressure of finger, despite instructions to the contrary
18. *Gegenhalten*	Resistance to passive movement that is proportional to the strength of the stimulus; appears automatic rather than willful
19. Ambitendency	The appearance of being "stuck" in indecisive, hesitant movement
20. Grasp reflex	Per neurologic examination
21. Perseveration	Repeatedly returns to the same topic, or persistence with movement
22. Combativeness	Usually aggressive in an undirected manner, with no, or only facile, explanation afterward
23. Autonomic abnormality	Abnormal temperature, blood pressure, pulse, or respiratory rate, and diaphoresis

Modified from Bush G, Fink M, Petrides G et al: Catatonia—I: rating scale and standardized examination, *Acta Psychiatr Scand* 93:129–136, 1996.

*The full 23-item Bush–Francis Catatonia Rating Scale (BFCRS) measures the severity of 23 signs on a 0 to 3 continuum for each sign. The first 14 signs combine to form the Bush–Francis Catatonia Screening Instrument (BFCSI). The BFCSI measures only the presence or absence of the first 14 signs, and it is used for case detection. Item definitions on the two scales are the same.

work-up, including human immunodeficiency virus and rapid plasma reagin testing; and autoimmune screening (erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies). A personal and family history of psychiatric illness is important but not diagnostic. Research on regional blood flow has shown basal ganglia asymmetry with left-sided hyperperfusion, hypoperfusion in the left medial temporal area, and decreased perfusion in the right parietal cortex. During working memory tasks and with emotional–motor activation, the orbitofrontal cortex appears to be altered in several cases studied with functional magnetic resonance imaging (fMRI).[43] However, none of these experimental findings are diagnostic.

Under the category of secondary causes, some now argue that there should be a catatonia subtype associated with delirium, which would include excited forms (as can occur in "delirious mania") and stuporous forms (as often seen in cases of encephalitis). Delirious mania is a syndrome with acute onset of excitement, grandiosity, emotional lability, delusions, and insomnia characteristic of mania and the disorientation and altered consciousness characteristic of delirium, as well as fever, tachycardia, hypertension, and tachypnea. It is often associated with catatonia and can often look like excited or malignant catatonia. Fink argues that when catatonic signs predominate, this syndrome may be classified as excited catatonia, whereas if catatonic symptoms are less prominent, the syndrome should be identified as delirious mania.[44] The diagnostic evaluation, including careful assessment for catatonic symptoms, is essential; the use of lithium and neuroleptics, common medications for the treatment of mania, may worsen the catatonic symptoms and lead to NMS. In fact, Fink argues that electroconvulsive therapy (ECT) is the treatment of choice for patients with delirious mania.

When catatonic symptoms are associated with a stuporous state in the setting of delirium, limbic encephalitis must be considered as a potential cause.[45] Limbic encephalitis has an acute to subacute onset, and it is associated

TABLE 21–2 Potential Etiologies of the Catatonic Syndrome

Primary: Psychiatric
Acute psychoses
Conversion disorder
Dissociative disorders
Mood disorders
Obsessive–compulsive disorder
Personality disorders
Schizophrenia

Secondary: Neuromedical
Cerebrovascular
- Arterial aneurysms
- Arteriovenous malformations
- Arterial and venous thrombosis
- Bilateral parietal infarcts
- Temporal lobe infarct
- Subarachnoid hemorrhage
- Subdural hematoma
- Third ventricle hemorrhage
- Hemorrhagic infarcts

Other Central Nervous System Causes
Akinetic mutism
Alcoholic degeneration and Wernicke's encephalopathy
Cerebellar degeneration
Cerebral anoxia
Cerebromacular degeneration
Closed head trauma
Frontal lobe atrophy
Hydrocephalus
Lesions of thalamus and globus pallidus
Narcolepsy
Parkinsonism
Postencephalitic states
Seizure disorders*
Surgical interventions
Tuberous sclerosis

Neoplasm
Angioma
Frontal lobe tumors
Gliomas
Langerhans' carcinoma
Paraneoplastic encephalopathy
Periventricular diffuse pinealoma

Poisoning
Coal gas
Organic fluorides
Tetraethyl lead poisoning

Infections
Acquired immunodeficiency syndrome
Bacterial meningoencephalitis
Bacterial sepsis
General paresis
Malaria
Mononucleosis
Subacute sclerosing panencephalitis
Tertiary syphilis
Tuberculosis
Typhoid fever
Viral encephalitides (especially herpes)
Viral hepatitis

Metabolic and Other Medical Causes
Acute intermittent porphyria*
Addison's disease
Cushing's disease
Diabetic ketoacidosis
Glomerulonephritis
Hepatic dysfunction
Hereditary coproporphyria
Homocystinuria
Hyperparathyroidism
Idiopathic hyperadrenergic state
Multiple sclerosis
Pellagra

Idiopathic
Peripuerperal
Systemic lupus erythematosus*
Thrombocytopenic purpura
Uremia

Drug-Related
Neuroleptics (typical and atypical): clozapine and risperidone* (all neuroleptics have been associated)
Non-neuroleptic
- Alcohol
- Anticonvulsants (tricyclics, monoamine oxidase inhibitors, and others)
- Anticonvulsants (e.g., carbamazepine, primidone)
- Aspirin
- Disulfiram
- Metoclopramide
- Dopamine depleters (e.g., tetrabenazine)
- Dopamine withdrawal (e.g., levodopa)
- Hallucinogens (e.g., mescaline, phencyclidine,* and lysergic acid diethylamide)
- Lithium carbonate
- Morphine
- Sedative–hypnotic withdrawal
- Steroids
- Stimulants (e.g., amphetamines, methylphenidate, and possibly cocaine)

Modified from Philbrick KL, Rummans TA: Malignant catatonia, *J Neuropsychiatry Clin Neurosci* 6:1–13, 1994.
*Signifies most common medical conditions associated with catatonic disorder from literature review done by Carroll BT, Anfinson TJ, Kennedy JC et al: Catatonic disorder due to general medical conditions, *J Neuropsychiatry Clin Neurosci* 6:122–133, 1994.

with confusion, cognitive impairment (including short-term memory dysfunction), seizures, and also, at times, with catatonia. Etiologies of limbic encephalitis include infectious, autoimmune, paraneoplastic, and idiopathic causes. Neuroimaging (MRI) and lumbar puncture (sometimes revealing a pleocytosis) with cerebrospinal antibody titer studies may be helpful in determining the diagnosis. Idiopathic encephalitis has sometimes been called encephalitis lethargica. Recently, several cases of limbic encephalitis in young women have been associated with ovarian teratomas that generate autoantibodies to NMDA receptors,[45] and a testicular teratoma was also associated with limbic encephalitis.[45] These cases respond well to removal of the teratoma, as well as to immunosuppressive

therapies. Therefore, if a patient presents with symptoms of limbic encephalitis, a healthy level of suspicion should be maintained for a gonadal tumor, and abdominal and pelvic imaging (computed tomography, MRI, positron-emission tomography, or pelvic ultrasound) should be considered.

Fortunately, although no one test can confirm a diagnosis of catatonia, some studies (e.g., an electroencephalogram [EEG], neuroimaging of the brain, optokinetic and caloric testing) may help establish the etiology.

An EEG read as normal might be consistent with primary catatonia, and although psychiatric patients may have diffuse, nonspecific changes on the EEG, this finding is found most often in patients with secondary catatonias. Also, catatonia may emerge as both an ictal and a postictal phenomenon. Plum and Posner[46] pointed out that those with idiopathic primary catatonia, as opposed to catatonia associated with structural neurologic disease, have normal optokinetic responses, normal pupillary responses, and ocular nystagmus on cold caloric tests. Patients with hysterical stupor, when turned on their sides, will elicit a downward gaze, as if resulting from gravity.[47] Neuroimaging, especially MRI of the brain, should be obtained, although a negative result does not rule out a neuromedical etiology. Creatine phosphokinase (CPK) levels are often elevated in patients with malignant catatonia, but they can also be high in simple catatonias.

When a patient is in a catatonic stupor, the slow IV administration of amobarbital may relieve the syndrome long enough for a skillful clinician to perform an interview,[18,23] which may lead to a diagnosis. Anecdotally, patients with neuromedical etiologies may become more confused on amobarbital than those with psychiatric etiologies.

As noted later, lorazepam and other benzodiazepines are now the first-line treatment for any catatonia, as they often lyse the catatonic episode completely. Benzodiazepines, which also relieve secondary neuromedical catatonias, are not useful in distinguishing between primary and secondary etiologies.

The specific number and nature of signs and symptoms required to make a diagnosis of catatonia remains controversial. Lohr and Wisniewski[21] proposed that one or more cardinal features (including catalepsy, positivism [such as is seen in automatic obedience], and negativism), and two of the other features should be present to diagnose catatonia. Rosebush and colleagues[25] suggested that catatonia was present when three cardinal features (e.g., immobility, mutism, and withdrawal [with refusal to eat or drink]), or when two cardinal features and two secondary characteristics, were present.

Taylor[1] contended that even one cardinal characteristic has as much clinical significance (for diagnosis and treatment) as the presence of seven or eight characteristics. The evidence does not support a relationship among the number of catatonic features, the diagnosis, and response to treatment. Fink and Taylor[7] later argued that a minimum of two classic symptoms was sufficient to diagnose the syndrome, and, more recently, Bush and co-workers[48] developed a rating scale and guidelines for the diagnosis of catatonia. They found that two or more signs identified all of their patients with catatonia (Table 21–3; see also Table 21–1). Their method is consistent with the DSM-IV criteria for catatonia.

TABLE 21–3 Standardized Examination for Catatonia

The method described here is used to complete the 23-item Bush–Francis Catatonia Rating Scale (BFCRS) and the 14-item Bush–Francis Catatonia Screening Instrument (BFSCI). Item definitions on the two scales are the same. The BFCSI measures only the presence or absence of the first 14 signs.

Ratings are based solely on observed behaviors during the examination, with the exception of completing the items for "withdrawal" and "autonomic abnormality," which may be based on directly observed behavior or chart documentation.

As a general rule, only items that are clearly present should be rated. If the examiner is uncertain as to the presence of an item, rate the item as "0."

Procedure

1. Observe the patient while trying to engage in a conversation.
2. The examiner should scratch his or her head in an exaggerated manner.
3. The arm should be examined for cogwheeling. Attempt to reposture and instruct the patient to "keep your arm loose." Move the arm with alternating lighter and heavier force.
4. Ask the patient to extend his or her arm. Place one finger beneath his or her hand and try to raise it slowly after stating, "Do *not* let me raise your arm."
5. Extend the hand stating, "Do *not* shake my hand."
6. Reach into your pocket and state, "Stick out your tongue. I want to stick a pin in it."
7. Check for grasp reflex.
8. Check the chart for reports from the previous 24-hour period. Check for oral intake, vital signs, and any incidents.
9. Observe the patient indirectly, at least for a brief period each day, regarding the following:
   - Activity level
   - Abnormal movements
   - Abnormal speech
   - Echopraxia
   - Rigidity
   - Negativism
   - Waxy flexibility
   - *Gegenhalten*
   - *Mitgehen*
   - Ambitendency
   - Automatic obedience
   - Grasp reflex

The catatonic syndrome may be divided into primary (psychiatric) and secondary (neuromedical) varieties as well as simple and malignant ones. A malignant catatonia is one accompanied by fever, hyperautonomia, and increased morbidity and mortality. There may be primary as well as secondary simple catatonias and primary and secondary malignant catatonias. An example of a secondary malignant catatonia is NMS.

NEUROLEPTIC MALIGNANT SYNDROME

CASE 2 Neuroleptic Malignant Syndrome

A 56-year-old woman with a history of bipolar disorder was admitted to the hospital after arguing with her husband. She became agitated and combative and required haloperidol (5 mg IM) on two occasions in the emergency room. Her psychiatric history was notable for depression, suicidal ideation, and auditory hallucinations as a teenager that required ECT and long-term treatment with perphenazine, lithium, and imipramine. Soon after her admission, she became psychomotorically withdrawn, hypokinetic, mute, and rigid. Her temperature reached 101.6° F and her CPK level was elevated (2260 U/L). An EEG revealed generalized slowing. A diagnosis of NMS was made, and her medications were discontinued. Her catatonic symptoms responded to lorazepam (2 mg IV, twice). Divalproex sodium and olanzapine were started 2 weeks after the resolution of her NMS.

Epidemiology and Risk Factors

Estimates of the risk for NMS have varied widely (from 0.02% to greater than 3%). Different diagnostic criteria, survey techniques, population susceptibilities, prescribing habits, and treatment settings all contribute to the variance. In one center with a large number of patients treated with antipsychotics, 1 out of every 500 to 1000 patients was thought to develop NMS.[49] Age and sex do not appear to be reliable risk factors, though young adult men may be more prone to extrapyramidal symptoms (EPS). The fact that NMS occurs around the world suggests that environmental factors are not significant predictors. Although it can occur in association with any disorder treated with a neuroleptic, certain conditions may elevate the risk. A history of catatonia is a major risk factor for progression to the malignant catatonia of NMS. Schizophrenia, mood disorders, neuromedical organic brain disorders, alcoholism, and substance abuse disorders have been associated with NMS. The period of withdrawal from alcohol or sedative–hypnotics may increase the risk because of aberrant thermoregulation and autonomic dysfunction. Agitation, dehydration, and exhaustion may also increase the risk. Basal ganglia disorders (e.g., Parkinson's disease, Wilson's disease, Huntington's disease, tardive dystonia) are thought to place patients at increased risk. Low serum iron appears to be a state-specific finding in patients with NMS, and patients with low serum iron in the context of catatonia may be at increased risk for NMS if placed on neuroleptic medications. A history of NMS conveys the risk of recurrence, with up to a third of patients having a subsequent episode when rechallenged. High-potency neuroleptics have been thought to produce an elevated risk and more intense cases of NMS. Clozapine, for example, may cause NMS with significantly less rigidity. Nevertheless, use of atypical antipsychotics can cause NMS. Studies have not supported any particular genetic predisposition, although case reports have implicated an association with cytochrome CYP 2D6.[49]

Clinical Features and Diagnosis

Philbrick and Rummans[20] suggested using the term *malignant catatonia* rather than *lethal catatonia* (because not all cases are lethal) to describe critically ill patients whose disease is marked by autonomic instability or hyperthermia, in contradistinction to patients with simple, nonmalignant catatonia. The causes of malignant catatonia are the same as those of simple catatonia. *Pernicious catatonia* is another term that has been used to describe this catatonic variant.[50]

Consideration of neuroleptics as potential causative agents is important because NMS is currently considered to be a severe form of neuroleptic-induced catatonia. NMS is a syndrome of autonomic dysfunction with tachycardia and elevated blood pressure, fever, rigidity, mutism, and stupor, associated with the use of neuroleptics. Hyperthermia, sometimes in excess of 42° C (108° F), is reported in 98% of the cases.[49] "Leadpipe" rigidity can occur. Parkinsonian features, including cogwheeling, may be present. NMS, most often in the setting of atypical antipsychotic use, can occur without rigidity or CPK elevation. Mental status changes occur in 97% of the cases.[49] Most often, the NMS patient will be in a catatonic state akin to akinetic mutism; such patients may be alert, delirious, stuporous, or comatose. Diagnostic criteria for NMS are found in Table 21–4.[51]

In 1985, Fricchione[52] suggested that NMS is to lethal catatonia what neuroleptic-induced catatonia is to simple catatonia. Moreover, if neuroleptic-induced catatonia is a form of catatonia, then NMS is a form of malignant catatonia with a similar pathophysiology.[52] Goforth and Carroll[53] also noted the overlap of catatonia and NMS. All 27 of their cases of NMS met the DSM-IV diagnostic criteria for catatonia; 24 met stricter research criteria. The authors concluded that the two syndromes were identical, with NMS presenting as a more severe and iatrogenic variant of malignant catatonia. Fink[54] also arrived at this conclusion. Table 21–5 shows the symptoms of catatonia and NMS that overlap.

TABLE 21–4 Diagnostic Criteria for Neuroleptic Malignant Syndrome

Treatment with neuroleptics within 7 days of onset (2 to 4 weeks for depot neuroleptics)
Hyperthermia (≥38° C)
Muscle rigidity
Five of the following:
1. Change in mental status
2. Tachycardia
3. Hypertension or hypotension
4. Tachypnea or hypoxia
5. Diaphoresis or sialorrhea
6. Tremor
7. Incontinence
8. Creatine phosphokinase elevation, or myoglobinuria
9. Leukocytosis
10. Metabolic acidosis

Exclusion of other drug-induced, systemic, or neuropsychiatric illness

Adapted from Caroff SN, Mann SC, Lazarus A et al: Neuroleptic malignant syndrome: diagnostic issues, *Psychiatr Ann* 21:130–147, 1991.

TABLE 21–5 Catatonia and Neuroleptic Malignant Syndrome (NMS): Shared Features

	NMS	CATATONIA
Clinical Signs		
Hyperthermia	Yes	Often
Motor rigidity	Yes	Yes
Mutism	Yes	Yes
Negativism	Often	Yes
Altered consciousness	Yes	Yes
Stupor or coma	Yes	Yes
Autonomic Dysfunction	Yes	Often
Tachypnea	Yes	Often
Tachycardia	Yes	Often
Abnormal blood pressure	Yes	Yes
Diaphoresis	Yes	Yes
Laboratory Results		
Creatine phosphokinase (CPK) elevated	Yes	Often
Serum iron reduced	Yes	Probable
Leukocytosis	Yes	Often

NMS and lethal catatonia appear to be part of a single syndrome, with minor differences in their presentations (e.g., there is a behavioral prodrome and hyperthermia in the pre-stuporous stage of lethal catatonia, as opposed to its occurrence in the stage with stupor and rigidity in NMS). Indeed, although early reports suggested that the level of CPK is increased in NMS and not in primary lethal catatonia, a survey of 13 cases of primary malignant catatonia revealed that CPK levels were elevated in all nine of the cases in which they were tested.[20]

Encephalograms are abnormal in roughly half of cases, most often with generalized slowing that is consistent with encephalopathy.[49] In contrast, CT of the brain and cerebrospinal fluid (CSF) studies are normal in 95% of NMS cases.[49]

In 1991, Rosebush and Mazurek[55] found decreased levels of serum iron in patients with NMS and suggested a role for lowered iron stores in the reduction of DA receptor function. Supporting the hypothesis of NMS as a severe variant of catatonia, Carroll and Goforth[56] reported a similar decrease of serum iron in three of 12 cases of catatonia, with NMS developing in two of the three cases. The third was without neuroleptic exposure and did not progress to NMS.[56] Lee[57] prospectively studied 50 patients with catatonia; serum iron was measured in 39 of the episodes. The low serum iron level found in 14 cases (44%) was associated with lethal catatonia and with a poorer response to benzodiazepines. In seven episodes of lethal catatonia, a low level of serum iron was detected. Neuroleptics were used in five cases, and all five progressed to NMS.

Providing further support for the relationship between primary psychogenic catatonias and neuroleptic-induced catatonias, White and Robins[58] reported five consecutive cases of NMS that were each preceded by a catatonic state; none of the patients had received prior neuroleptics and none had a prior psychiatric history. White[59] concluded that NMS and lethal catatonia are not separate disorders. Mann and colleagues[60] also viewed NMS as a neuroleptic-induced iatrogenic form of organic lethal catatonia.

Most commonly, NMS develops over a few days, often beginning with rigidity and mental status changes followed by signs of hypermetabolism. The course is usually self-limited, lasting 2 days to 1 month (once neuroleptics are stopped and supportive measures are begun).[49] Persistent cases are usually secondary to the use of depot neuroleptics, and ECT is highly effective in these cases. Although the mortality rate has been reduced through better recognition and management, there is still an approximately 10% risk of death.[49] Myoglobinuric renal failure and rhabdomyolysis may have long-term consequences.

Neuropathophysiology

Catatonia is thought to reflect a disruption in basal ganglia thalamocortical tracts (including the motor circuit [rigidity], the anterior cingulate–medial orbitofrontal circuit [akinetic mutism and, perhaps through lateral hypothalamic connections, hyperthermia and dysautonomia], and the lateral orbitofrontal circuit [imitative and repetitive behaviors]) (Figure 21–1).[60] Such disruption may lead to a relative state of hypodopaminergia in these circuits through reduced flow in the medial forebrain bundle, the nigrostriatal tract, and the tuberoinfundibular tract. DA activity in the dorsal striatum and in the ventral striatum and paralimbic cortex is thus reduced, perhaps secondary to reduced $GABA_A$ inhibition of $GABA_B$, substantia nigra, and ventral tegmental area interneurons. This would lead to a dampened DA outflow, whereas activation at $GABA_A$, through use of agonists such as lorazepam, would indirectly disinhibit DA cell activity.[3,52] Another possible site of pathophysiology involves reduced $GABA_A$ inhibition of frontal corticostriatal tracts, leading to *N*-methyl-D-aspartate (NMDA) changes in the dorsal striatum, and indirectly in the substantia nigra and ventral tegmental area.[3] Multiple etiologies, if they affect the basal ganglia, thalamus, or paralimbic or frontal cortices, will have the potential to cause those neurotransmitter alterations that will disrupt basal ganglia thalamocortical circuits, leading to the phenomenology of catatonia.

In the mesostriatal and mesocorticolimbic systems, the long feedback loops from DA neurons are regulated by GABA pathways. Given its extensive projections on both limbic and motor structures, the nucleus accumbens may be a hub for the linkage between motivation and movement.[61] By extrapolating from animal evidence (i.e., $GABA_A$ antagonists lead to catalepsy, and $GABA_A$ agonists protect against catalepsy), and from the hypothesis that neuroleptic-induced catatonia may result from reduced DA and $GABA_A$ activity in the mesostriatum, it has been proposed that primary psychogenic catatonia results from a similar destabilization.[52] $GABA_A$ agonists could be restorative by inhibiting the pars reticulata's inhibitory $GABA_B$ neurons, resulting in disinhibition of the neighboring pars compacta's DA cells with a resultant striatal DA agonism.[52]

Electroconvulsive therapy may be effective for catatonia on the basis of this GABA-DA interaction. Sackeim and associates[62] proposed that the neural state following ECT is produced by increased GABA transmission. They cited animal studies in which the concentration of GABA in the striatum became elevated after ECT. Some investigators have believed that ECT may increase the sensitivity

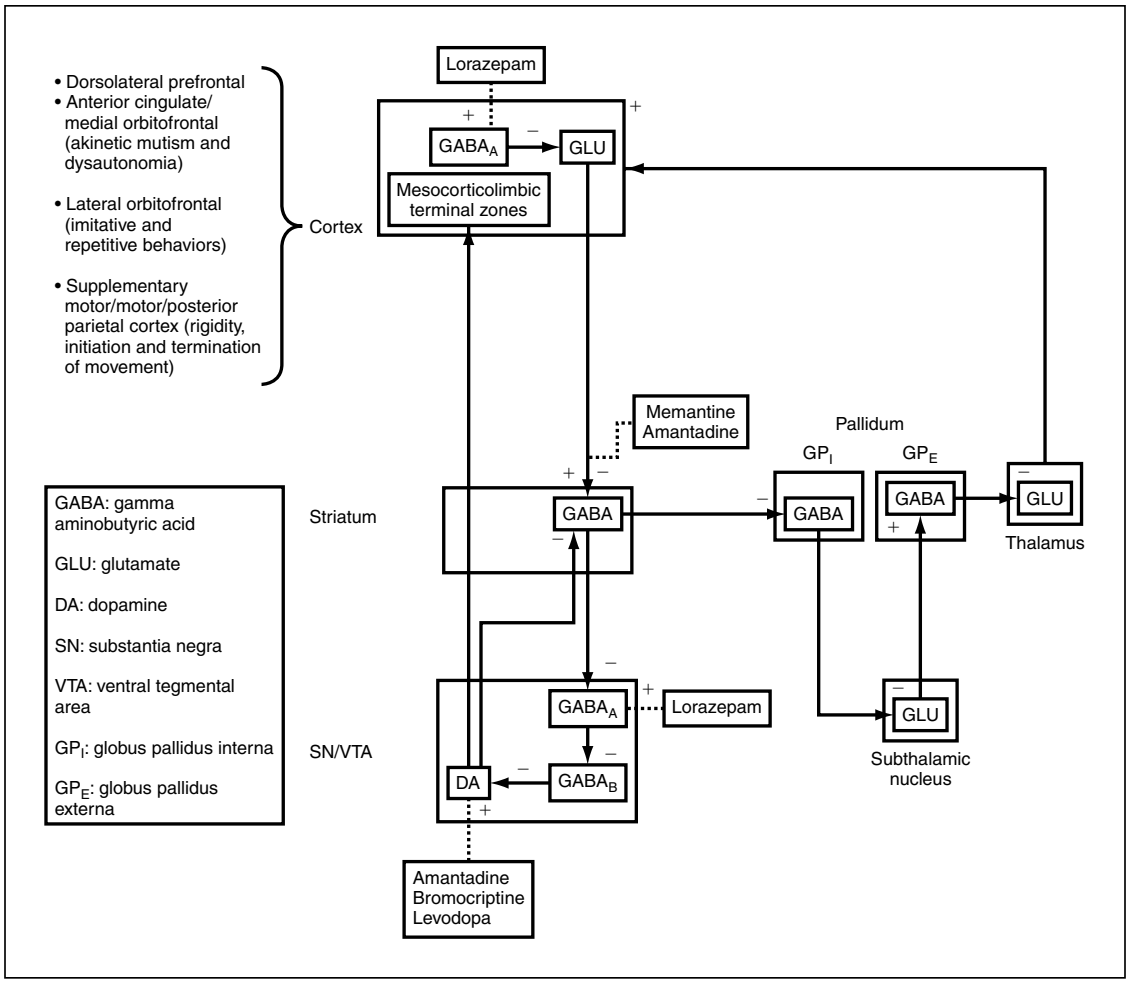

Figure 21–1. Basal ganglia thalamocortical circuits and catatonia: a candidate loop. (*From Fricchione GL, Huffman JC, Bush G et al*: Catatonia, neuroleptic malignant syndrome, and serotonin syndrome. *In Stern TA, Rosenbaum JF, Fava M et al, editors*: *Massachusetts General Hospital comprehensive clinical psychiatry*, *Philadelphia, 2008, Mosby, pp 761–771*.)

of postsynaptic DA receptors to available DA. An animal model of catatonia supports this hypothesis. Stevens and colleagues[63] instilled bicuculline, a $GABA_A$ antagonist, into the ventral tegmentum of cats; slinking, hiding, looking fearful, staring, sniffing, and taking a catatonic stance were noted. Waxy flexibility of the limbs developed and animals stood still and stared for extended periods.[63] When bicuculline was given in the ventral tegmentum after systemic haloperidol, marked dystonic postures were produced. Picrotoxin, an antagonist at the chloride channel of the benzodiazepine-$GABA_A$ recognition site, was administered in the ventral tegmental area as well. Smaller doses induced fear and staring, whereas larger doses produced prolonged severe dystonia, especially following haloperidol. Microinjection of the $GABA_A$ agonist muscimol into the ventral tegmental area of the rat caused a dose-dependent motor activation. This response was antagonized by administration of bicuculline or by haloperidol administration.[64] Neuroleptics reduce the conditioned avoidance response, which is thought to be secondary to decreased DA activity in the nucleus accumbens and the striatum. Stress has been shown to increase medial prefrontal cortical DA release, which in turn is thought to reduce DA activity in subcortical DA terminal fields in the mesolimbic and mesostriatal systems.[65,66] Friedhoff and coworkers[67] were able to show that rats undergoing twice-daily tail-shock stress for 8 days displayed conditioned avoidance response inhibition, along with a reduction in nucleus accumbens DA use. The findings provided support for a restitutive hypothesis involving an endogenous DA-dependent system that mimicked the effects of neuroleptics in the context of repeated stress–induced medial prefrontal cortical hyperdopaminergia. When such a system down-regulates too much because of neurologic or medical insult, primary psychiatric dysfunction, or neuroleptic medication, or a combination of all three, catatonic stupor may occur. These state changes may be tied to a genetic trait vulnerability for acute NMS, perhaps having to do with defective calcium regulation that leads to a dysregulated hyperactive sympathetic nervous system response in the presence of severe psychic stress and neuroleptic-induced hypodopaminergia.[68] NMS has been postulated to be secondary to DA blockade in the mesostriatum (which is responsible for the motor disorder), the mesolimbic

system (which is responsible for the mutism), and the preoptic anterior hypothalamus (which is responsible for the hyperthermia).[69]

A "universal field hypothesis" of catatonia and NMS has been proposed.[70] It speculates that some type of neurochemical predisposition, be it low activity at the D_2 or $GABA_A$ receptor for which most evidence exists, NMDA receptor dysregulation, or even high $5\text{-}HT_{1A}$ receptor activity, can modulate the circuits involved in catatonia and NMS and lower the threshold for the syndrome. In any event, the DA and $GABA_A$ disturbances in the basal ganglia thalamocortical circuits appear to be the primary physiologic derangements.

By examining the nature of basal ganglia thalamolimbic-cortical loops, we can hypothesize why such a wide array of neuromedical and psychiatric etiologies can present with the catatonic syndrome and why the treatments discussed later may be therapeutic (see Figure 21–1).

Management and Treatment

Whatever its etiology, catatonia is accompanied by significant morbidity and mortality from systemic complications. In addition, many of the physical illnesses responsible for catatonia can be hazardous (Table 21–6). Thus, timely diagnosis and treatment are essential. If a neurologic or medical condition is found, then treatment for that specific illness is indicated. Agents thought to exacerbate catatonia, including antipsychotic medications and dopamine-blocking drugs (e.g., metoclopramide), should be discontinued, and if dopamine agonists were recently stopped, they should be restarted. Occasionally psychiatric therapies are used to treat catatonia as a secondary behavioral manifestation of a medical illness. For example, lorazepam has been found to be effective in certain cases of catatonia secondary to medical illness, and it has become the first-line treatment for catatonia regardless of etiology.[25] In addition, ECT has been used to treat lupus patients with catatonia,[55] and other secondary catatonias, and remains the most effective treatment for catatonia.[28] Response to treatment is usually good for individuals with acute primary catatonia; 67% are improved by time of discharge.[71] Patients with manic features respond particularly well. Rates of long-term recovery range from 33% to 75%.[1] Fatality rates of 50% or more were the rule before the introduction of ECT.[72] Two or three ECT treatments are usually sufficient to lyse the catatonic state, although a course of four to six treatments is usually given to prevent relapse, and 10 to 20 treatments are sometimes needed in difficult cases. Nevertheless, patients' families are often reluctant to agree to ECT because of the stigma associated with it and the fear of side effects.

Intravenous amobarbital can be rapidly successful in some patients with catatonic stupor.[73] However, these effects tend to be short-lived, and there is a narrow therapeutic window. One approach is to administer 50 to 75 mg/mL IV at 1 mL/min for first 2 minutes; each additional 1 mL is given over 1 minute, with a 1-minute wait period to assess effect. Throughout the intervention, efforts should be made to keep the patient talking. When yawning, speech slurring, or nystagmus begins, stop the drug and check for orientation, memory, and a history of illness. Many centers now require practitioners to have certification in conscious sedation before performing an amobarbital interview. Furthermore, in one study, only 50% of psychiatric patients with catatonic mutism responded to an amobarbital interview.[74] Repeated IV doses lead to oversedation; amobarbital administered orally does not appear to prolong its benefits.

In the past, neuroleptics were frequently used to treat catatonia. In addition to the variable response of catatonia to these drugs, neuroleptics may complicate matters; their use also has precipitated catatonic reactions and NMS.[19] At times, higher doses of antipsychotics are used to treat psychosis and agitation, but it may worsen catatonia. Moreover, among the 292 patients with malignant catatonia reviewed by Mann and associates,[18] 78% of those treated with a neuroleptic alone died, compared with an overall mortality rate of 60%. In 18 cases reviewed by Philbrick and Rummans,[20] only one patient received a neuroleptic alone—this patient also died. Therefore, neuroleptics may be contraindicated during an acute episode of malignant catatonic stupor.[18,20]

In 1983, Lew and Tollefson[75] reported on the usefulness of IV diazepam, and, at the same time, Fricchione and colleagues[76] reported on the benefit of IV lorazepam given to patients in neuroleptic-induced catatonic states (including NMS) and suggested its use in primary psychiatric catatonia. In 1984, McEvoy and Lohr[77] successfully administered IV diazepam to two catatonic patients whose conditions

TABLE 21–6 Some Medical Complications Associated with Catatonia

Simple Nonmalignant Catatonia
Aspiration
Burns
Cachexia
Dehydration and its sequelae
Pneumonia
Pulmonary emboli
Thrombophlebitis
Urinary incontinence
Urinary retention and its sequelae
Malignant Catatonia
Acute renal failure
Adult respiratory distress syndrome
Cardiac arrest
Cheyne–Stokes respirations
Death
Disseminated intravascular coagulation
Dysphagia due to muscle spasm
Electrocardiographic abnormalities
Gait abnormalities
Gastrointestinal bleeding
Hepatocellular damage
Hypoglycemia (sudden and profound)
Intestinal pseudo-obstruction
Laryngospasm
Myocardial infarction
Myocardial stunning
Necrotizing enterocolitis
Respiratory arrest
Rhabdomyolysis and sequelae
Seizures
Sepsis
Unresponsiveness to pain

Modified from Philbrick KL, Rummans TA: Malignant catatonia, *J Neuropsychiatry Clin Neurosci* 6:1–13, 1994

had not improved with haloperidol regimens (that had been initiated after the onset of catatonia). Rosebush and co-workers[25] reported that 80% of 15 catatonic episodes showed a complete and dramatic response within 2 hours of lorazepam treatment (1 to 2 mg oral, IM, or IV); one showed a partial response, and two showed no response. Side effects were uncommon. Catatonia related to a CNS abnormality was evident in 8 of 12 responders, which suggested that a beneficial response to lorazepam was not limited to patients with psychogenic catatonia.

Bush and co-workers[78] studied the use of lorazepam and ECT in the treatment of catatonia. Twenty-eight prospectively identified patients entered their open-trial protocol (which included parenteral lorazepam, oral lorazepam [1 to 2 mg orally two to three times a day], or both for 3 to 5 days, with referral for ECT if lorazepam failed). Of 21 patients (76%) who received a complete trial of lorazepam (11 received an initial 2-mg IV challenge), 16 had resolution of catatonic signs. All four patients referred for ECT (after failing lorazepam therapy) responded promptly. Bush and co-workers[78] specifically suggested a trial of lorazepam 2 mg IM or IV, with monitoring of respiratory status. Sometimes higher doses were required. With a drug distribution that is less rapid and less extensive, a relatively high plasma level can be maintained, thus prolonging the clinical benefit of IV lorazepam.[2] Given intramuscularly in the deltoids, lorazepam is more reliably absorbed than other IM benzodiazepines.[2] A switch to regular doses of lorazepam or diazepam maintains the therapeutic effect. Lorazepam given orally or via nasogastric tube in a daily dose of 6 to 20 mg also has been used effectively. Diazepam 10 to 50 mg/day or clonazepam 1 to 5 mg/day also has been used successfully, as has midazolam.[2] If lorazepam is unsuccessful within 5 days, ECT should be considered.[2]

Alternatives to ECT in simple catatonias include zolpidem 5 to 10 mg orally, which has been used as a test for catatonia, [79] amantadine 100 mg twice a day orally, memantine 5 to 10 mg twice a day orally,[80,81] and topiramate 100 mg twice a day orally.[82] Carbamazepine, valproate, calcium channel blockers, anticholinergics, lithium, thyroid medication, and corticosteroids have each had anecdotal success in catatonia.[20] In 1985, when it was suggested that psychogenic catatonia and neuroleptic-induced catatonia (including NMS) shared a common pathophysiology, use of specific dopaminergic or GABA-ergic drugs in psychogenic catatonia untreated by neuroleptic medication also was suggested.[52] Accordingly, it is of interest that 2.5 mg of oral bromocriptine twice a day was used successfully in a 16-year-old girl with catatonia that preceded neuroleptic exposure,[83] and that Rogers[84] used L-dopa to treat a patient with a 50-year history of severe catatonic schizophrenia (off neuroleptics for 5 years) with improvement in catatonic akinesia and without worsening of positive symptoms. Neppe[85] also has successfully used L-dopa to treat catatonic stupor.

In a study of lorazepam treatment for NMS, rigidity and fever abated in 24 to 48 hours, whereas secondary features of NMS dissipated within 64 hours (without adverse effects).[86] If lorazepam does not briskly reverse the lethal catatonia, the clinician should not wait for 5 days to begin ECT. Mann and associates[87] found that in one series of cases of lethal catatonia where ECT was used, 40 of 41 patients survived. In another series,[62] although 16 out of 19 patients who had received ECT within 5 days of symptom onset survived, none of the 14 patients who had received ECT after 5 days after symptom did.

Philbrick and Rummans[20] reviewed 18 cases of lethal catatonia and found that 11 out of 13 patients treated with ECT survived, whereas only one out of five not treated with ECT died. In terms of NMS, 39 reported cases of ECT treatment have been reported; 34 of them improved. The message is clear: When a patient presents with malignant catatonia of any type, ECT should be used expeditiously. Although an initial trial of lorazepam, a dopaminergic agent, or both, is reasonable for malignant catatonia, ECT should be instituted early (i.e., within 5 days) if a medication trial is unsuccessful. Adrenocorticotropic hormone and corticosteroids also have been reported to work in cases of lethal catatonia.[18] Dopaminergic agents, bromocriptine, and amantadine anecdotally have been used successfully in NMS.[88] In a retrospective review of 734 cases, Sakkas and associates[89] concluded that these agents and the muscle relaxant dantrolene led to improvement; bromocriptine and dantrolene also were associated with a significant reduction in the mortality rate. However, in a prospective study of 20 patients, Rosebush and colleagues[90] found that bromocriptine and dantrolene were not efficacious. Another DA agonist, lisuride, has been used intravenously with success in four patients with NMS, three of whom had failed to respond to other dopaminergic agents.[91]

Table 21–7 outlines recommendations for the treatment of simple and malignant (including NMS) catatonias, and Table 21–8 reviews management principles.

The treatment strategy for patients who have catatonia secondary to schizophrenia may be challenging, because the catatonia found in those with schizophrenia can at times be less responsive to lorazepam. In these patients, amantadine and more recently memantine have shown some effectiveness in isolated cases, suggesting that NMDA antagonists may add some benefit.[92,93]

Even if lorazepam has been helpful in lysing the catatonic state, the patient is often left with psychotic symptoms and may eventually need antipsychotic medications. A reasonable approach is to try an atypical neuroleptic while maintaining the patient on lorazepam as a buffer against reemergence of catatonia. Although atypical antipsychotics may be less likely to worsen catatonia than typical antipsychotics, all atypical neuroleptics have the potential to worsen catatonic symptoms, and there are no clear recommendations in the literature about which atypical is superior to use in the treatment of a patient with psychosis and catatonia. Aripiprazole, a unique atypical antipsychotic given its partial dopamine agonism, may be preferred in the setting of catatonia, and it has been used successfully, along with IV lorazepam, in the treatment of psychosis and catatonia.[94] However, there have also been case reports of aripiprazole causing NMS. Limitations for the treatment of concurrent schizophrenia with catatonic features include the lack of randomized clinic trials, as most recommendations stem from case reports. Long-term dosing and optimal duration of treatment have yet to be established, and the psychiatrist must rely on clinical judgment.

Rechallenging a patient who has had NMS with an antipsychotic is controversial. Most investigators suggest

TABLE 21–7 Treatment of Simple and Malignant Catatonia

A. Test for catatonia. Lorazepam 1 to 2 mg IV or zolpidem 5 to 10 PO mg may result in temporary relief.
B. *Simple catatonia* (including neuroleptic-induced catatonia): lorazepam* 1 to 4 mg IV/IM/PO trial followed by 3 to 20 mg/day in divided doses, or diazepam 5 to 20 mg followed by 10 to 40 mg/day. Monitor for respiratory depression.
   → If still catatonic, consider adding dopamine (DA) agonist.
   → If still catatonic, electroconvulsive therapy (ECT).†
C. *Malignant catatonia* (including neuroleptic malignant syndrome [NMS]):
   1. Lorazepam IV trial expeditiously (effective in 75% of NMS cases). May add dantrolene ± DA agonist, but less evidence for these.
   2. If still catatonic and especially if temperature is higher than 102° F, or if there is severe encephalopathy, ECT should be instituted before day 5 of syndrome, if possible.

Modified from Fricchione G, Bush G, Fozdur M et al: The recognition and treatment of the catatonic syndrome, *J Intensive Care Med* 12:135–147, 1997.
*Lorazepam effectiveness, 80% in one study,[25] 76% in another.[78]
†ECT effectiveness: 82% to 96% in 5 studies.

that antipsychotics should not be given until at least 2 weeks after an episode of NMS has resolved, and that rechallenge should be with an atypical or with a typical of a lower potency.

Prognosis and Complications

Catatonia is a fascinating condition that graphically links emotion and behavior, motivation, and movement. For patients with catatonia, the long-term prognosis is fairly good in almost half the cases.[95] Those with an acute onset, depression, or a family history of depression have a better prognosis.[96] Periodic catatonias can have good short- and long-term prognoses. However, given the potential morbidity and mortality, concerted efforts at supportive care are essential to avoid the myriad complications that are associated with simple catatonia and more so with malignant catatonia (see Table 21–6).

When catatonia is of the malignant variety, treatment should take place in the intensive care unit (ICU). All potential offending agents, especially neuroleptics and DA blockers (e.g., metoclopramide), should be discontinued. If antiparkinsonian dopaminergic agents have recently been discontinued or tapered, they should be reinstituted. Lorazepam (or another benzodiazepine) should be used in an effort to lyse catatonia, be it simple or malignant. ECT should be considered early because it is the definitive treatment for catatonia in the acute setting, and it can be lifesaving, especially in malignant instances of the syndrome. When any patient with malignant catatonia is first seen, the surrogate decision-maker should be approached in anticipation of the need for ECT should a lorazepam trial fail. Maintenance ECT may improve long-term prognosis.

If the condition is not life-threatening and if ECT is not available and lorazepam has not resolved the catatonia, DA agonists or dantrolene or other medications mentioned earlier may be tried in addition to supportive measures. If the condition is life-threatening, as is the case with malignant catatonia, and if lorazepam has not worked and ECT is not available, expeditious transfer to a facility where ECT is performed is appropriate.

TABLE 21–8 Principles of Management of Catatonia

1. Early recognition is important. Once catatonia has been diagnosed, the patient must be closely observed and vital signs taken frequently.
2. Supportive care is essential. Such care involves hydration, nutrition, mobilization, anticoagulation (to prevent thrombophlebitis), and precautions against aspiration.
3. Discontinue antipsychotics or other drugs, such as metoclopramide, which can cause or worsen catatonia.
4. Restart recently withdrawn dopamine agonists, especially in patients with parkinsonism.
5. Institute supportive measures (e.g., a cooling blanket if hyperthermia is present, or parenteral fluids and antihypertensives or pressors if autonomic instability emerges and if malignant catatonia is suspected).
6. Maintain a high index of suspicion for the development of medical complications and for new medical problems.

Modified from Philbrick KL, Rummans TA: Malignant catatonia, *J Neuropsychiatry Clin Neurosci* 6:1–13, 1994.

SEROTONIN SYNDROME

CASE 3 Serotonin Syndrome

A 69-year-old woman with a history of depression partially responsive to paroxetine 40 mg/day had her dose increased to 60 mg/day; 2 weeks later, buspirone 5 mg tid was added, along with trazodone 100 mg for sleep. She became confused, diaphoretic, febrile (to 101.2° F), hyperreflexic, and mildly rigid and was admitted to the hospital. Paroxetine, prazodone, and buspirone were discontinued. Over the next 2 days, her condition improved (with acetaminophen and supportive care).

Definition

Serotonin is a neurotransmitter involved in many psychiatric disorders, and many pharmacologic agents have been designed that affect central serotonergic tone. As the serotonin level increases, it is likely to have certain nervous system effects, including toxicity when available in excess. Heightened clinical awareness is necessary to prevent, recognize, and intervene when a toxic syndrome secondary to serotonin excess emerges. Serotonin syndrome, as it is called, most commonly occurs as a result of an interaction between serotonergic agents and monoamine oxidase inhibitors (MAOIs). Signs of SS include mental status changes (e.g., confusion, anxiety, irritability, euphoria, dysphoria), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, incontinence), behavioral manifestations (e.g.,

restlessness and agitation), neurologic findings (e.g., ataxia or incoordination, tremor, myoclonus, hyperreflexia, ankle clonus, muscle rigidity), and autonomic nervous system abnormalities (e.g., hypertension, hypotension, tachycardia, diaphoresis, shivering, sialorrhea, mydriasis, tachypnea, hyperthermia).[97,98]

Epidemiology

The incidence of SS is unknown. There are no data to suggest that gender differences confer any particular vulnerability to the syndrome. Given the overlap of symptoms with NMS, SS is often mistaken for it and thus may be underreported. The existence of the syndrome in varying degrees also may confound its recognition, as can unawareness on the part of the majority of physicians.[99] SS most often occurs in individuals being treated with psychotropics for a psychiatric disorder. It occurs in about 14% to 16% of SSRI-overdosed patients.[100]

Most often, SS involves some combination of an SSRI, an MAOI, an antiparkinsonian agent, and lithium. At the outset, patients develop a peripheral tremor, confusion, and ataxia; these features are followed by systemic signs (e.g., hyperreflexia, diaphoresis, shivering, agitation). If the condition becomes more severe, fever, myoclonic jerking, and diarrhea may develop. The syndrome can last from hours to days after the offending agents have been stopped and supportive treatment has been initiated.

Clinical Features and Diagnosis

As with NMS, taking a detailed history is crucial. Use of two or more serotonergic agents confers a greater risk of developing SS. Obtaining a history of neuroleptic use can be especially important, because NMS shares many clinical features with SS, as do other toxic syndromes (Table 21–9).

Based on his review of 38 cases, Sternbach[101] proposed the first operational definition of the syndrome in humans. Diagnosis requires the following three criteria:

1. A serotonergic agent is added to an established medication regimen, or its dosage level is increased, in addition to at least three of the following features: mental status changes, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, and incoordination.
2. Other etiologies need to be ruled out.
3. A neuroleptic must not have been started or increased in dosage prior to the onset of the signs and symptoms listed previously.

Based on a review of other diagnostic criteria, Keck and Arnold[97] modified Sternbach's criteria to include mental status changes, agitation, restlessness, myoclonus, hyperreflexia, diaphoresis, tremor, shivering, incoordination, autonomic nervous system dysfunction, hyperthermia, and muscle rigidity. Most recently, the Hunter Serotonin Toxicity Criteria were proposed.[102] If a patient has been exposed to a serotonergic drug within the past 5 weeks and spontaneous clonus emerges, the patient has SS. If there is inducible clonus or ocular clonus plus either agitation or diaphoresis, SS is present. If there are tremor and hyperreflexia, SS can be diagnosed. If there are hypertonicity, temperature greater than 38° C (100.4° F), and either ocular or inducible clonus, SS is present. This approach to SS diagnosis may be more sensitive to serotonin toxicity and less prone to produce false-positive cases.

There is a temporal relationship between the start of pharmacotherapy and the development of the syndrome. The syndrome ranges from mild to severe, with a mildly affected patient showing restlessness, tremor, tachycardia, shivering, diaphoresis, and the start of hyperreflexia. Moderately severe cases show tachycardia, hypertension, and fever, sometimes as high as 40° C (104° F). There are also mydriasis, strong bowel sounds, hyperreflexia, and clonus (greater in the lower extremities than the upper ones).

TABLE 21–9 Comparison of Serotonin Syndrome with Neuroleptic Malignant Syndrome

FEATURE	SEROTONIN SYNDROME	NEUROLEPTIC MALIGNANT SYNDROME
Temperature	Hyperthermia variable	Hyperthermia
Mental status	Anxiety	Coma
	Coma	Confusion
	Confusion	Delirium
	Delirium	Stupor
	Euphoria	
	Irritability	
	Stupor	
Neurologic	Ankle clonus	Hyperreflexia (uncommon)
	Hyperreflexia, Incoordination	Muscle rigidity
	Muscle rigidity variable	Tremor
	Myoclonus	
	Tremor	
Behavioral	Agitation	Agitation
	Restlessness	Restlessness
Autonomic	Diaphoresis	Diaphoresis
	Hypertension/ hypotension	Hypertension/ hypotension
	Incontinence	Incontinence
	Mydriasis	Mydriasis
	Shivering	Sialorrhea
	Sialorrhea	Tachycardia
	Tachycardia	Tachypnea
	Tachypnea	
Gastrointestinal	Diarrhea	
	Nausea	
	Vomiting	
Laboratory	Elevated (uncommon)	Elevated (common)
	Creatine phosphokinase (CPK)	CPK
	White blood cell count (WBC)	WBC
	Liver function tests (LFTs)	LFTs

Modified from Keck PE, Arnold LM: The serotonin syndrome, *Psychiat Ann* 30:333–343, 2000, p 339.

Horizontal ocular clonus is also seen in moderately severe cases, as well as mental status changes of agitation, pressured speech, and autonomic hyperactivity. Head rotation movement with neck extension has also been reported. In severe cases, there are severe autonomic hyperactivity and severe hyperthermia with temperatures sometimes over 41.1° C (106° F). There is an agitated delirium accompanied by severe muscular rigidity, again greater in the lower extremities. This severe hypertonicity may obscure the appearance of clonus and hyperreflexia and thereby confound the diagnosis.

Laboratory abnormalities are mostly nonspecific or are secondary to the medical complications of the syndrome. A complete laboratory evaluation is nevertheless essential to rule out other causes for the signs and symptoms that are shared with SS. Leukocytosis, rhabdomyolysis, and liver function test abnormalities have all been reported in patients with SS, along with hyponatremia, hypomagnesemia, and hypocalcemia. These latter disturbances are thought to be related to fluid and electrolyte abnormalities. Disseminated intravascular coagulation (DIC) also has been reported in SS. Acute renal failure secondary to myoglobinuria can occur and has been associated with fatalities, as has DIC.

It is interesting to note that certain secreting tumors like carcinoid and oat cell carcinoma have been associated with SS. X-ray examinations and imaging of the abdomen and lung may sometimes be helpful in working up SS. An EEG and neuroimaging are often useful in uncovering a seizure disorder or another neurologic condition as well.

The most common drug interactions associated with SS include combinations of MAOI and SSRI, MAOI and tricyclic antidepressants, and MAOI and venlafaxine. In general, when an SSRI is used in combination with an MAOI, an SS is more likely to occur. Drugs associated with SS are included in Table 21–10.

Overdoses of MAOIs have also caused SS. Because of the potential problems of using an MAOI and any medicine with serotonergic properties, caution on the part of the prescribing physician is required. A 2-week washout interval after discontinuation of an MAOI is required before starting any serotonergic medications. In the case of fluoxetine discontinuation, there should be a washout period of at least 5 weeks before an MAOI is initiated.

TABLE 21–10 Central Nervous System Serotonergic Agents

Enhanced Serotonin Synthesis
L-Tryptophan
Increased Serotonin Release
Amphetamines
Cocaine
Dextromethorphan
Fenfluramine
Meperidine
Methylenedioxymethamphetamine
Sibutramine
Serotonin Agonists
Buspirone
Dihydroergotamine (DHE)
Lithium
Meta-chlorophenylpiperazine (mCPP)
Sumatriptan
Trazodone
Inhibited Serotonin Catabolism
Isocarboxazid
Moclobemide
Phenelzine
Selegiline
Tranylcypromine
Inhibited Serotonin Reuptake
Amitriptyline
Bromocriptine
Clomipramine
Desipramine
Dextromethorphan
Fenfluramine
Fluoxetine
Fluvoxamine
Imipramine
Meperidine
Mirtazapine
Nefazodone
Nortriptyline
Paroxetine
Pethidine
Sertraline
Tramadol
Trazodone
Venlafaxine

Modified with permission from Keck PE, Arnold LM: The serotonin syndrome, *Psychiat Ann* 30:333–343, 2000, p 336.

Pathophysiology

In both animal and human studies, the role of 5-HT has been implicated in the pathogenesis of SS. Nucleus raphe serotonin nuclei (located in the midbrain and arrayed in the midline down to the medulla) are involved in mediating thermoregulation, appetite, nausea, vomiting, wakefulness, migraine, sexual activity, and affective behavior. The animal model of SS seems to be associated with receptors in the lower brainstem and spinal cord. Ascending serotonergic projections are likely to play a role, particularly in hyperthermia, mental status, and autonomic changes. The 5-HT_{2A} and 5-HT_{1A} receptors appear to be overactive in this condition,[100] which has led some to use 5-HT_{1A} antagonists in the management of SS. There also appears to be CNS norepinephrine overactivity. This is clinically significant because clinical outcomes may be associated with hypersympathetic tone.[99] The roles of catecholamines and 5-HT_2 and 5-HT_3 receptor interactions are unclear, as are the contributions of glutamate, GABA, and DA.

Management and Treatment

No prospective studies have looked at treatment of SS. Recommendations for treatment are based solely on anecdotes. SS is often self-limited, and removal of the offending agents frequently results in resolution of symptoms within 24 hours. Therefore, the initial step in managing

SS is to discontinue the suspected offending agent or agents. The next step is to provide supportive measures to prevent potential medical complications. These supportive measures include the use of antipyretics and cooling blankets to reduce hyperthermia, monitoring and support of the respiratory and cardiovascular systems, IV hydration to prevent renal failure, use of clonazepam for myoclonic jerking, use of anticonvulsants if seizures arise, and use of hypertensive agents (such as nifedipine) for significantly elevated blood pressures. The syndrome rarely leads to respiratory failure. When it does, it usually is because of aspiration, and artificial ventilation may be required.

Benzodiazepine management of agitation, even when mild, is essential for patients with SS. This is because benzodiazepines, such as diazepam and lorazepam, can reduce autonomic tone and temperature and thus may have positive effects on survival.[99] Physical restraints should be avoided if at all possible because muscular stress can lead to lactic acidosis and elevated temperature.

Specific 5-HT receptor antagonism has occasionally been advocated for the treatment or prevention of the symptoms associated with SS. Cyproheptadine (4 to 24 mg/day) has been used.[99] Ketanserin a 5-HT_2 antagonist and propranolol, which has 5-HT_{1A} receptor-blocking properties, have been used in a small number of cases. For the management of hypertension, nitroprusside and nifedipine, and for tachycardia, esmolol, have been advocated.[99] Because the rise in temperature is muscular in origin, antipyretics are of no use in SS, and paralytics are required when fevers are high.

Prognosis and Complications

The SS occurs as a toxic state secondary to serotonin excess produced by high doses or combinations of serotonergic medications. It usually begins soon after the addition of a serotonin agent or an increase in the dose of one. This syndrome is often mild and goes unrecognized, so it may not be as rare as portrayed; it also is self-limiting. Symptoms often disappear soon after the offending agents are discontinued. When severe, SS can lead to death from medical complications, and supportive measures are required. Nonspecific serotonin receptor antagonists may be helpful in the treatment of the SS. Prevention, early recognition, and intervention benefit from a heightened clinical awareness of medications that can cause serotonin excess.

In SS, rhabdomyolysis is the most common and serious complication; it occurs in roughly 25% of the cases.[49] Generalized seizures occur in approximately 1%, with 39% of these patients dying. Myoglobinuric renal failure accounted for roughly 5% of medical complications, as did DIC. Nearly two thirds of those with DIC died.

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Patients with Disordered Sleep

22

Patrick Smallwood, M.D.
Davin K. Quinn, M.D.
Theodore A. Stern, M.D.

Scholars have long sought the cause and nature of sleep and sleep disorders, yet theories have far exceeded clear facts. Plato, for example, believed that sleep was caused by vapors arising from the stomach and condensing in the head, and Hippocrates believed that sleep was the result of blood and its warmth retreating into the body. Sixteenth- and 17th-century scholars debated whether sleep was induced by oxygen deprivation, accumulated toxins, or the daily thickening of blood that impaired spirits from entering the nerves.[1] Despite these age-old theories, only in recent years have the mysteries of sleep been slowly unraveled. Indeed, we now know that sleep is an active biochemical process complete with various physiologic markers, stages, and patterns that, like vital signs, provide a basic indication of overall well-being. This chapter examines the biological and psychiatric aspects of normal and disordered sleep, followed by a brief discussion of the diagnosis and treatment of common sleep disorders.

SLEEP STAGES AND NORMAL SLEEP

Aserinsky and Kleitman (1953) were the first to investigate eye movements during sleep. Kleitman postulated that depth of sleep could be assessed through eye motility, and he and Aserinsky began testing this hypothesis through direct observation of eye movements of infants during sleep.[2] They noted slow rolling eye movements during the early stages of sleep that disappeared as sleep progressed, and they saw periods of rapid eye movements associated with irregular breathing and increased heart rate.[2,3] They coined the terms *non–rapid eye movement* (NREM) to indicate the slow rolling rhythmic eye movements and *rapid eye movement* (REM) to indicate the fast erratic eye movements. In 1957 Kleitman and Dement discovered that REM and NREM sleep occurred cyclically throughout the night and named this overall NREM–REM pattern *sleep architecture*.[2,3]

Polysomnography

Polysomnography is the gold standard method for evaluating disordered sleep. It involves simultaneously recording multiple physiologic variables in a standardized fashion known as the *polysomnogram* (PSG).[4] The parameters recorded by the PSG include, but are not limited to, the following:

- Electroencephalogram (EEG): A recording of the electrical activity of cortical neurons via scalp electrodes that are placed in standardized positions according to the International 10–20 System.
- Electro-oculogram (EOG): A recording of eye movements.
- Electrocardiogram (ECG): A recording of heart rhythm.
- Electromyogram (EMG): A recording of the activity of the left and right tibialis anterior muscles and the submental (chin) muscles.
- Respiratory efforts: A recording of nasal and oral airflow by means of nasal thermistors and recording of thoracoabdominal movements by means of strain gauges.
- Pulse oximetry: A recording of oxygen saturation in the blood.
- Snore monitor: A detection and recording of snoring by means of a microphone placed on the lateral aspect of the neck.

Through the use of the PSG, wakefulness, sleep onset, NREM sleep, and REM sleep can be identified and studied.

The *waking state* is defined by polysomnography in the following manner: the EEG reveals an 8 to 14 Hz wave pattern known as *alpha waves*, the EMG reveals muscle tone and activity, and the EOG demonstrates variable eye movements, including blinking.[2] In the normal subject, *sleep onset* follows the transition from awake to NREM stage 1 sleep.[2,5–8] Being a state of altered consciousness, sleep onset is not reliably determined by asking the subject; it must be determined by specific polysomnographic criteria, which include a decrease in alpha activity, emergence of relatively low-voltage mixed-frequency (RLVMF) activity, and slow rolling eye movements on the EOG.[5] The EMG usually, but not always, registers a modest decrease in muscle activity. Some patients do not perceive themselves as asleep and can engage in *automatic behavior*, a phenomenon in which very complex cognitive and behavioral tasks are performed outside awareness.[5,9]

Sleep is normally entered through NREM sleep. NREM is divided into four stages; each one is identified by specific criteria on the PSG.[2,5]

- Stage 1: Alpha waves, present during the waking state, account for less than 50% of an epoch (a 30-second interval on the PSG). RLVMF waves emerge, with the most prominent ones being theta waves (4 to 7 Hz).
- Stage 2: Theta activity continues. During this stage, two new wave types emerge: sleep spindles (rhythmic 12 to 14 Hz waves lasting 0.5 seconds or more) and K-complexes (high amplitude negative waves followed by a positive deflection, lasting 0.5 seconds or more).

- Stage 3: Delta waves (high-amplitude, slow-frequency 0.5 to 2.0 Hz waves) occur. Delta waves occupy at least 20%, but not more than 50%, of an epoch. The EMG begins to show less muscle activity.
- Stage 4: Almost identical to stage 3, except delta waves now occupy greater than 50% of an epoch.

Stage 3 and 4 NREM sleep is also known as *delta* or *slow wave sleep*. The distinction between stage 3 and stage 4 NREM sleep, while scientifically intriguing, has no known clinical significance at this time.

REM sleep, also known as *paradoxical sleep* owing to its similarity to wakefulness and NREM sleep, is defined by three principal features. First, the EEG demonstrates RLVMF wave patterns that are virtually indistinguishable from those of NREM stage 1. Second, the EMG reveals an absence of, or a marked decrease in, muscle activity. Finally, conjugate rapid eye movements become evident on the EOG.[4]

Sleep Cycle and Architecture

NREM and REM sleep do not occur randomly throughout the night; instead, they alternate in a rhythmic fashion known as the *NREM–REM cycle*.[2,5,6] In healthy persons, this cycle begins with NREM stage 1 and it progresses to NREM stages 2, 3, 4, 3, 2, and then REM. This pattern generally repeats itself every 90 to 120 minutes throughout the night. NREM stages 3 and 4 are most prominent in the first half of the night; they diminish during the latter half of the night. REM sleep, however, is less prominent in the first half of the night, and it increases as the night progresses. *Sleep latency* is the time from "lights out" to the first NREM stage 1; it typically lasts 10 to 20 minutes. The time from sleep onset to the first REM is known as *REM latency*, which is usually 90 to 100 minutes. *Sleep efficiency* is the actual amount of sleep per total time in bed multiplied by 100. The average amount of sleep per night for adults is between 6 and 9 hours. The time spent awake after sleep onset is less than 5%.

The distributions of sleep stages across an average night are as follows: NREM stage 1, 2% to 5%; NREM stage 2, 45% to 55%; NREM stages 3 and 4, 13% to 23%; and REM sleep, 20% to 25%.

Sleep Across the Life Span

Sleep and sleep quality change across the lifespan.[10] Infants spend about two thirds of the day sleeping, whereas in adulthood this amount decreases to less than one third. As a result of degenerative changes in the central nervous system (CNS), sleep architecture becomes altered as people age. These changes include increases in sleep latency, nocturnal awakenings, time spent in NREM stage 1 sleep, and decreases in delta sleep, REM sleep, REM latency, and overall sleep efficiency.[11–13]

NEUROANATOMIC BASIS FOR SLEEP

The actual neuroanatomic basis for the sleep–wake cycle remains uncertain, but current research reveals that specific regions of the brain are critical for wakefulness and for sleep. These neuronal systems are located in the brainstem, hypothalamus, and basal forebrain, and they project diffusely throughout the neocortex.[14–16] Any disruption of these regions invariably leads to alterations in the sleep–wake cycle and gives rise to sleep disorders.

Although sleep architecture is influenced by a host of variables, the amount of wakefulness is largely determined by an internal biological cycle known as the *circadian rhythm*.[1,10] This biological clock is an endogenous rhythm of bodily functions that is influenced by environmental cues, or *zeitgebers*, of which the main one is daylight. The cycle is unique to each individual, averaging 25 hours for most people, but possibly 50 hours for others. Sleep disorders related to the circadian rhythm emerge when a person's circadian rhythm clashes with environmental and societal expectations.

The suprachiasmatic nuclei (SCN), a collection of approximately 50,000 cells in the anterior hypothalamus, is the brain region that moderates sleep–wake demand and environmental demands. The SCN receives input from the eyes via the retinohypothalamic tract, and it sends output to the thalamus and hypothalamus. Melatonin, a neuropeptide secreted by the pineal gland, is associated with suppression of the SCN and it induces sleep in mammals, but does not yet have a clear role in sleep homeostasis.[17]

Wakefulness is also maintained by tonic activity in the ascending reticular activating system (RAS) and is strongly influenced by sensory stimuli, the most powerful of which are sound and pain. Sleep develops when there is decreased activity in the ascending reticular activating system and activation of a hypnagogic sleep system located predominantly in the dorsal raphe nucleus. This homeostatic sleep–wake system interacts with the circadian rhythm system of the SCN and is either mitigated or amplified by it.[18] Although no specific neural generator for REM sleep has been identified, REM sleep is known to be an active process involving both the nucleus ceruleus and the gigantocellular tegmental field.

SLEEP DISORDERS

Although several classification systems for sleep disorders exist, the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)[19] and the *International Classification of Sleep Disorders*, second edition (ICSD-2)[20] are the most widely used (see Table 22–1 for the classification schema). The ICSD-2 system offers a comprehensive nosology of sleep disorders and is the official classification recognized by the American Sleep Disorders Association (ASDA); it classifies the 70 sleep disorders into eight categories based on symptoms and etiology. The DSM-IV-TR classification is complaint-based (as such, it is perhaps the simplest and easiest to understand); it divides sleep disorders into primary and secondary sleep disorders based on presumed etiology.

Insomnia

Insomnia is a repeated difficulty with sleep initiation, duration, consolidation, or quality, despite adequate opportunity for sleep, that produces daytime impairment. Patients complain of deficient, inadequate, or unrefreshing sleep; malaise; and fatigue. Sufferers often experience hyperarousal and anxiety at bedtime and have decreased daytime function with mild to moderate impairment in concentration and psychomotor function.[21]

TABLE 22–1 Outline of Sleep Disorders in DSM-IV and ICSD-2

DSM-IV SLEEP DISORDERS

Primary Sleep Disorders

Dyssomnias
Primary insomnia
Primary hypersomnia
Narcolepsy
Breathing-related sleep disorder
Circadian rhythm sleep disorder
Dyssomnia not otherwise specified (NOS)

Parasomnias
Nightmare disorder
Sleep terror disorder
Sleepwalking disorder
Parasomnia not otherwise specified

Sleep Disorders Related to Another Mental Condition
Insomnia related to an Axis I or II condition.
Hypersomnia related to an Axis I or II condition

Other Sleep Disorders
Sleep disorder due to a general medical condition
Substance-induced sleep disorder

ICSD-2 SLEEP DISORDERS

Insomnia
Insomnia (acute insomnia)
Psychophysiologic insomnia
Paradoxical insomnia
Idiopathic insomnia
Insomnia due to a mental disorder
Inadequate sleep hygiene
Behavioral insomnia of childhood
Insomnia due to a drug or substance
Insomnia due to a medical condition
Insomnia not due to a substance or known physiologic condition, unspecified (nonorganic insomnia NOS)
Physiologic (organic) insomnia, unspecified

Sleep-Related Breathing Disorders

Central sleep apnea syndromes
Primary central sleep apnea
Central sleep apnea due to high-altitude periodic breathing
Central sleep apnea due to a medical condition (not Cheyne–Stokes)
Central sleep apnea due to a drug or substance
Primary sleep apnea of infancy (formerly primary sleep apnea of newborn)

Obstructive sleep apnea syndromes
Obstructive sleep apnea, adult
Obstructive sleep apnea, pediatric

Sleep-Related Hypoventilation and Hypoxemic Syndromes
Sleep-related nonobstructive alveolar hypoventilation, idiopathic
Congenital central alveolar hypoventilation syndrome

Sleep-related hypoventilation/hypoxemia due to a medical condition
Sleep-related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology
Sleep-related hypoventilation/hypoxemia due to lower airway obstruction
Sleep-related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders

Other sleep-related breathing disorders
Sleep apnea or sleep-related breathing disorder, unspecified

Hypersomnias of Central Origin Not due to a Circadian Rhythm Sleep Disorder, Sleep-Related Breathing Disorder, or Other Cause of Disturbed Nocturnal Sleep
Narcolepsy with cataplexy
Narcolepsy without cataplexy
Narcolepsy due to a medical condition
Narcolepsy, unspecified
Recurrent hypersomnia
Kleine-Levin syndrome
Menstrual-related hypersomnia
Idiopathic hypersomnia with long sleep time
Idiopathic hypersomnia without long sleep time
Behaviorally induced insufficient sleep syndrome
Hypersomnia due to a medical condition
Hypersomnia due to a drug or substance
Hypersomnia not due to a substance or known physiologic condition (nonorganic hypersomnia NOS)
Physiologic (organic) hypersomnia, unspecified (organic hypersomnia NOS)

Circadian Rhythm Sleep Disorders
Circadian rhythm sleep disorder, delayed sleep phase type (delayed sleep phase disorder)
Circadian rhythm sleep disorder, advanced sleep phase type (advanced sleep phase disorder)
Circadian rhythm sleep disorder, irregular sleep–wake type (irregular sleep–wake rhythm)
Circadian rhythm sleep disorder, free-running type (nonentrained type)
Circadian rhythm sleep disorder, jet lag type (jet lag disorder)
Circadian rhythm sleep disorder, shift-work type (shift work disorder)
Circadian rhythm sleep disorder due to a medical condition
Other circadian rhythm sleep disorder (circadian rhythm disorder NOS)
Other circadian rhythm sleep disorder due to a drug or substance

Parasomnias

Disorders of arousal (from NREM sleep)
Confusional arousals
Sleepwalking
Sleep terrors

Parasomnias usually associated with REM sleep
REM sleep behavior disorder (including parasomnia overlap disorder and status dissociatus)
Recurrent isolated sleep paralysis
Nightmare disorder

Other parasomnias
Sleep-related dissociative disorders
Sleep-related groaning (catathrenia)
Exploding head syndrome
Sleep-related hallucinations
Sleep-related eating disorder
Parasomnia, unspecified
Parasomnia due to a drug or substance
Parasomnia due to a medical condition

Sleep-Related Movement Disorders
Restless legs syndrome
Periodic limb movement disorder
Sleep-related leg cramps
Sleep-related bruxism
Sleep-related rhythm movement disorder

Continued

TABLE 22–1 Outline of Sleep Disorders in DSM-IV and ICSD-2—*cont'd*

Sleep-related movement disorder, unspecified
Sleep-related movement disorder due to a drug or substance
Sleep-related movement disorder due to a medical condition

Other Sleep Disorders
Other physiologic (organic) sleep disorder
Other sleep disorder not due to a substance or known physiologic condition
Environmental sleep disorder

Sleep Disorders Associated with Conditions Classifiable Elsewhere
Fatal familial insomnia
Fibromyalgia
Sleep-related epilepsy
Sleep-related headaches
Sleep-related gastroesophageal reflux disease
Sleep-related coronary artery ischemia
Sleep-related abnormal swallowing, choking, and laryngospasm

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; ICSD-2, *International Classification of Sleep Disorders,* 2nd edition.

Diagnosis

To diagnose this disorder, there must be objective daytime sleepiness or subjective feelings of not being well rested; the presence of psychiatric or medical conditions that better account for the symptoms is called *insomnia due to a medical condition or mental disorder*. Objective findings include prolonged sleep latency (an inability to fall asleep in less than 30 minutes) and shallow or fragmented sleep as evidenced by multiple arousals on a PSG. The etiology of insomnia is multifactorial but the final common pathway is a state of increased arousal; there is evidence of increased arousal during sleep as well as during waking in neuroimaging studies in insomniac patients.[22] The subtypes of insomnia correspond to different presumed pathophysiologic processes that result in increased arousal.

Psychophysiologic insomnia is caused by somatized tension and by learned sleep-preventing associations. Sufferers react to stress with increased physiologic arousal, such as increased muscle tension and vasoconstriction. Learned associations consist mainly of an overconcern with an inability to sleep, which results in a vicious cycle of overconcern, increased arousal, insomnia, and reinforcement of concern. Environmental cues also become associated with an inability to sleep, and sufferers often report sleeping better in unfamiliar surroundings.

Paradoxical insomnia, also known as sleep-state misperception, is a primary insomnia in which sufferers complain of inadequate sleep or poor sleep, or both, but objective findings on the PSG are lacking. Invariably, patients with sleep-state misperception underestimate their total sleep time and their efficiency and overestimate sleep latency. Theories to explain this discrepancy include excessive mentation during sleep and obsessiveness about sleep.[23]

Idiopathic insomnia is a chronic primary insomnia that develops in childhood and is most likely the result of an innate abnormality in the sleep–wake cycle. Prolonged sleep latency, poor sleep efficiency, and REM sleep without eye movements are seen on PSG.[24]

Treatment

Insomnias are perhaps the hardest sleep disorders to treat; treatment involves selecting a specific modality based on the cause. Nonpharmacologic techniques, such as application of good sleep hygiene, use of the relaxation response, or meditation, should be attempted before any pharmacologic interventions. Table 22–2 provides a guideline for proper sleep hygiene. Sleep-restriction therapy, a specific method of graded matching of time spent in bed to actual sleep, is useful for more persistent and severe cases, but it often requires consultation with a sleep-disorders specialist. Other behavioral techniques can be learned through self-help audio/visual programs or manuals or from consultation with a mental health clinician.

TABLE 22–2 Basic Sleep Hygiene

Limit time in bed to the amount present before the sleep disturbance
Lie down only when sleepy, and sleep only as much as necessary to feel refreshed
Use the bed for sleep only
Maintain comfortable sleeping conditions and avoid excessive warmth and cold
Wake up at a regular time each day
Avoid daytime naps
Exercise regularly, but early in the day
Limit sedatives
Avoid alcohol, tobacco, and caffeine near bedtime
Eat at regular times daily and avoid large meals near bedtime
Eat a light snack, if hungry, near bedtime
Practice evening relaxation routines, such as progressive muscle relaxation, meditation, or taking a very hot, 20-minute, body temperature–raising bath near bedtime

If behavioral techniques are unsuccessful, brief intermittent use of a sedative–hypnotic may be appropriate. Useful sedative–hypnotic agents include trazodone, tricyclic antidepressants (TCAs), atypical antipsychotics, benzodiazepines, benzodiazepine receptor agonists, melatonin receptor agonists, antihistamines, and barbiturates.

Trazodone is the most commonly used agent and is commonly used in patients with a history of substance abuse or hypnotic abuse.[25] Doses from 25 mg to 200 mg are often used. TCAs are also often used for insomnia, but they can be lethal in overdose, and they induce anticholinergic-mediated side effects.

Second-generation antipsychotic agents, such as quetiapine and olanzapine, may also be helpful in resistant insomnia, but they can cause a metabolic syndrome, weight gain, orthostasis, extrapyramidal symptoms, and anticholinergic side effects.

The long-term use of benzodiazepines, although controversial, is a common practice, and it may be appropriate for patients who have insomnia secondary to an anxiety disorder.

Benzodiazepines should either be used cautiously or avoided in patients with a history of alcohol or substance abuse, with a personality disorder, or with a sleep-related breathing disorder. To avoid dose escalation with these agents, prescriptions should be carefully monitored, when used for more than 4 weeks. Newer benzodiazepine receptor agonists (such as zolpidem, eszopiclone, and zaleplon) are often preferred, owing to their lower abuse potential, shorter half-lives, and approval for long-term use (up to 6 months).[26,27]

Ramelteon, a melatonin receptor agonist, improves sleep latency alone and is effective for patients with poor sleep initiation. Melatonin itself remains incompletely studied, but it produces mixed results[28]; some authors suggest that 2 mg at bedtime may be effective.

Sedating antihistamines can be used as alternatives to benzodiazepines; however, they can cause delirium in the elderly or in those with a compromised CNS. Chloral hydrate, short-acting barbiturates, and ethchlorvynol are less effective and more toxic than other agents; they should be used rarely, if ever, and then only under closely monitored conditions.

Sleep-Related Breathing Disorders

Sleep related breathing disorders, and especially sleep apnea syndromes, are the most commonly encountered hypersomnias. The essential feature of these disorders is disrupted sleep due to repeated apnea and oxygen desaturation.

Diagnosis

Apnea is defined as the cessation of nasobuccal airflow longer than 10 seconds. The type of apnea that a person experiences during sleep is based on its proposed cause and the presence or absence of respiratory effort during the event.

Central apneas are identified by the cessation of airflow with no attempt to initiate thoracoabdominal respiratory effort. The ICSD-2 distinguishes between several different central sleep apnea syndromes, according to etiology; primary central apnea, although debated, is thought to lie in abnormal CNS processes. ICSD-2 also identifies a separate category of sleep-related hypoventilation and hypoxemia syndromes that do not feature apneic episodes with arousals but that are characterized by low tidal volumes during sleep that lead to decreased oxygen saturation.

Obstructive apneas, on the other hand, are identified by the cessation of airflow as a result of a collapse in the upper airway. Unlike central apneas, obstructive apneas demonstrate continued or even increased respiratory effort. These obstructions can be so complete and the effort so powerful that the chest and abdomen can move in opposite directions, a phenomenon known as *paradoxical breathing*.

Mixed apneas, the most common type of apneas encountered, are events in which a central apnea is followed by an obstructive apnea.

A *hypopnea* is simply a reduction, rather than cessation, of nasobuccal airflow or thoracoabdominal movements during sleep. To be clinically significant, a hypopnea must result in a 50% reduction in air flow, at least a 4% decrease in the oxygen saturation, or be associated with an arousal pattern on the EEG.

The *apnea index* is the number of clinically significant apneas per hour of sleep, and the *hypopnea index* is the number of clinically significant hypopneas per hour of sleep. The *respiratory disturbance index* (RDI),[29] also known as the *apnea–hypopnea* index (AHI), is the sum of the apnea index and the hypopnea index. An apnea index of greater than 5, a hypopnea index of greater than 5, or a respiratory disturbance index of greater than 10 is considered pathologic and warrants treatment.[29]

Of all the sleep apnea spectrum disorders and disorders of excessive daytime sleepiness (EDS), obstructive sleep apnea (OSA) syndrome is the most common, accounting for 40% to 50% of all patients seen in sleep disorders centers.[2,30,31] The estimated prevalence of OSA is 1% to 4% of the adult male population, and the prevalence increases to 8.5% of men between the ages of 40 and 65 years.[3,10,32,33] Women account for 12% to 35% of OSA patients, with the majority of them being postmenopausal, suggesting that female hormones may be somewhat protective against OSA.[19]

The most significant risk factors for OSA are being: male, 40 to 65 years old, obese, a smoker, a user or abuser of alcohol, in poor physical health, and having a neck circumference greater than 17 inches.[30,31,33,34] The principal defect is repetitive occlusion of the upper airway at the level of the pharynx (which results from an abnormal decrease in oropharyngeal muscle tone), excessive tissue mass in the pharynx and tongue, malposition of the jaw or tongue, or a narrow airway.

Nocturnal signs and symptoms include snoring, choking, enuresis, reflux, hypoxemia, hypercapnia, and cardiac dysrhythmias. Daytime signs and symptoms include headaches, hypersomnolence, automatic behavior, neuropsychiatric abnormalities, and hypertension.[35–37]

Treatment

The treatment of OSA involves identifying and correcting the underlying etiology. Patients should be encouraged to lose weight and to avoid alcohol and use of sedatives that prolong apneas by increasing vagal tone, relaxing muscles, and preventing arousal for breathing.

Because apneas are affected by gravity, positional therapy can be used in mild to moderate OSA. No medication has been shown to be of clear benefit in the treatment of OSA, although pharmacologic agents (e.g., protriptyline, fluoxetine, and medroxyprogesterone) have been used.[10,11,19,38] Stimulants, such as modafinil, can ameliorate EDS. Oral appliances aimed at altering the position of structures of the upper airway to create a larger airway or to prevent further collapse are indicated for patients who have primary snoring, mild OSA, or moderate to severe OSA and who are intolerant of, or refuse, continuous positive airway pressure (CPAP) or surgical interventions.[10,39,40]

Uvulopalatopharyngoplasty (UPPP), mainly used to prevent snoring, is an option selected by some patients; it aims to increase the volume of the oropharynx by removing the tonsils, adenoids, posterior soft palate, and redundant tissue on the sides of the pharynx by means of primary or laser-assisted surgery.[5,19] The overall success rate for uvulopalatopharyngoplasty, as measured by at least a 50% reduction in apnea index, is only 40% to 50%; moreover, there is often a gradual return of apneas to pretreatment levels.[3,5,19]

Until recently, tracheostomy was considered the treatment of choice for severe OSA. First-line therapy now includes nasal CPAP and bi-level positive airway pressure

(BiPAP), both of which work by providing an air pressure splint to the upper airway.

For patients who receive no treatment and who have an apnea index of greater than 20, the probability of a cumulative 8-year survival is reported at 63% ± 17%. With the use of nasal CPAP, regardless of the initial apnea index, the probability of a cumulative 8-year survival rises to 100%.[41]

Narcolepsy and Hypersomnias of Central Origin

Narcolepsy

Narcolepsy is a primary hypersomnia associated with a tetrad of symptoms:

- *Sleep attacks*: Irresistible and brief sleep episodes with sleep-onset REM periods (SOREMPs) that occur several times a day, often at inappropriate times;
- *Cataplexy*: Sudden and brief bilateral loss of motor tone without impairment of consciousness, triggered by strong emotions (such as laughter, anger, or surprise);
- *Sleep paralysis*: Brief episodes of muscular paralysis associated with the transitions of sleep onset or awakening; and
- *Hypnagogic* or *hypnopompic hallucinations*: Vivid visual and auditory phenomena that are associated with the transitions to sleep onset or awakening.

Narcolepsy occurs in approximately 0.07% of the general population; it typically arises in the second decade of life. Symptoms usually begin with sleep and are associated with excessive sleepiness. Current research suggests that genetics plays a role in this disorder because a strong association exists between narcolepsy and the human leukocyte antigen *HLA-DR2* and *DQ1* phenotypes. The most specific antigen associated with narcolepsy in all ethnicities is *HLA-DQB1*0602*,[20] and sufferers of narcolepsy without this antigen are extremely rare. The probability of developing narcolepsy is 40 times greater if an immediate family member suffers from it.[21,42,43]

Although the exact abnormality of narcolepsy is unknown, leading theories implicate a mutation in the gene that codes for the production of the neurotransmitter *hypocretin*.[44] Also known as orexin, this neurotransmitter is produced in the posterior hypothalamus, and it inhibits activity in the ventrolateral preoptic area (VLPO). Hypocretin deficiency destabilizes sleep–wake partitioning, and in narcolepsy with cataplexy there is a loss of hypocretin-secreting cells.[45]

The diagnosis of narcolepsy is made on the multiple sleep latency test (MLST), a series of five scheduled naps 2 hours apart each. Short sleep latency (less than 8 minutes per nap), and two episodes of sleep-onset REM are diagnostic for narcolepsy.

Treatment is aimed at reducing both daytime sleepiness and cataplexy. Daytime sleepiness is effectively treated with psychostimulants, particularly methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and to a lesser extent, pemoline (Cylert).[46,47] Modafinil (Provigil), a central adrenergic stimulant, can promote wakefulness, has minimal side effects, and has a low potential for abuse.[48–51] Due to their ability to suppress REM sleep, antidepressants, particularly the TCAs, are the treatment of choice for cataplexy, sleep paralysis, and hypnagogic hallucinations. Gamma hydroxybutyrate (GHB; Xyrem) is a gamma-aminobutyric acid (GABA) metabolite that can improve nocturnal sleep and EDS, but it has high abuse potential. Prophylactic naps, when feasible, can reduce the total daily dose of stimulants.

Hypersomnias of Central Origin

Other hypersomnias of central origin include idiopathic hypersomnia, or *Kleine-Levin syndrome*, a rare, often self-limiting condition that primarily affects male adolescents. Symptoms include hypersomnia, hyperphagia, and hypersexuality. Although the exact cause is unknown, it often follows an acute viral infection. Treatment includes the use of psychostimulants, selective serotonin reuptake inhibitors (SSRIs), and monamine oxidase inhibitors (MAOIs).

Idiopathic hypersomnia is characterized by constant or recurrent EDS, typically with sleep episodes lasting 1 hour or longer, despite normal nocturnal sleep patterns. *HLA-Cw2* is associated with this disorder.[20]

Behaviorally induced insufficient sleep syndrome results from voluntary but unintentional chronic sleep deprivation. Patients do not appreciate the difference between the need for sleep and the amount they actually obtain. Prescribing longer periods of sleep reverses its symptoms.

Circadian Rhythm Sleep Disorders

Circadian rhythm sleep disorders emerge when societal expectations conflict with a person's endogenous sleep–wake cycle. Although patients who have these disorders might complain of insomnia, hypersomnia, sleepiness, and fatigue, the timing of sleep—not its quality and architecture—is adversely affected. The most commonly encountered circadian rhythm disorders include jet lag syndrome, shift-work sleep disorder, delayed sleep phase disorder, advanced sleep phase disorder, and non–24-hour day (or hypernyctohemeral) syndrome.

Jet lag occurs when a person rapidly crosses several time zones, often from western to eastern time zones. This results in an advancement in the sleep–wake cycle, leaving the person feeling tired earlier in the evening.[52]

Shift-work sleep disorder occurs when the circadian rhythm conflicts with a work schedule that does not coincide with a conventional day–night cycle.[53]

Delayed sleep phase disorder occurs in persons whose circadian rhythm is set for a later time than the conventional sleep–wake cycle.[54] Considered "night owls," these persons are most alert in the evening and at night and become sleepy several hours after the conventional bedtime. If left undisturbed, they can sleep 7 to 8 hours, with problems arising when they are required to adhere to conventional daytime schedules.

Advanced sleep phase disorder occurs in persons whose circadian rhythm is set for an earlier time than the conventional sleep–wake cycle.[55] Considered "larks," these persons (who are often elderly) are most alert in the earlier morning, and they become sleepy several hours earlier than the conventional bedtime. Although they sleep for 7 to 8 hours, they might awaken at 2 to 3 AM complaining of an inability to stay asleep all night.

The *non–24-hour day* (or *hypernyctohemeral*) *syndrome* is a phenomenon seen most commonly in persons who are totally blind and who are unable to perceive visual *zeitgebers*. These patients, who function on a natural circadian rhythm of 24.5 to 25.0 hours, go to sleep and wake up about 45 minutes later each day.[56] As opposed to persons who follow a conventional sleep–wake schedule, their sleep–wake cycle will literally go "around the clock" in approximately 3 weeks.

The diagnosis of circadian rhythm disorders is based primarily on the history that can be obtained through a detailed sleep–wake diary maintained for several weeks. Because most circadian rhythm disorders are self-limited and resolve as the person adjusts to the new sleep–wake schedule, aggressive treatment is not necessary. Common treatment options include gradually delaying sleep until the patient achieves a new schedule, receiving light therapy, or taking melatonin.

Parasomnias

Parasomnias are a group of primary sleep disorders in which abnormal behaviors or physiologic events arise during specific sleep stages or during the transitions between wakefulness and sleep. These events are often bizarre; however, they rarely are a cause for great concern for the patient or the physician. Unlike with dyssomnias (insomnia and hypersomnia), children are more commonly affected by parasomnias than are adults. The parasomnias are subdivided into arousal disorders, REM sleep disorders, and other parasomnias.

Arousal Disorders

In s*leepwalking disorder* or somnambulism, the patient experiences episodic motor behaviors while emerging from delta sleep, most often during the first third of the night. Some behaviors are simple (e.g., walking, sitting up in bed, or picking at bed sheets), but more complex and serious behaviors can occur (e.g., running, eating, driving, or committing violent attacks).[57] Patients are often unresponsive to efforts to wake them, confused and disoriented when actually awakened, and amnestic to the sleep-related event the next day. Sleepwalking is not uncommon in childhood; it is rare in adulthood, a fact that should prompt a search for a possible underlying medical, neurologic, or pharmacologic etiology. No definitive treatment for sleepwalking exists, but some patients respond to low-dose benzodiazepines or to sedating antidepressants. Adjunctive therapies include reassurance, hypnosis, and provision of a safe sleep environment, because patients have been known to trip or to fall out of open windows.

Like sleepwalking disorder, *sleep terror disorder*, also known as *night terrors*, *pavor nocturnus*, or *incubus*, occurs during partial arousal from delta sleep, usually during the first third of the night. As in sleepwalking disorder, patients are difficult to awaken, they lack dream recall, and they are amnestic for the episodes. Caretakers are often bothered more by this disorder than are patients. Symptoms include repeated awakenings followed by intense fear, screaming, flailing, and autonomic hyperarousal (e.g., tachycardia, tachypnea, and mydriasis).[58] In adults, this disorder is associated with posttraumatic stress disorder (PTSD), generalized anxiety disorder, and borderline personality disorder. Treatment includes use of low-dose benzodiazepines, which suppress delta sleep. Adjunctive therapies include psychotherapy and stress reduction techniques.

Confusional arousals, also known as sleep drunkenness, occur when persons are awakened from delta sleep, from a nap, or induced to wake in the morning. They are characterized by disorientation, by amnesia, and occasionally by violent or sexual behavior. Allowing enough time for disorientation to wear off is usually sufficient treatment.[20]

REM Sleep Disorders

The hallmarks of this group of parasomnias are the occurrence in REM sleep, dreaming, and awareness of the specific events. The most commonly encountered REM sleep disorders are nightmare disorder and REM sleep behavior disorder. The essential feature of *nightmare disorder* is repeated episodes of terrifying dreams that awaken the patient. In contrast to patients with sleep terror disorder, patients with nightmare disorder often have vivid recall of the events, are atonic during the experience, lack autonomic arousal, and experience the events in the latter half of the night when REM sleep is longest and most dense. The specific etiology for nightmares is often underlying emotional stress; treatment targets stress reduction, but it can include psychotherapy, rehearsal instructions, and reassurance.

REM sleep behavior disorder (RBD) is perhaps the most dramatic of all the parasomnias. As in sleepwalking disorder, patients with RBD can exhibit simple to quite complex behaviors while asleep, including jumping out of bed, walking, running, or singing.[59] In contrast to sleepwalking disorder, RBD, like all REM sleep disorders, occurs later in the night when REM is longest, and it is accompanied by vivid dream recall. Unlike other REM sleep disorders, however, patients with RBD lack the muscle atonia that normally accompanies REM sleep; this results in the literal acting out of dream content.[60] The disorder is idiopathic in more than half of the cases, but it can result from underlying organic processes such as Parkinson's disease, vascular and Alzheimer's dementia, multiple system atrophy, focal brain stem lesions, and alcoholism. It is more common in the elderly, and it affects men nine times more frequently than women. Low-dose clonazepam, which suppresses REM density and length, has an 80% to 90% success rate. Other treatment options, if clonazepam is ineffective, include levodopa–carbidopa, clonidine, or carbamazepine.

Other REM sleep disorders include *recurrent isolated sleep paralysis*, which involves the inability to move voluntarily at sleep onset or awakening. It can last up to several minutes, and it disappears spontaneously or with external stimulation.

Sleep-Related Movement Disorders

Periodic limb movement disorder (PLMD), sometimes called *nocturnal myoclonus*, is a common parasomnia that affects up to 40% of people older than 65 years of age and 11% of sleep disorder clinic patients who complain of insomnia.[61–63] PLMD manifests as brief (0.5 to 5.0 seconds), stereotypic, and involuntary contractions of the lower limbs (often the dorsiflexors of the foot and flexors of the lower legs), at intervals of 20 to 40 seconds. Contractions appear more commonly during NREM stages 1 and 2. Although patients

are unaware of them, the EEG demonstrates nocturnal arousals and actual awakenings. Sleep is often unrefreshing, with hypersomnia being the most common complaint.

Diagnosis is made by overnight PSG and is confirmed when the *myoclonus index* (the number of leg jerks per hour of sleep that are accompanied by arousals) reaches five or more. Although the pathogenesis of PLMD is unknown, it is associated with a variety of medical conditions such as renal failure, diabetes, chronic anemia, peripheral nerve injuries, and even uncomplicated pregnancy. Medications including antidepressants, neuroleptics, lithium, diuretics, and narcotics, especially with narcotic withdrawal, are also associated with it. Treatment is symptomatic and includes use of dopaminergic facilitating agents (e.g., selegiline), and benzodiazepines (particularly clonazepam).[64]

A disorder closely related to PLMD is the *restless legs syndrome*. Restless legs syndrome is characterized by intense aching or crawling sensations inside the legs and calves that occur while sitting or lying; it causes an irresistible urge to move or rub the legs. Symptoms arise mainly at bedtime and are partially relieved by movement, which unfortunately interrupts sleep initiation because the patient often paces. Like PLMD, restless legs syndrome is associated with various medical problems, especially kidney failure, diabetes, iron-deficiency anemia, and peripheral nerve injury, as well as with use of medications, particularly SSRIs. Symptomatic relief may be provided by iron supplementation, avoidance of alcohol, exercise, and tapering offending medications. Medications such as pramipexole and ropinirole are effective dopamine agonists. Other agents that might provide relief include gabapentin and clonazepam.[65,66]

Nocturnal leg cramps can occur multiple times a night, several times per week, and are often seen in the elderly. *Rhythmic movement disorder* involves stereotyped repetitive movements of large muscles, often of the head and neck, occurring before sleep and sustained into light sleep. A normal aspect of infancy, rhythmic movement disorder beyond childhood may be associated with mental retardation, developmental delay, or psychopathology.

Sleep Disorders Resulting from a Medical Condition

Sleep disturbance is extremely common as a secondary symptom of other medical, psychiatric, or neurologic conditions. The ICSD-2 categorizes sleep disturbances resulting from medical conditions according to the subtype of sleep disorder; what follows is a general discussion of psychiatric, medical, neurologic, and substance-induced conditions and their associated sleep disturbances. Secondary sleep disorders often masquerade as primary sleep disorders; they require skill and vigilance on the part of psychiatrists and primary care physicians to ensure proper treatment for the principal disorder.

Sleep Disorders Related to Another Mental Disorder

Sleep disturbance is such a common feature of psychiatric illness that it is often the first neurovegetative symptom about which psychiatrists inquire. In patients with known psychiatric illness, however, care must be taken to avoid attribution of a sleep disturbance solely to the mental disorder because psychiatric patients also have primary sleep disorders and co-morbid medical problems with associated disturbances of sleep. If a primary sleep disorder is not present and the complaint of sleep disturbance is not the predominant complaint but is temporally related to a mental disorder, then a sleep disorder related to another mental illness may be diagnosed. Although a patient might complain of either hypersomnia or insomnia, insomnia is the most common sleep-related complaint that results from psychiatric disorders. Because the mental disorder is the cause of the sleep disturbance, treatment consists of treating the primary psychiatric condition.

Mood Disorders

Sleep abnormalities occur in up to 60% of outpatients and 90% of inpatients with depression. Consequently, more is known about sleep disturbances in depressed patients than in any other psychiatric illness. Most patients who have depression complain of initial, middle, and terminal insomnia and early morning awakening; in addition, they experience restlessness and fatigue. Hypersomnia and neurovegetative reversal, however, tends to occur in atypical depression.

Objective findings on the PSG include prolonged sleep latency, decreased delta sleep, decreased REM latency, increased duration and density of the first REM period, and early morning awakening. Evidence suggests that these abnormalities can persist after remission and that they precede the onset of another episode. In addition, some studies suggest that decreased REM latency or decreased delta sleep can predict relapse in depressed patients.[67]

Sleep disturbance in bipolar illness depends on which phase of the illness the patient is experiencing. During a depressed phase, for example, bipolar patients tend to experience hypersomnia and have an increased percentage of REM sleep, whereas during a manic episode they experience insomnia and have a lower percentage of REM sleep. Unlike other patients with insomnia, however, patients with mania rarely complain of their inability to sleep.

Psychotic Disorders

The most common sleep abnormalities in patients with psychotic disorders are difficulties with sleep initiation and sleep maintenance, which become apparent during the acute phase of these illnesses. Patients with psychosis, like those with depression, also have decreases in REM latency, total sleep time, sleep efficiency, and delta sleep. Because many of the medications used for treating psychosis can cause similar disruptions in sleep architecture, medication side effects must be ruled out. Current evidence suggests, however, that many of these sleep abnormalities, particularly delta sleep deficits, are the function of a psychotic disorder rather than the result of medication use.[68]

Anxiety Disorders

Although anxiety disorders are perhaps the most common cause of insomnia, their exact effect on sleep architecture is tenuous. As a general rule, patients with anxiety disorders often complain of disturbed sleep and have poor sleep efficiency.[69] Patients suffering from panic disorder can experience attacks during sleep, usually during the transition from NREM stage 2 sleep and early delta sleep.[70,71] Patients with obsessive–compulsive disorder (OCD) report difficulties with initiating and maintaining sleep, which

is often a result of pre-sleep anxiety and bedtime rituals before sleep onset. Of all the anxiety disorders, PTSD is the best studied. Sleep findings in patients with PTSD include easy arousability, nightmares, night terrors, and increased sleep-related movements.[72] In addition, total sleep time is often reduced owing to recurrent awakenings and impaired sleep maintenance.[69,72] Patients suffering from generalized anxiety have difficulty falling asleep and can awaken with anxious ruminations throughout the night.

Sleep Disorders Related to a General Medical Condition

Because pain, discomfort, and unremitting symptoms can interfere with sleep continuity, sleep complaints are common in a host of medical conditions. To diagnose a sleep disorder related to a general medical condition, the history and physical examination must demonstrate a solid connection between the sleep disorder and the underlying medical problem; in addition, the sleep disturbance must be severe enough to warrant independent clinical attention.

The most common sleep complaint is insomnia, but general medical conditions can produce sleep disturbances that mimic any sleep disorder. The list of medical conditions that result in a sleep disorder is quite lengthy, and this section highlights the more common ones. As with all secondary sleep disorders, the definitive treatment rests on treatment of the underlying medical condition.

Patients who have pain syndromes often complain of symptoms that worsen at bedtime. Consequently, these patients often have disrupted sleep patterns, insomnia, early morning awakening, and daytime fatigue.[73–75] Polysomnographic features include increased NREM stage 1 sleep, decreased delta sleep, an increased number of arousals, and an alpha pattern known as *alpha–delta sleep anomaly*. This anomaly can also be seen in sleep-deprived persons and in persons in whom deep pain has been induced.[74,76,77] Adequate pain control can substantially improve sleep for these patients. Sedating antidepressants or benzodiazepines, although they do not directly treat the pain, can help with sleep initiation and maintenance.

Patients who have respiratory conditions, such as asthma and chronic obstructive pulmonary disease, often complain of frequent nocturnal awakening, light sleep, terminal insomnia, and daytime hypersomnia. Many of these symptoms are attributable to an inability to enter or to maintain REM sleep owing to decreases in ventilatory drive, which cause hypoxia and hypoxemia that signals the patient to awaken. In such cases, supplemental oxygen can improve the quality of sleep. Other polysomnographic features are identical to those found in patients with OSA, because many patients with primary respiratory disorders also suffer from co-morbid breathing-related sleep disorders.

Several neurologic disorders are commonly associated with sleep disturbance, including cerebral degeneration, dementia, Parkinson's disease, and epilepsy. In cerebral degenerative disorders (e.g., Huntington's disease, spinocerebellar degeneration, and Rett syndrome) sleep fragmentation is common, as are periodic leg movements, reduced REM and delta sleep, and apneas. Patients with dementia often experience sleep disturbance with delirium, agitation, wandering, and vocalizations. Their PSGs show sleep fragmentation and decreases in sleep efficiency, delta sleep, and REM sleep. Those with Parkinson's disease have similar PSG findings, including prolonged sleep latency, increased number of awakenings, and decreased REM sleep. They also demonstrate REM periods outside of REM sleep, as well as periodic leg movements, tremors at sleep-stage transitions, and brief EMG bursts without movement.[20]

Epilepsy is classified as sleep-related if more than 75% of seizures occur during sleep. Suspicion for this condition is raised if a person experiences abrupt nocturnal awakenings, unexplained urinary incontinence, or abnormal movements during sleep. Epileptic discharges are typically activated by NREM sleep and suppressed by REM sleep. Sleep-related seizures are quite rare and are often confused with parasomnias, such as sleep terror disorder, REM sleep behavior disorder, sleepwalking disorder, enuresis, or nocturnal panic attacks.[78] Seizures occur predominantly during the first 2 hours of sleep and most often during light NREM sleep or in transitional states to and from REM sleep. Seizure type may be either generalized or partial, with temporal and frontal lobe seizures being the most commonly encountered variety of partial seizures.[79] The chief complaint is often nonspecific and can include disturbed sleep, tousled bed linens, confusion, or muscle soreness. Some patients may be unaware that they have sleep-related seizures until someone observes a convulsion. The treatment for sleep-related seizures, as with most forms of seizures, involves use of anticonvulsants.

Sleep complaints are common in other chronic medical problems, but they are less well investigated. Patients with angina and cardiac arrhythmias can experience exacerbations of their symptoms during sleep, most often during REM sleep. Patients in congestive heart failure often suffer orthopnea, paroxysmal nocturnal dyspnea, and nocturia, which may be confused with a primary sleep disorder, such as breathing-related sleep disorder, sleep terror disorder, nocturnal panic disorder, and sleep-related seizures.[80]

A discussion of sleep disorders associated with medical conditions would be incomplete without mention of paroxysmal nocturnal hemoglobinuria, even though it is not a true sleep disorder. A rare condition, paroxysmal nocturnal hemoglobinuria is an acquired hemolytic anemia exacerbated by sleep. Patients complain of rust-colored morning urine that is the result of hemolysis.[81] Paroxysmal nocturnal hemoglobinuria rarely affects the life span. Death most often results from thrombosis or various cytopenias. Treatment includes blood transfusions, immunosuppressive therapies, or a bone marrow transplant.

Substance-Induced Sleep Disorder

Substances, whether prescribed or illicit, can have profound effects on sleep. These effects can arise during regular use, acute ingestion, or withdrawal and can masquerade as any primary sleep disorder. As a general rule, if the substance is a CNS depressant, intoxication results in sedation and withdrawal results in insomnia. Similarly, if the substance is a CNS stimulant, intoxication results in insomnia and withdrawal results in sedation. Diagnosis of these disorders can only be made if the sleep disturbance is severe enough to warrant independent clinical attention, it is caused by the direct physiologic effects of a substance, if it developed during or within a month of intoxication or withdrawal from the substance, and if it is not the result of a mental disorder or delirium. Once a substance-related sleep disorder

is suspected, a thorough substance-abuse history must be obtained to recognize the offending substance. Treatment consists of judicious discontinuation of the substance, management of any acute withdrawal, and treatment of any underlying co-morbid psychiatric problems that initiated or contributed to the substance abuse in the first place.

Alcohol is perhaps the most commonly used sleep aid, but its soporific value is limited by significant side effects, including dependence, addiction, and withdrawal. Its effects on sleep are well documented and depend on the pattern of use and the state of intoxication or withdrawal. During acute intoxication, alcohol alters sleep architecture by decreasing sleep latency, increasing delta sleep, and decreasing REM sleep for the first 3 to 4 hours of sleep. In the last 2 to 3 hours of sleep, wakefulness and REM are increased. During acute withdrawal, however, its effects on sleep architecture are reversed; initial insomnia, decreased delta sleep, short REM latency, an increased percentage of REM sleep, decreased total sleep time, and decreased sleep efficiency all develop. Each of these features may be a contributing factor for alcohol relapse in dependent patients.[82–84] For recovering alcoholics, insomnia, poor sleep continuity, and decreased delta sleep can persist for several years after detoxification.[82,83] The definitive treatment for alcohol-related sleep complaints is detoxification and abstinence, in addition to treatment of co-morbid psychiatric conditions. Benzodiazepines, hypnotics, and sedating antidepressants should, in general, be avoided due to cross-tolerance, risk of alcohol relapse, and synergistic sedative effects that can lead to CNS depression should the patient relapse.

The effects of nonalcoholic substances on sleep are not as well established as are the effects of alcohol. In general, intoxication with either amphetamine or cocaine prolongs sleep latency, decreases the amount of REM sleep, disrupts sleep continuity, and shortens total sleep time. During the first week of withdrawal from these substances, patients often experience hypersomnia (a "crash") and excessive REM sleep, followed perhaps by several days of insomnia.[85]

Sedative–hypnotics, particularly benzodiazepines, shorten sleep latency, increase delta sleep, and decrease REM sleep. Caution must be taken when prescribing benzodiazepines, particularly those with a short half-life, because 1 or 2 days of withdrawal-based insomnia can occur after just a few days of benzodiazepine use.[86] Opiates are also known to increase sleep and to reduce REM sleep, with rebound insomnia occurring upon their discontinuation.

SSRIs can produce arousal and insomnia in some patients and sedation in others. The effects of SSRIs on sleep architecture include decreased REM sleep and decreased delta sleep. They can also aggravate sleepwalking and REM sleep behavior disorder, and they can induce REM during NREM sleep.[87]

APPROACH TO THE PATIENT WITH DISORDERED SLEEP

Once a sleep complaint has reached clinical attention, it is important to conduct a careful evaluation to correctly assess, diagnose, and treat any potential sleep disorder. Because this process can be complex and time consuming, the skills of a board-certified sleep specialist might be required. The following discussion is based on the general approach that many sleep specialists recommend for proper diagnosis and management of sleep complaints and disorders.

The initial step in the diagnostic process is to obtain a detailed sleep history, either through direct inquiry of the patient and his or her bed partner or by means of a sleep questionnaire. Table 22–3 provides a list of specific areas that should be addressed.[88] In addition to a detailed sleep history, patients are encouraged to keep a 2-week sleep diary that details the time and amount of sleep, the number and length of any naps, the number of awakenings, wake-up times, any medications taken, and subjective mood during the day. For patients in whom hypersomnia is the major complaint, an Epworth Sleepiness Scale—a simple, self-administered questionnaire that requires patients to rate their degree of sleepiness in a variety of routine situations)—is often given. A score of 10 or more on the Epworth Sleepiness Scale distinguishes normal patients from patients with various hypersomnias, including OSA, narcolepsy, and idiopathic hypersomnia (Table 22–4).[89] In addition to the sleep history and screening examinations, a medical history including past medical history, current medications, alcohol and drug history, family history, and psychiatric history is completed.

After a comprehensive history, and if clinically indicated, the patient receives a detailed physical examination. For patients who have hypersomnia, this examination focuses on the distribution of obesity, the respiratory system, the cardiovascular system, and the oronasomaxillofacial region, with careful attention to the tongue, tonsils,

TABLE 22–3 Sleep History

What are the times of retiring and arising? Note any variations between weekdays and weekends.
Note changes in sleep–wake schedule.
What is the subjective quality of sleep?
How much sleep is needed to feel ideally alert and energetic during daily function? Note any drugs needed.
How frequently is the ideal amount of sleep achieved compared to the average amount of sleep obtained? Note any disagreement between the patient and the bed partner about time spent asleep.
What are the sleep habits and requirement in childhood and other major periods of life? Note the subjective quality of sleep and attitudes toward sleep during those periods.
Have there been difficulties with initiation, maintenance, or early termination of sleep? Note daytime symptoms and effect on daily functioning.
Have there been problems with daytime sleepiness? Note if the problem is worsening. Note any snoring, intermittent snoring with gagging, episodes of muscle weakness with laughter, leg jerking in sleep, or other troublesome events during sleep.
Are drugs and alcohol used before 6 PM or after 6 PM?
Are there general emotional and physical problems? Note treatment modalities.
What is the sleep hygiene?

Modified from Roffward H, Erman M: Evaluation and diagnosis of the sleep disorders: implications for psychiatry and other clinical specialties. In Hales RE, Frances AJ, editors: Psychiatry update: American Psychiatric Association annual review, vol 4, Washington, DC, 1985, American Psychiatric Press, pp 204–328.

TABLE 22–4 Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

SITUATION	SCORE
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g., a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____
TOTAL	_____

From Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale, *Sleep* 14(6):540–545, 1991.

uvula, and pharynx.[12,13,90,91] If indicated, laboratory examinations including a complete blood cell count, blood gas analysis, pulmonary function tests, an electrocardiogram, thyroid function tests, serum iron analysis, and electrolyte count are ordered. Cephalometric x-rays of the skull and neck may be obtained to evaluate for skeletal discrepancies if craniofacial malformations are suspected as a possible etiology for any breathing-related sleep disorder.[10,12,13,90,91] Polysomnography completes the evaluation and often confirms the diagnosis.

Once a diagnosis has been confirmed, patients are offered appropriate treatment. Table 22–5 summarizes nonpharmacologic and pharmacologic treatments for the most commonly encountered primary sleep disorders.

TABLE 22–5 Treatment Options for Commonly Encountered Primary Sleep Disorders

PRIMARY SLEEP DISORDER	NONPHARMACOLOGIC TREATMENT	PHARMACOLOGIC TREATMENT
Dyssomnias		
Primary insomnia	Sleep hygiene Stimulus control Sleep restriction Biofeedback Relaxation training Paradoxical intention Cognitive therapy Psychotherapy	**Benzodiazepines** Triazolam 0.125-0.25 mg hs Temazepam 7.5-30 mg hs Oxazepam 15-30 mg hs Lorazepam 0.5-2 mg hs Diazepam 2.5-10 mg hs Clonazepam 0.5-2 mg hs **Imidazopyridines** Zolpidem 5-20 mg hs Eszopiclone 1-3 mg hs **Pyrazolopyrimidines** Zaleplon 5-20 mg hs **Antihistamines** Diphenhydramine 25-50 mg hs **Sedating antidepressants** Amitriptyline 10-75 mg hs Imipramine 25-100 mg hs Doxepin 10-75 mg hs Trazodone 25-200 mg hs **Atypical Antipsychotics** Quetiapine 12.5-200 mg hs Olanzapine 2.5-10 mg hs

Continued

TABLE 22–5 Treatment Options for Commonly Encountered Primary Sleep Disorders—*cont'd*

PRIMARY SLEEP DISORDER	NONPHARMACOLOGIC TREATMENT	PHARMACOLOGIC TREATMENT
Primary hypersomnia	Regular bedtime Avoid daytime naps	**Amphetamines** Dextroamphetamine 5-60 mg/day Methylphenidate 5-80 mg/day **Nonamphetamines** Pemoline 18.75-112.5 mg/day Modafinil 100-400 mg/day
Narcolepsy	Regular bedtime Daytime naps	**Amphetamines** Dextroamphetamine 5-60 mg/day Methylphenidate 5-80 mg/day **Nonamphetamines** Pemoline 18.75-112.5 mg/day Modafinil 200-400 mg/day
Breathing-related sleep disorders	Weight loss Avoidance of sedating substances Positional therapy UPPP Tracheostomy CPAP/BiPAP	**Tricyclic Antidepressants** Imipramine 25-100 mg/day Desipramine 25-100 mg/day **Other Agents** Fluoxetine 20-60 mg/day Venlafaxine 75-300 mg/day
PLMD and RLS	None	**Dopaminergic agents** Carbidopa/levodopa 12.5/50 to 50-200 mg hs Pergolide 0.025-0.5 mg hs Pramipexole 0.125-1.0 mg hs **Benzodiazepines** Clonazepam 0.5-2 mg hs **Opioids** Codeine 15-30 mg hs Oxycodone 5-10 mg hs **Others** Gabapentin 100-800 mg hs
Parasomnias		
Sleepwalking disorder	Reassurance Maintenance of safe environment Psychotherapy Hypnosis	Diazepam 2.5-10 mg Clonazepam 0.5-2.0 mg
Sleep terror disorder	Reassurance Stress reduction	Diazepam 2.5-10 mg hs Clonazepam 0.5-2.0 mg hs
Nightmare disorder	Reassurance Stress reduction Psychotherapy Desensitization Rehearsal therapy	None
REM sleep behavior disorder	Reassurance Maintenance of safe environment	Clonazepam 0.5-2.0 mg hs

BIPAP, Bilevel positive airway pressure; *CPAP*, continuous positive airway pressure; *PLMD*, periodic limb movement disorder; *RLS*, restless leg disorder; *UPPP*, Uvulopalatopharyngoplasty.

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The Psychiatric Management of Patients with Cardiac Disease

23

Guy Maytal, M.D.
Jeff C. Huffman, M.D.
James L. Januzzi, Jr., M.D.
Theodore A. Stern, M.D.

Caring for cardiac patients can present a host of dilemmas for the general hospital psychiatrist. Patients with psychiatric conditions may exhibit cardiac symptoms, psychotropic agents can result in electrocardiographic abnormalities, and psychiatric manifestations may result from cardiac conditions. Moreover, patients with cardiac conditions can exhibit psychiatric symptoms, and cardiac drugs can result in psychiatric and neuropsychiatric symptoms. Because the overlap between psychiatry and cardiology is so great, knowledge of ways to manage specific problems can be of tremendous benefit. For instance, knowing how to deal with chest pain in the face of a psychiatric syndrome, an electrocardiographic complication from a psychotropic agent, or delirium due to invasive technology or cerebral hypoperfusion can facilitate comprehensive and compassionate care.

This chapter focuses on three main psychiatric syndromes related to the cardiac patient: anxiety, depression, and delirium. For each of these syndromes, we will consider epidemiology, clinical manifestations, differential diagnosis, psychopharmacologic approaches, and practical management strategies for patients with cardiac disease in the general hospital. Additional information on the interface between psychiatric and cardiac care will also be provided in other chapters.

ANXIETY IN THE CARDIAC PATIENT

Anxiety and the heart have long been linked. In 1836 Williams[1] published a text called *Practical Observations on Nervous and Sympathetic Palpitations of the Heart*. In 1871 Da Costa[2] described *irritable heart*, a condition in which chest discomfort was caused by emotional upset. In 1882 Osler[3] discussed the difficulty of differentiating cardiac and noncardiac etiologies of chest pain and described a subset of patients with atypical chest pain and nervousness. Since then, numerous authors have linked anxiety and chest pain and have described such symptoms using terms that have included Da Costa syndrome, soldier's heart, neurocirculatory asthenia, and effort syndrome. For years it has been suggested that anxiety and worry might cause heart conditions; more recent work has shown that both acute and chronic anxiety (as measured, for example, on the Cornell Medical Index[4]) are associated with sudden cardiac death (SCD) and coronary artery disease (CAD).[5,6]

The assessment of anxiety in the cardiac patient in the general hospital is often complex. First, it may be difficult to ascertain whether the patient is experiencing distress as a result of a myocardial event, an acute confusional state, a primary anxiety condition, or a complex interaction among these factors. Furthermore, there are many potential causes of anxiety for the cardiac patient, from an adjustment reaction to a serious cardiac event to the anxiogenic effects of cardiac medications administered to treat such events. Among hospitalized inpatients, the threshold for treatment of anxiety tends to be lower than it is in the outpatient setting, insofar as the elevations in catecholamine levels and vital signs associated with mild to moderate anxiety may have profound cardiovascular effects in the patient who has recently experienced a myocardial infarction (MI), coronary artery bypass grafting (CABG), or congestive heart failure (CHF).

Epidemiology

Anxiety Among Cardiac Patients

Patients who have an acute coronary syndrome or who undergo CABG are commonly anxious. Cardiac patients who are more critically ill (e.g., those on intraaortic balloon pumps [IABPs]) also experience significant anxiety; the presence of technology (e.g., automatic implanted cardiac defibrillators [AICDs]) can exacerbate such symptoms. Furthermore, patients who are initially identified as "cardiac" patients—including those who are admitted with chest pain but who have no known cardiac cause for their symptoms—may also have severe anxiety. Such anxiety may be both the cause of their chest pain and the result of being told that the cause for their symptoms is unknown.

Approximately 50% of patients with an acute coronary syndrome experience abnormal anxiety,[7] and 25% are at least as anxious as the average inpatient on a psychiatric unit.[8] These symptoms peak in the first 2 hospital days, then slowly drop over the next few days[8,9]; however, those with elevated levels of anxiety while in the hospital continue to be anxious 1 year later.[10] In addition, up to 40% of patients who have undergone CABG have clinically significant anxiety[11]; such symptoms are generally greatest before CABG,[12] but they can persist throughout the hospitalization.

Cardiac patients with invasive technology may also experience panic and fear associated with these devices. Approximately 10% to 15% of outpatients with pacemakers and AICDs have elevated levels of anxiety.[13,14] Not

surprisingly, patients whose AICDs discharged frequently (10 or more shocks received) are significantly more anxious; more than half of such patients had abnormal anxiety in one study.[14] Over the past several years, there has been a sharp increase in the number of studies examining psychopathology after AICD implantation. During the past 2 years, the number of studies examining psychopathology and quality of life after AICD implantation has increased dramatically. Multiple variables have been studied (including recipient age, gender, and social support network; the development of new depression and anxiety disorder diagnoses; and premorbid personality structure). A great deal of contradictory data have emerged. However, it is clear that in a significant minority of AICD recipients, the device worsens anxiety, probably more so if it fires.[15–18] In addition to high levels of free-floating anxiety, cardiac patients also experience elevated rates of formal anxiety disorders. Approximately 20% of all patients who arrive at emergency departments with chest pain meet criteria for panic disorder (PD).[19] Patients who visit outpatient cardiology clinics for evaluation of their chest pain have rates of PD that are even higher. A study of patients presenting to primary care clinics with chest pain found that although half of the patients met criteria for PD or infrequent panic attacks, few of the patients received the appropriate diagnosis of panic, and the presence of panic was associated with more testing and higher costs.[20] However, not all patients with PD are free of cardiac disease; in fact, patients with CAD appear to have PD at approximately four times the rate of the general population.[19] Furthermore, panic attacks may initiate or exacerbate cardiac events. Patients with co-morbid CAD and PD are among the most difficult for the general hospital psychiatrist because the cause of chest pain, palpitations, and other symptoms is often unclear. Therefore once PD is diagnosed, the clinician must remain open to the possibility of co-morbid cardiac illness as well.[21]

Cardiac patients who experience events as traumatic during their hospitalization may exhibit symptoms of post-traumatic stress disorder (PTSD). Recent studies have found that 8% to 16% of patients who have an MI develop symptoms of PTSD[22–24]; such PTSD symptoms also arise at a similar rate among patients who undergo CABG.[24,25] Studies of patients receiving intensive care for burn injuries and acute respiratory distress syndrome[26,27] suggest that PTSD may be even more prevalent among cardiac patients in intensive care units (ICUs). Finally, generalized anxiety disorder (GAD), though not formally studied in cardiac patients, appears to be common among patients with CAD. As noted previously, anxiety is prevalent 1 year after MI, and this may correlate with elevated rates of GAD. Furthermore, a study of chest pain in patients with GAD, but without cardiac disease, found that 48% of patients reported chest pain and 24% of patients had sought out medical evaluation for their pain.[28]

Association Between Anxiety and Cardiac Illness

Epidemiologic studies suggest that cardiac illness may lead to increased anxiety and that anxiety may also exacerbate cardiac illness. Acute and chronic emotional stress has been linked to the development of ventricular arrhythmias[29] and to the exacerbation of silent myocardial ischemia.[30]

A number of studies have also found a correlation between anxiety and sudden cardiac death (SCD). The Normative Aging Study,[31] an epidemiologic study of 2280 men, found that those with two or more anxiety symptoms on the Cornell Medical Index[4] had a fourfold greater risk of SCD than those without anxiety symptoms. Furthermore, prospective epidemiologic studies[32,33] of phobic anxiety have found a significantly increased rate of SCD. However, a few studies have not found a relationship between anxiety and cardiac mortality.[18]

Several specific anxiety disorders have been associated with adverse cardiac outcomes.[34] GAD predicted major cardiac events in a 2-year follow-up study of patients with CAD.[35] GAD has also been associated with increased rates of cardiovascular disorder risk factors (e.g., smoking, diabetes, hypercholesterolemia).[36] Furthermore, recent research has begun to explore physiologic markers common to both CAD and anxiety disorder. For example, a recent study by Bankier and co-workers evaluated 120 consecutive, stable CAD outpatients for the association between anxiety and inflammatory biomarkers. Even after adjusting for relevant demographic, medical, and psychiatric co-variables, the data demonstrated an association between C-reactive protein and GAD.[37]

One anxiety disorder in particular, PD, has been associated with a number of cardiovascular illnesses, (e.g., episodic and baseline hypertension,[38,39] small-vessel cardiac ischemia,[40] and the development of idiopathic cardiomyopathy[41,42]); idiopathic cardiomyopathy has been hypothesized to result from elevated catecholamine levels that cause a dilated cardiomyopathy.[43] Furthermore, a large community survey of more than 5000 patients found that, controlling for demographic factors, patients with PD had more than four times the risk of MI than those without PD.[44,45] Small longitudinal studies have suggested that PD may be associated with a greater overall cardiovascular mortality than those without PD; this effect appears to be greatest in men.[46] However, a recent study by Bringager and associates[47] evaluated the link between PD and cardiac morbidity and mortality in 199 patients referred for chest pain. After a 9-year review, the researchers found that PD was associated with increased chest pain intensity scores and poorer health-related quality of life measures but that it had no significant associations between baseline PD and mortality from cardiac illness at follow-up.[47] It is important to note that these links are at the level of association; it is not yet clear that PD *causes* these cardiovascular conditions; rather, patients with PD have them more frequently.

In the post-MI setting, anxiety may be associated with worse in-hospital and longitudinal outcome. Moser and Dracup[48] found that patients with post-MI anxiety were nearly five times more likely to have in-hospital ischemic or arrhythmic complications than those who did not. Frasure-Smith, Lespérance, and Talajic[49] found that patients with elevated levels of anxiety immediately after MI were more than twice as likely to have recurrent cardiac events over the next year. Furthermore, in a study of 129 post-MI patients, Huffman and co-workers found that post-MI anxiety was an independent factor associated with in-hospital cardiac complications (e.g., recurrent ischemia, re-infarction, CHF, and ventricular arrhythmias).[50] However, three other studies[51–53] found that post-MI anxiety did not

predict cardiac morbidity over the following year. One of these studies[51] did find that anxiety predicted poor quality of life, greater recurrent chest pain, more use of primary care services, and reduced adherence with medical recommendations. Despite these different findings, the studies were largely similar, using similar inclusion and exclusion criteria, standard instruments, and comparable numbers of patients.

Anxiety among patients undergoing CABG appears to have a similar effect. Two studies found that pre-CABG anxiety predicted poor psychosocial adjustment and quality of life both before and after surgery.[54,55] These studies are consistent with the literature on psychiatric outpatients with PD and GAD; investigators have found that these anxiety disorders were associated with a lower quality of life as well as increases in functional morbidity and the use of primary care services.[56–58]

Anxiety has also been shown to negatively affect patients with CHF. Friedmann and colleagues recently studied the prevalence of depression and anxiety in CHF as well as the relationship of psychosocial factors to mortality in outpatients with CHF. They found that anxiety was prevalent at a rate of 45% in their sample. However, they did not find an association between increased anxiety and increased mortality (though depression and social isolation were associated with it).[59] Furthermore, the tachycardia associated with anxiety can worsen CHF symptoms and lead to even worse cardiac output. This can become a spiraling process wherein patients' anxious concerns about their physical capacity can lead them to resist physical activity and hamper attempts at cardiac rehabilitation.[60]

In sum, cardiac patients have high rates of situational anxiety and formal anxiety disorders (e.g., PD, GAD, and PTSD). Such anxiety has been associated with elevated rates of myocardial ischemia, SCD, and other cardiac diseases, and in the post-MI setting may be associated with worse in-hospital and longitudinal cardiac outcomes. Furthermore, in addition to suboptimal medical outcomes, anxiety among cardiac patients in the general hospital is also associated with poor psychosocial outcomes.

Differential Diagnosis of Anxiety in the Cardiac Patient

Anxiety in the general hospital is often a primary psychiatric problem caused by stressful medical events. However, anxiety in the cardiac patient can also be caused by a number of general medical conditions and medications commonly associated with cardiac care (Table 23–1).

Not uncommonly, cardiac events cause anxiety. Myocardial ischemia, arrhythmias, and CHF can each cause anxiety owing to the sympathetic discharge associated with these conditions *and* because of what they may represent to the patient (e.g., the fear of dying, the worsening of medical illness, the loss of role identity). Other general medical conditions may cause or exacerbate anxiety in the cardiac patient; important among these is pulmonary embolism in the sedentary cardiac patient. Anxiety may also be a side effect of medications administered to cardiac patients, and it can result from substance intoxication or withdrawal (e.g., cocaine intoxication, alcohol withdrawal). Finally, impaired sleep in the coronary care unit (as the result of an unfamiliar setting, frequent nursing interventions, and significant noise) can lead to or exacerbate anxiety.

TABLE 23–1 Selected General Medical Causes of Anxiety Among Cardiac Patients in the General Hospital

Cardiac Events
Myocardial ischemia
Atrial and ventricular arrhythmias
Congestive heart failure
Other Medical Conditions
Pulmonary embolism
Asthma/chronic obstructive pulmonary disease (COPD) exacerbation
Hyperthyroidism
Hypoglycemia
Medications
Sympathomimetics
Thyroid hormone
Bronchodilators
Stimulants
Corticosteroids
Illicit Substances
Cocaine or amphetamine intoxication
D-Lysergic acid diethylamide (LSD) or phencyclidine (PCP) intoxication
Alcohol or benzodiazepine withdrawal

The general hospital psychiatrist should consider general medical causes of anxiety when evaluating cardiac patients; this is especially true when the anxiety has developed during an uneventful hospitalization, when the patient has no history of anxiety, or when anxiety persists despite appropriate treatment.

Psychopharmacologic Issues in the Anxious Cardiac Patient

Agents used to treat anxiety in the general hospital patient include benzodiazepines, antidepressants, and antipsychotics. Benzodiazepines are the medications most frequently used in the treatment of anxiety in cardiac patients. These medications rapidly relieve anxiety and appear to have a number of beneficial cardiovascular effects.

Benzodiazepines: Among patients with myocardial ischemia or infarction, benzodiazepines reduce catecholamine levels[61,62] and decrease coronary vascular resistance.[63] Although β-blockers, now commonly prescribed to cardiac patients, have similar effects, anxious patients tend to have elevations in vital signs, catecholamines, and coronary pressures as the result of their anxiety, despite the use of β-blockers; benzodiazepines can effectively treat these abnormalities. In addition, there is some evidence that benzodiazepines may inhibit platelet aggregation[64] and raise the ventricular fibrillation (VF) threshold.[65,66] Furthermore, benzodiazepines are generally well tolerated by the general hospital population; low rates of hypotension, virtually no anticholinergic effects, and very low rates of respiratory compromise develop when standard doses of benzodiazepines are used.[67] Benzodiazepines also appear to be safe even in seriously ill patients. A naturalistic study of 173 seriously ill medical inpatients (25% of whom died while in the hospital) who received IV diazepam for a variety of indications found that rates of any adverse effect from the benzodiazepine were low (3.5%).[68] Although clinicians

may be concerned about the development of benzodiazepine dependence, when these agents are used in the acute care setting, at adequate doses and for appropriate indications, the risk of dependence is minimal.[69]

Studies of benzodiazepines in cardiac patients have found that these agents effectively reduce anxiety and may have beneficial effects on cardiovascular outcome in selected cardiac populations. For example, patients with cocaine-induced chest pain are effectively treated with benzodiazepines; a recent study of patients who presented to an emergency department with chest pain after cocaine use found that the use of IV lorazepam in combination with nitroglycerin was safe and more efficacious in relieving cocaine-associated chest pain than was the use of nitroglycerin alone.[70] In addition, benzodiazepines may have beneficial effects in patients with more conventional causes of acute myocardial ischemia. A report by Wheatley[71] combined the results of three studies using benzodiazepines in post-MI patients; Wheatley found that the addition of benzodiazepines to standard cardiac medications led to significantly lower rates of reinfarction over the study period. It should be noted that the patients in these studies, however, were not taking β-blockers.

In short, benzodiazepines are rapidly effective in the treatment of anxiety in the cardiac patient. They are well tolerated and are associated with low rates of adverse effects and minimal risk of dependence when used in acute care settings. Benzodiazepines have favorable effects on catecholamines and coronary pressures and may have favorable effects on cardiac outcome when administered in the post-MI period. One important caveat for the use of benzodiazepines is that they can exacerbate confusion and paradoxically worsen agitation in patients with delirium or dementia; therefore other agents (e.g., antipsychotics) may be more appropriate for the treatment of anxiety, fear, and distress in the delirious or demented cardiac patient.

Antidepressants: Antidepressants can also be used in the treatment of anxiety in the general hospital. However, these agents often take several weeks to work and are best used to treat Axis I anxiety disorders, such as PD, GAD, or PTSD. For acutely anxious cardiac patients in the general hospital, when antidepressants are prescribed, it is often wise to co-administer benzodiazepines to acutely reduce anxiety during a vulnerable cardiovascular state.[72] Among the antidepressants, selective serotonin reuptake inhibitors (SSRIs) are generally the agents of choice for cardiac patients, given that tricyclic antidepressants (TCAs) can cause orthostasis, tachycardia (resulting from anticholinergic effects), and arrhythmias. The SADHART trial by Glassman and colleagues[73] established that the SSRI sertraline appears to be safe when administered 1 month after MI, with no adverse effects on cardiac function; smaller studies[74,75] and our own clinical experience have found that sertraline and other SSRIs may be used safely in the days and weeks after MI. Antidepressants will be discussed more extensively in the section on depression.

Antipsychotics: Antipsychotics can also be used for the treatment of heightened anxiety in the general hospital. Although the use of antipsychotics for anxiolysis has not been widely studied, the Massachusetts General Hospital (MGH) Consultation–Liaison (C-L) Service has long used antipsychotics when fear impairs reason in general hospital patients; both typical and atypical antipsychotics appear effective for this indication. Atypical antipsychotics, especially quetiapine[75] but also olanzapine and risperidone, are also being used more frequently in the treatment of acute anxiety. A recent review of the use of antipsychotics for anxiety noted that although there is ample clinical experience to support the efficacy of antipsychotic use to treat anxiety disorders, there is no large, well-designed study of antipsychotics in the treatment of primary or co-morbid anxiety symptoms or disorders.[76] These agents have the additional beneficial effects of symptomatically treating co-morbid delirium, and they do not cause the paradoxical disinhibition that is sometimes associated with benzodiazepines. Antipsychotics, however, can cause orthostasis and anticholinergic effects (associated with low-potency typical agents and, to a lesser degree, some atypical agents) and may be associated with prolongation of the corrected QT (QTc) interval. Antipsychotics will be discussed more extensively in the section on delirium.

Other Agents: Anticonvulsants, such as valproate and gabapentin, have been used in the acute treatment of anxiety. These agents are associated with essentially no risk of physiologic dependence, and they do not cause orthostasis or anticholinergic effects. Like antipsychotics, their efficacy in the treatment of acute anxiety in hospitalized cardiac patients has not been examined. They may be especially effective in patients with anxiety and co-morbid neuropathic pain.[77]

Approach to the Anxious Cardiac Patient

The psychiatric consultant is frequently called to cardiac floors to assess and treat anxiety. A careful, stepwise approach to these consultations can ensure an accurate diagnosis and appropriate treatment.

Consider a broad differential diagnosis for the patient's distress. A primary role of the general hospital psychiatrist is to accurately characterize a patient's distress as anxiety, denial, depression, delirium, or another psychiatric phenomenon. When the psychiatrist is consulted for so-called anxiety, it is easy to be biased toward making a diagnosis of anxiety. However, patients who appear anxious and tremulous may in fact be disoriented, paranoid, and frightened—that is, delirious. Therefore the consultant should be careful in the interview to assess affect, behavior, and cognition.

If the patient's primary psychiatric symptom appears to be anxiety, the consultant should then consider the potential contribution of medications or medical symptoms to this anxiety. As noted earlier, there is a long list of conditions that can cause or exacerbate anxiety, and the consultant should carefully consider these and recommend appropriate diagnostic studies, if appropriate. It may be especially useful to note correlations between anxiety levels and the initiation or discontinuation of potentially offending medications or substances. For example, the development of anxiety, tremulousness, insomnia, and fluctuations in vital signs 24 to 48 hours after admission might suggest alcohol withdrawal, even in a patient who denies alcohol use.

Evaluate sources of anxiety and assess how the patient has dealt with difficult situations in the past. A careful psychiatric interview of the anxious patient will help determine what factors are causing his or her anxiety. Is the preoperative CABG patient anxious because a relative died during

cardiac surgery years ago? Is the post-MI mother of three worried because she is afraid that no one will be able to care for her children if she dies as a result of cardiac disease? Is the patient with an AICD fearful that his defibrillator will painfully discharge again? By determining the sources of anxiety, the consultant will be able to address these anxieties through education, reassurance, medication, or brief psychotherapy. Often, many of these worries (e.g., worries about being able to sleep in the hospital and worries that family members have not been contacted) can be directly addressed. Furthermore, knowledge of the factors that contribute to anxiety may allow the consultant to estimate the duration of such symptoms; for example, a patient who reports that he will be "just so relieved" once the surgery to place his AICD is performed is likely to have a relatively short course of anxiety, whereas the patient with chronic, uncontrollable worries is likely to have anxiety throughout the hospitalization.

A related task is to determine the patient's coping style and coping strengths. How does he or she manage anxiety outside of the hospital? How has he or she managed difficult situations in the past? The consultant can use this information to identify the patient's strengths and determine the best approach to the patient's anxieties. Patients who identify themselves as survivors or as people who persevere and succeed despite difficult obstacles often take quite well to a consultant who also identifies this quality in them.

Another question for patients involves stimulation and control. Some cardiac patients crave control and wish to know every detail of their care; they feel anxious when they do not feel that they have comprehensive information about their illness and when they are not part of all treatment decisions. In contrast, other patients find such information and the pressure to make decisions overstimulating and feel less anxious when told only the general details of their condition.

Recommend appropriate behavioral and therapeutic interventions. Having learned about the patient's sources of anxiety, coping strengths, and preferences regarding control, the consultant is in an excellent position to design a treatment plan that reduces a patient's anxiety. For example, if a patient reports that the hospitalization is overwhelming, members of the treatment team can be encouraged to limit detailed information and reassure the patient that they see this condition frequently (if true) and that they plan to provide excellent care to the patient. On the other hand, for the patient whose anxiety increases with the perceived lack of control, the treatment team can be encouraged to provide the patient with detailed information and written materials. The patient should also be included in treatment decisions; inclusion in even small decisions (e.g., the best time for dressing changes) can allay anxiety and allow the patient to feel in control.

In other cases, worried cardiac patients simply need to express their anxieties to someone. If the consultant, treating physician, and nursing staff can set aside short periods to reflectively listen to the patient's fears, this investment of time often results in significantly less anxiety, greater compliance with treatment, and less chaos for patient and staff alike. If the patient seems to have an insatiable desire to discuss his or her fears, staff can be taught to consistently set aside time to listen to the patient while setting limits on his or her time; for example, a nurse may tell the patient that she will sit with him or her for 5 minutes at the beginning, middle, and end of the shift to talk about his or her worries. If the patient attempts to engage the nurse in further conversation about this topic, the nurse can calmly tell the patient that they can discuss it at their next appointment.

Intelligently use psychiatric medications for specific target symptoms. Benzodiazepines are often the agents of choice for the anxious cardiac patient. If the anxiety appears to be short-term or situation-specific (e.g., whenever a procedure is performed), a short-acting benzodiazepine can be used on an as-needed basis, (e.g., lorazepam 0.5 to 1.0 mg as needed for acute anxiety). However, for most patients, longer-acting benzodiazepines given on a standing basis provide the smoothest and most consistent reduction of anxiety. Most anxious cardiac patients can be started on clonazepam 0.5 mg at night or twice per day; doses can be adjusted upward if this dose is well tolerated and anxiety persists. In general, these agents can be discontinued on discharge from the hospital if they were only used on a short-term basis.

Benzodiazepines may not be the agents of choice for patients with acute or chronic organic brain syndromes (e.g., delirium, dementia, traumatic brain injury), tenuous respiratory function (including obstructive sleep apnea), or a history of substance dependence. For these patients antipsychotics are often useful, alleviating agitation and confusion in delirious patients while also reducing anxiety. We often start with doses of quetiapine at 12.5 to 25.0 mg at night or twice per day or olanzapine at 2.5 to 5.0 mg at night or twice per day.

Anticonvulsants may be useful when a patient has anxiety that is co-morbid with neuropathic pain or with a chronic brain disturbance, such as a dementia or head injury. Antidepressants may be useful in the treatment of Axis I anxiety disorders and when depression is co-morbid with anxiety; we generally co-administer a benzodiazepine to reduce initial anxiety associated with initiation of antidepressants.

Return frequently to see the patient. Anxious patients generally are relieved to see a familiar face, especially one that has attempted to understand and address their anxiety. Such frequent follow-up, therapeutic in itself, allows for careful monitoring of behavioral and pharmacologic interventions.

CASE 1

Mr. A, a 53-year-old executive without a psychiatric history, was admitted for CABG after cardiac catheterization revealed three-vessel cardiac disease. He initially had an uneventful perioperative course. However, on the day after his operation, psychiatry was consulted to assess his capacity to leave the hospital against medical advice.

On interview, Mr. A was alert, oriented, lucid, and initially quite angry. He reported, "I have no assurance that I'm getting the right care; the doctors and nurses come in and out of my room and bark orders to one another but they don't include me at all. They haven't even listened to the fact that I always take my sleeping pill at 9 PM every night instead of 11 PM like they give it to me. I'm fed up." By the end of his tirade, Mr. A's anger had changed to fear and anxiety.

The consultant told Mr. A that he would bring his concerns to the team. The consultant met with members of the treatment team and encouraged them to provide as much information as possible about his care and to allow him to mandate his treatment when possible (e.g., getting his sleeping pill at 9 PM). The consultant, nurse, and Mr. A then met together so that Mr. A could express his concerns and the nurse and consultant could outline the ways their procedures would change so that he could have more information and more control. Mr. A agreed to this plan and also agreed to clonazepam 0.5 mg twice per day to reduce his anxiety.

The consultant checked back frequently with Mr. A to assess his response to this treatment plan. Small changes in the plan were instituted at his request, and his anxiety steadily decreased. He was discharged to cardiac rehabilitation and thanked the nursing staff for their "compassionate care."

DEPRESSION IN THE CARDIAC PATIENT

Over the past 2 decades, substantive research has firmly established a bidirectional link between depression and cardiac disease: Patients with depression are more likely to develop cardiac disease, and patients with cardiac disease are more likely to suffer from depression.[78] Initial studies by Frasure-Smith and colleagues[79,80] suggested that depressive symptoms immediately after MI are associated with greater cardiac mortality 6 and 18 months later. Such findings renewed interest in the treatment of post-MI depression and led to further studies of the safety and efficacy of antidepressants in the post-MI period. In addition, patients undergoing cardiac surgery are more likely to have adverse medical outcomes if they are depressed before surgery.[81] These findings have underscored the importance of the general hospital psychiatrist's role in identifying depressed cardiac patients and considering appropriate treatments.

Depression in Patients with Established Cardiac Illness

Depression is common among patients with CAD, with prevalence rates of major depression hovering around 20%.[82–85] This rate of depression is greater than the prevalence of depression in the general population (approximately 15%).[86] Such elevated rates of depression are also present among cardiac patients in the general hospital: 15% to 30% of post-MI patients have major depression, and 65% manifest at least minor depression.[87,88] Moreover, a study by Baker and associates[89] found that more than 30% of pre-CABG patients were depressed. Adequate treatment of depression is essential given that it is a serious and debilitating illness. Furthermore, as will be discussed later, optimal treatment of depression may reduce cardiac morbidity and mortality.

With regard to depression, post-MI patients have been the most extensively studied cardiac population. As mentioned previously, Frasure-Smith and colleagues demonstrated that patients diagnosed with major depression disorder (MDD) after MI had higher mortality rates than patients without MDD.[79] The Stockholm Female Coronary Risk Study[90] followed 292 women for 5 years and found that women with two or more depressive symptoms had an increased risk (hazard ratio 1.9) of future cardiac events (acute MI, cardiovascular mortality, and revascularization procedures) compared with women who had one or no depressive symptoms. In a more recent study, Frasure-Smith and Lespérance examined the cardiac prognostic importance of MDD and GAD in 804 patients with stable CAD.[35] They found that compared with patients without psychiatric diagnoses, those with MDD or GAD had a significantly higher risk of major adverse cardiac events (cardiac death, MI, cardiac arrest, or nonelective revascularization). Furthermore, a meta-analysis of 22 studies of post-MI subjects found that post-MI depression was associated with a 2- to 2.5-fold increased risk of negative cardiovascular outcomes.[91]

Despite the high prevalence of depression and the risks it carries for cardiac patients, only 10% of post-MI depressed patients are recognized as such.[92] Several factors likely account for these low rates of recognition. The pattern of depression (with hostility, listlessness, and withdrawal being more common than sad mood) is often somewhat atypical[93]; furthermore, depression is often seen as a normal consequence of a serious medical event, such as MI. Finally, most patients with uncomplicated MI have brief inpatient stays, and it may be difficult to assess a patient's mood or to obtain psychiatric consultation during this limited time frame.

In a review of post-MI depression, Strik, Honig, and Maes[87] delineated a number of putative risk factors for the development of post-MI depression. These risk factors included smoking, hypertension, female gender, social isolation, medical complications during acute hospitalization, a history of depression, and first-time prescription of benzodiazepines (suggesting potential co-morbidity between anxiety and depression).

The course of post-MI depression may be relevant in its relationship to ischemic heart disease and cardiac morbidity. When a depressive episode occurs immediately after an MI, it is considered an incident episode. The causes and effects of such episodes may be distinct from those of depressive episodes that occur long before or after the MI (i.e., ongoing or recurrent depression). The Depression after Myocardial Infarction Study followed 468 MI patients for 2.5 years after an index MI. The authors found that 25.4% of patients experienced a depressive episode in the year after the MI, and 44.6% of these were incident MIs. Patients with incident depression were more likely to have new cardiovascular events (hazard ratio 1.65), whereas patients with nonincident depression were not.[94,95] In an 8-year study of 588 individuals following MI, Dickens and co-workers found that new-onset depression after MI was associated with increased cardiac mortality (hazard ratio 2.33), whereas pre-MI depression did not add any additional risk of cardiac mortality.[96] Post-MI depression is frequently persistent; Travella and associates[97] reported that the average length of a depressive episode after MI is 4 to 5 months. Frasure-Smith and colleagues[98] found that more than half of patients with post-MI depression remained depressed after 1 year. Even more strikingly, Lespérance and colleagues[99] found that only 26% of the patients who were depressed immediately after MI were alive and known to be depression-free at follow-up.

Other cardiac patients may also have elevated rates of depression. Shapiro and colleagues[100] followed 30 recipients of left ventricular assist devices and found that 17% became depressed in the postoperative period. Candidates for cardiac transplantation have elevated rates of anxiety and depression[101]; depressive symptoms can persist for years after transplantation.[102] Dew and co-workers[103] found that one quarter of transplant recipients developed MDD in the 3 years after transplantation. Furthermore, rates of MDD have also been found to be elevated in longitudinal studies of patients with CHF.[60] In a study of 152 patients with New York Heart Association (NYHA) Class III heart failure, Majani and colleagues found a significantly higher incidence of MDD compared with controls.[104]

In short, depression is common among cardiac patients, and it has been best studied in those with recent MI. Post-MI depression is highly prevalent, poorly recognized, and frequently persistent.

Depression as a Risk Factor for Cardiac Disease

Evidence from many community studies over the past 20 years indicates that depression is an independent risk factor for cardiovascular disease.[105] Several studies have found that patients with depressive symptoms are 1.5 to 3.5 times more likely to have an MI than are those without such symptoms.[78,106–111] Patients with full-blown MDD appear to have an even greater risk (4.5 times greater than nondepressed patients) of suffering an MI.[109] Another study of patients with asymptomatic CAD (noted on coronary angiography) found that 18% were depressed, a rate of depression that is more than 3 times greater than in the general population.[110] In addition, the Johns Hopkins Precursor Study[106] found that, in a 40-year follow-up of male physicians, depression was associated with a strongly significant twofold risk of developing heart disease.

Although much of the research on the association between MDD and cardiac disease has been done in men, recent data indicate that this association also holds true for women. The Women's Ischemia Syndrome Evaluation (WISE) study followed 505 women referred for coronary angiography for an average of 4.9 years. The study found that even adjusting for other factors related to cardiac disease (e.g., age, smoking, diabetes, hypertension, body mass index, stenosis score on angiography), women with elevated Beck Depression Inventory scores or prior treatment for depression (or both) had significantly increased rates of mortality and cardiovascular events (e.g., CHF, stroke, unstable angina, MI, revascularization).[112]

Recent studies have also examined the relationship between depression and cardiac disease in the elderly. Several large longitudinal studies have demonstrated that for individuals over the age of 65, a new diagnosis of depression is associated with a significantly higher risk of new cardiovascular events or death resulting from cardiovascular causes.[113,114]

Critics of all of these studies have raised two important arguments. First, relative to the human life span, the follow-up periods of these studies are too short. Second, depression measured only by way of elevated depressive symptom scales may reflect generalized distress and may not be specific enough to capture true depressive disorder. In response to these concerns, the Stockholm Heart Epidemiology Program (SHEEP) study examined the risk of MI among individuals hospitalized for depressive disorder over a 26-year period.[115] This case-control study examined 1799 cases and 2339 controls and demonstrated a significantly increased risk (relative risk 2.3) for acute MI among patients hospitalized for depression—even after controlling for cardiac risk factors.

A recent meta-analysis examined these and other studies to determine the role of depression as a predictor of CAD.[116] Van der Kooy and colleagues identified 28 relevant studies that comprise more than 80,000 subjects. Despite differences in study design and quality, the meta-analysis demonstrated that depression was associated with an increased risk of cardiovascular disease (RR 1.46). This analysis also found that the strongest association was made when patients were diagnosed by clinical interview. Also, studies using depression scales demonstrated a dose–response relationship between depressed mood and the development of cardiovascular disease. The authors concluded that depression predicts the development of CAD among initially healthy persons. In addition to predicting the development of CAD in healthy people, depression has also been associated with significantly higher rates of cardiac death and overall mortality among patients with established CAD. In the specific population of post-MI patients, numerous studies have examined the relationship between post-MI depressive symptoms and cardiac mortality; the majority of these studies,[53,79,80,117,118] though not all,[51,52] have found that depressive symptoms after MI predict cardiac mortality 6 to 18 months later. These effects on mortality appear to be largely independent of the severity of cardiac disease, demographic variables, medications, or other confounding factors. The best known of these studies (by Frasure-Smith and co-workers[79,80]) found that depressive symptoms immediately after MI were associated with a fourfold to sixfold augmentation of risk of cardiac mortality 6 and 18 months after MI. Bush and colleagues[117] found that even minimal depressive symptoms were associated with an elevated risk of cardiac mortality, though more severe depressive symptoms more strongly predicted cardiac mortality.

Depressive symptoms also appear to predict cardiac morbidity and mortality in other cardiac populations as well. At least three studies have found that pre-CABG depressive symptoms have been associated with an increase in cardiac morbidity at 6 or 12 month follow-up.[81,89,119] Among patients undergoing cardiac transplantation, persistent depression was associated with increased rates of incident CAD.[103] Furthermore, a study by Zipfel and associates[120] found that preoperative depressive symptoms predicted mortality in cardiac transplant recipients. Finally, Friedmann and colleagues found that in patients with CHF, depression and social isolation predicted higher mortality independent of demographic factors or clinical status.[59]

Numerous mechanisms have been offered to explain the link between depression and cardiovascular disease.[121] Some are behavioral and include continued poor health habits (e.g., smoking, lack of exercise) and noncompliance with medical care. Depressed patients appear to have decreased adherence to medication regimens,[122] and depressed cardiac patients attend cardiac rehabilitation

programs less frequently than their nondepressed peers.[123] Furthermore, patients who are depressed after MI are less likely to follow recommendations about diet, exercise, and smoking cessation.[124,125]

The possible physiologic mechanisms by which depression may contribute to increased cardiac morbidity and mortality rates are several, though none has been clearly outlined. The increased morbidity rate may be attributable to increased catecholamine levels. Depressed patients have increases in baseline levels of circulating catecholamines and exaggerated rises in catecholamine levels during stress[126]; elevated catecholamine levels can result in increased myocardial oxygen demand and elevations in blood pressure and heart rate. Furthermore, elevated catecholamine levels have been associated with infarct initiation, infarct extension, and the development of VF in patients with myocardial ischemia.[127,128]

The association between depression and cardiac morbidity may be mediated by changes in autonomic nervous system tone, which may be manifested as decreased heart rate variability (HRV) or as abnormalities in baroreflex sensitivity. HRV is a measure of autonomic regulation of cardiac activity, and decreased HRV has been established as an independent risk factor for the development of SCD. Both depressed psychiatric outpatients and patients with post-MI depression have been found to have decreased HRV,[129,130] and depressed patients with CAD have been shown to have elevated rates of ventricular arrhthymias.[131] Therefore depressed patients with CAD may have decreased HRV, leading to increased susceptibility to ventricular arrhythmias and SCD; this may explain increases in cardiac morbidity and mortality.

Several other mechanisms have been proposed to explain the link between depression and heart disease. Recently, an association has been demonstrated between MDD and elevated levels of the inflammatory biomarker C-reactive protein.[132] Another mechanism involves platelet aggregation; depressed patients with CAD appear to have increased platelet aggregation,[82,133] and this could increase vulnerability to myocardial ischemia. Another involves the inflammatory changes and endothelial dysfunction seen in depression that may worsen risk of acute cardiac events.[134,135] Another explanation rests on the observation that sleep and circadian rhythm dysfunction are associated with both increased risk of cardiac disease and depressive disorder.[136]

The link between depression in cardiac patients and increased cardiac morbidity is likely mediated by multiple factors. One crucial question that remains unanswered is whether treatment of depression among cardiac patients improves cardiac prognosis.

Differential Diagnosis of Depression in the Cardiac Patient

As with anxiety in the cardiac patient, there are a number of medical conditions and medications that can cause or exacerbate depressive symptoms. Table 23–2 lists a number of these medical influences on mood. Conditions associated with depressed mood that are common in the cardiac patient include hypothyroidism (both idiopathic and secondary to amiodarone, which is increasingly prescribed to cardiac patients), Cushing's disease (idiopathic or cushingoid symptoms secondary to steroid administration), neoplasm (especially pancreatic), vitamin B_{12} and folate deficiency, and depression associated with vascular dementia.

TABLE 23–2 Selected General Medical Causes of Depression Among Cardiac Patients in the General Hospital

Medical Conditions
Hypothyroidism (idiopathic or amiodarone-induced)
Cushing's disease
Vitamin B_{12} or folate deficiency
Neoplasm (especially pancreatic, lung, or central nervous system tumors)
Vascular dementia
Movement disorders (e.g., Parkinson's disease or Huntington's disease)
Medications
Angiotensin-Converting Enzyme (ACE) inhibitors
Methyldopa
Reserpine
Corticosteroids
Interferon
Illicit Substances
Chronic alcohol or benzodiazepine abuse
Cocaine or amphetamine withdrawal

A number of medications sometimes used in cardiac populations have been associated with depression. Steroids, methyldopa, and reserpine have each been linked with increased rates of depression. Substances can also influence mood; chronic alcohol use and withdrawal from cocaine or amphetamines commonly lead to depression. β-blockers have long been associated with depression; however, a recent reexamination of the literature suggests a minimal association between β-blockers and depression.[137]

Because depression can have significant effects on cardiac and psychosocial outcome in cardiac patients and because the causes of depression are often reversible or treatable, the general hospital psychiatrist should consider these in all depressed cardiac patients.

Psychopharmacologic Issues in the Depressed Cardiac Patient

Antidepressants are effective in the treatment of depression. However, older antidepressants (i.e., TCAs and monoamine oxidase inhibitors [MAOIs]) have effects that make their use in cardiac patients difficult. TCAs have anticholinergic effects (including tachycardia) and can cause orthostasis; these effects make their use questionable in patients with significant cardiac disease. Even more concerning is the propensity of TCAs to prolong cardiac conduction and to have a pro-arrhythmic effect in some patients as a result of their guanidine-like properties.[138,139] A recent study, controlling for medical and demographic factors, found that depressed patients on TCAs had more than a twofold risk of MI, whereas SSRIs did not enhance risk of MI.[140] For these reasons, the use of TCAs is generally not recommended for patients with cardiac conduction disease[141] and in the 2- to 3-month period after MI;[139,142] unfortunately, this peri-MI period appears to be the time when post-MI depression is both most prevalent and most dangerous.

Newer antidepressants (e.g., SSRIs, bupropion, and mirtazapine) do not appear to have the negative cardiovascular effects of TCAs. They are generally not associated with significant anticholinergic effects or orthostasis, and they do not appear to result in adverse effects on cardiac conduction. These properties make SSRIs and other new agents a more logical choice for most patients with cardiac disease. This recommendation is supported by a study (by Roose and associates[143]) that compared paroxetine and nortriptyline in depressed patients with ischemic heart disease. The two agents were equally efficacious, but the TCA was associated with a significantly higher rate of serious adverse cardiac events.

One cardiac population in whom the cardiac safety of SSRIs has been scrutinized is the post-MI population. Though a small study of fluoxetine found this agent to be safe in a post-MI population,[144] the most extensive study has been on the SSRI sertraline. The preliminary SADHAT trial by Shapiro and co-workers[75] found that the open-label administration of sertraline to 26 post-MI patients was associated with clinical improvement of depression and resulted in no significant changes in heart rate, blood pressure, cardiac conduction, left ventricular ejection fraction, or coagulation measures. This study paved the way for the more extensive multicenter SADHART trial by Glassman and colleagues.[73] This study used a double-blind, placebo-controlled design to administer sertraline or placebo to 369 post-MI patients. The investigators found that compared with placebo, sertraline significantly improved depressive symptoms and was not associated with changes in ejection fraction, cardiac conduction, or adverse cardiac events. Two important limitations of this study were that patients did not begin treatment until an average of 34 days after their MI and that the patients were followed for only 24 weeks. Most intriguing was the finding that the incidence of severe cardiac events was numerically lower in patients receiving sertraline, but this result did not reach statistical significance. The SADHART trial was not designed to detect a difference in morbidity and mortality, but it did achieve its principal aim of proving the safety of sertraline for use in depressed post-MI patients when administered to patients approximately 1 month after MI.

More recently, the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial studied the safety and efficacy of citalopram and interpersonal therapy (IPT) in 284 depressed patients with CAD in a double-randomized, placebo-controlled design.[145] They found citalopram safe and effective in treating depression in this patient population. Interestingly, there was no discernible added value to IPT over clinical management as usual.

Therefore it appears that citalopram and sertraline (and likely other SSRIs) are safe to use in patients with cardiac disease. Our clinical experience with SSRI administration in cardiac patients has also found SSRIs to be safe, and we have safely prescribed SSRIs in post-MI patients earlier than 1 month after the MI when indicated by the severity of depression or the follow-up circumstances.

Though other new non-SSRI antidepressants appear to have properties that would render them safe in cardiac populations, these agents have been less extensively studied. Bupropion, at therapeutic doses, does not have adverse effects on blood pressure, heart rate, or other cardiovascular parameters.[146] Furthermore, a study of bupropion in depressed patients with CAD found that this agent had a favorable cardiovascular side effect profile in this specific population.[147] Although bupropion overdose can cause hypertension and tachycardia,[148] it generally does not lead to adverse cardiovascular events[149,150]; however, some studies of bupropion overdose have noted cardiovascular effects, including tachycardia, hypertension, wide-complex tachycardia, and cardiac arrest.[151] Therefore bupropion should be used cautiously in depressed cardiac patients with a history of overdose or significant impulsivity. The use of bupropion in the cardiac patient is made more appealing by its ability to aid smoking cessation.[152,153] Bupropion (at 300 mg per day) has been found to be effective for this indication, and therefore cardiac patients who are depressed and who continue to smoke might be excellent candidates for bupropion therapy.

Mirtazapine is another new antidepressant that has a favorable cardiovascular side effect profile. It has few effects on cardiac conduction or vital signs, even in overdose,[154] and is otherwise well tolerated. Recently, the Myocardial Infarction Depression Intervention Trial (MIND-IT), a 24-week randomized, placebo-controlled study, evaluated the safety and efficacy of mirtazapine in 209 post-MI patients diagnosed with depression within the first year of their cardiac event.[155] The study found mirtazapine to be safe in post-MI patients. It also found a dose-dependent relationship between depressive symptom severity and left ventricular ejection fraction. Finally, the MIND-IT investigators did not find statistically significant changes in the Hamilton-Depression (Ham-D) scores at 8 and 24 weeks of treatment (primary outcome measure). However, there were statistically significant improvements on self-report rating scales and, in their statistical analysis, the authors concluded that they found a significant difference favoring mirtazapine over placebo.[156] One potential drawback of the use of mirtazapine in cardiac patients is its propensity to cause weight gain in some patients as a result of its interaction with histamine receptors.

Psychostimulants have also been shown to be rapidly acting, efficacious antidepressants in medically hospitalized patients.[157,158] Though they may elevate blood pressure or heart rate, stimulants may be indicated in cardiac patients whose depression requires rapid treatment (e.g., depression that is severe, is negatively affecting rehabilitation owing to anergia or minimal oral intake, or is affecting the patient's capacity to make medical decisions). Stimulants are relatively contraindicated in patients with a history of ventricular tachycardia, recent MI, CHF, uncontrolled hypertension or tachycardia, or those who are concurrently taking MAOIs. However, in many cardiac patients, psychostimulants can be safely used with slow dosage titration, beginning with 2.5 to 5.0 mg in the morning and increasing up to 20 mg per day.

Several studies have also examined the efficacy of psychotherapy to treat depression in cardiac patients. Interestingly, there is no convincing evidence for using manualized psychotherapy techniques (e.g., cognitive behavior therapy [CBT] or IPT) in cardiac patients. The Enhancing Recovery in Coronary Heart Disease (ENRICHD) trial enrolled 2481 patients after an MI with depression or low

social support in either CBT or usual care. Antidepressant therapy was allowed (in a nonrandomized manner) as a supplement in patients with persistent depressive symptoms. The study found no impact of CBT on the end point of death or nonfatal MI. However, the investigators found a 40% lower risk of either death or nonfatal MI in patients treated with antidepressant medications.[159] Likewise, the CREATE trial discussed previously[145] found no impact of IPT on depressive symptoms in post-MI patients with depression. These data suggest that psychotherapy interventions that are effective in depressed patients in the general population may not be effective in those with ischemic heart disease.

Approach to the Management of the Depressed Cardiac Patient

The approach to the depressed cardiac patient is in many ways similar to the approach to the anxious cardiac patient. The consultant must first confirm that depression is the primary psychiatric symptom and evaluate for co-morbid psychiatric conditions. Furthermore, the psychiatrist must consider the presence of medical conditions or medications that can cause or exacerbate mood symptoms. Once these steps have been completed, an approach to treatment involves an identification of the patient's coping strengths and support network; it may also involve the weighing of the risks and benefits of antidepressant treatment. In the subsequent paragraphs, we outline the approach to the depressed cardiac patient.

Consider appropriate psychiatric and medical differential diagnoses. As with consultations on cardiac floors for apparent anxiety, we also find that consultations for apparent depression often reveal that a patient's distress is caused by another psychiatric syndrome. Commonly, disordered sleep, inability to engage with caregivers, and social withdrawal may result from a hypoactive delirium rather than from depression, and therefore cognitive status must be addressed. Furthermore, anxiety is often prominent in cardiac patients, and the patient's distress may be more accurately assessed and treated as anxiety.

The consultant should also note the course of depressive symptoms to see if the onset or worsening of such symptoms correlated with the administration of a new medication or new physical symptoms or if there are other indications that a physical disorder might be implicated in the evolution of the depressive symptoms. The general hospital psychiatrist should also order laboratory tests and other studies as indicated (e.g., vitamin B_{12} and folate in an elderly patient with poor nutrition; thyroid function tests in a patient with recent cold intolerance, weight gain, loss of appetite, and thinning of hair; or toxicologic screening tests when clinical suspicion of substance use arises).

Attempt to identify the patient's coping style and the triggers for depressive symptoms. Determining the external factors that exacerbate depressive symptoms may help the consultant reduce the patient's stressors. Is the patient feeling more depressed because he must face his mortality? Does he feel that his children will not respect him? Is he stuck in the hospital and unable to attend an important family function? The consultant can use this information to implement solutions that are psychotherapeutic in nature (e.g., discussing mortality and life goals) or more concrete (e.g., having family members call the patient to let him know he is missed and important to them). Identification of the patient's coping strengths—especially, how the patient has previously managed difficult situations—will inform the treatment team's approach to the patient.

Of particular interest to the psychiatric consultant is recent data indicating that patients with CAD who use a repressive coping style are at particular risk of adverse cardiac events and death.[160,161] Perhaps because these individuals report low levels of anxiety and depression, they were once thought to be at low psychological risk for clinical events. However, it is now thought that these individuals often fail to detect or report significant emotional distress, which could contribute to their increased risk of MI and death. The consultant should be particularly mindful of patients whose emotional cool seems at variance with the severity of their clinical circumstances.

Make use of existing social supports or help develop a network. Social support has been associated with superior medical outcomes in depressed patients after MI[162]; therefore if such social support does not exist, the consultant can work with the treatment team to consider options to improve the patient's support system. Such options could include participation in cardiac rehabilitation, having visiting nurses, joining a support group, or beginning psychotherapeutic treatment for depressive symptoms (CBT has been found to be effective in the treatment of post-MI depression,[163] and it carries no concern of drug–drug interactions). Such interventions should not be limited to post-MI patients; all cardiac patients can benefit from increased social support, and creating a more coherent system of support for a cardiac patient improves the chances of recovery.

Carefully consider the use of antidepressant medication. SSRIs, bupropion, and mirtazapine appear to be both safe and effective for patients with CAD, with few cardiovascular side effects. Therefore in most cardiac patients who meet criteria for MDD, these antidepressants can be administered at standard doses. The SSRIs sertraline, citalopram, and escitalopram have the additional advantage of having few drug–drug interactions and little interaction with the cytochrome P450 system; therefore we use these agents more frequently in cardiac patients on multiple medications. Bupropion also has few drug–drug interactions and may be the agent of choice in patients with co-morbid MDD and a desire to stop smoking.

The risks and benefits of antidepressant medications should be more carefully considered in patients with recent MI and probably by extension all patients with severe cardiac disease, a history of ventricular arrhythmia, or recent cardiac surgery. For most patients who have just had an MI or a CABG, we typically do not prescribe antidepressants for the onset of depressive symptoms within days after MI, both because such patients have not yet met criteria for MDD and because extensive data establishing the safety of these agents in the post-MI or postcardiac surgery period do not exist. For most patients who become depressed after an MI, a reasonable and conservative approach is to have the patient follow up with a psychiatrist (or primary care physician) within 2 to 3 weeks; then, if the patient remains depressed, he or she can start sertraline or another antidepressant.

Certain factors may cause a clinician to lean toward the earlier prescription of antidepressants. These include the following:

- Depression with suicidal ideation
- Severe depression that inhibits participation in rehabilitation or self-care
- The development of depressive symptoms during hospitalization in a patient with a history of severe depression
- An inability or unwillingness to follow up in the next 2 to 3 weeks (We often see patients who wish to see only their primary care physicians, and then only every 2 to 3 months. These patients are quite compliant with their medication regimen and would therefore take an antidepressant if prescribed on discharge, but they would be unlikely to return to see their physician in the next 6 weeks.)

When one or more of these factors is present, we frequently initiate antidepressant therapy in the hospital in coordination with cardiology. As noted previously, when anxiety is present co-morbidly, it is best to use benzodiazepines when beginning an antidepressant, given that most antidepressants can cause initial anxiety or insomnia in the first few days of use.

CASE 2

Mr. B, a 52-year-old gentleman with a history of MDD, was admitted to the hospital with chest pain. His electrocardiogram showed ST-segment depression in the anterolateral leads, his cardiac enzymes were elevated, and he ruled in for an MI. Though he had not been depressed in the year before admission, he developed depressive symptoms in the days after his MI; psychiatric consultation was obtained.

On interview, Mr. B was dysphoric but alert, oriented, and able to actively engage in conversation with the interviewer. He reported depressed mood, anhedonia, and low energy, along with disturbed concentration and appetite; he denied significant anxiety. He denied feeling suicidal or being unable to care for himself. Mr. B reported one episode of relatively mild MDD 3 years ago that responded well to citalopram (20 mg per day, for 1 year); he had also had several episodes of "feeling low" for 3 to 5 days that spontaneously resolved. He appeared to be invested in getting better, he had a strong social support network, and he planned to follow up with his cardiologist shortly after his hospitalization.

Given Mr. B's relatively mild current depressive symptoms, his history of having only one mild episode of MDD, and his ability and willingness to follow up with his cardiologist, the consultant decided to defer antidepressant treatment while Mr. B was in the hospital. The consultant contacted Mr. B's cardiologist and they agreed that citalopram should be started (given Mr. B's history of good response to this medication) if he continued to be depressed at his follow-up appointment in 2 weeks.

Mr. B had an uneventful medical course and was discharged 3 days after his MI. He followed up in 2 weeks with his cardiologist; he remained depressed and was started on citalopram. He tolerated the citalopram (20 mg per day) well, and his depressive symptoms subsided over the next 8 weeks.

DELIRIUM IN CARDIAC PATIENTS

Patients with cardiac disease have long been found to have a propensity for delirium. In an era when open-heart surgery was common, the incidence of postcardiotomy delirium (PCD) was found to be 32%.[164] Despite advances in the treatment of cardiac illness and the use of noninvasive procedures to open coronary arteries and replace abnormal valves, general hospital patients with cardiac disease continue to suffer delirium at high rates (ranging from 3% to 72% depending on the specific illness and type of procedure).[165] High rates of co-morbid medical illness, complex medication regimens, and central nervous system (CNS) hypoperfusion due to poor cardiac output all contribute to elevated rates of delirium among cardiac patients. The general hospital psychiatrist should be aware of the special issues in the diagnosis and management of delirium in cardiac patients.

Epidemiology

Delirium and Cardiac Disease

Delirium is more generally reviewed elsewhere in this handbook; this section focuses more specifically on delirium in patients with cardiac illness.

Among cardiac patients in the general hospital, rates of delirium are high. A study of patients suffering acute MI found that approximately 20% suffered delirium during the hospitalization.[166] Though estimates vary widely, postoperative delirium affects about 20% to 25% of the patients undergoing cardiac surgery.[167–169] Furthermore, two studies of patients receiving IABP therapy found that 34% of such patients were delirious.[170,171]

Reports of risk factors for the development of delirium in cardiac patients have varied, but it is universally agreed that the etiology of delirium in cardiac patients is multifactorial, with different factors varying in importance from patient to patient. The risk factors for delirium in cardiac patients can be divided into three categories: patient demographic factors, biological and iatrogenic factors, and psychological factors.[165] Among patient demographic factors, increased age is associated with increased risk of delirium. There appears to be no difference in the rate of PCD between men and women.[172,173]

Among biological and iatrogenic factors, there are multiple preoperative risk factors for PCD (including a history of MI or stroke, diabetes, aortic insufficiency, decreased cardiac output, dehydration, electrolyte imbalance, and the use of anticholinergic drugs).[167,174,175] Intraoperatively, the use of on-pump CABG surgery is associated with an increased rate of intracerebral microemboli and dysfunction of several neurotransmitter systems (serotonergic, noradrenergic, dopaminergic, and anticholinergic). Cerebral microemboli and widespread neurotransmitter dysfunction are both associated with neurocognitive dysfunction and delirium.[176,177]

Postoperatively, factors related to the hospital setting may also increase the risk of delirium.[178] Sleep deprivation as the result of light, noise, and an unfamiliar setting can predispose patients to delirium. Furthermore, discomfort (resulting from a prolonged need to remain supine, IV catheters, or multiple painful procedures) may

be treated with narcotics or benzodiazepines, which can then induce delirium. Also, several cardiac medications (including β-blockers, angiotensin-converting enzyme [ACE] inhibitors, and digoxin) have been associated with delirium, particularly in the days before and after the surgery.[165]

Several psychological factors have been implicated as risk factors for PCD. In particular, preoperative depression, dementia, and executive dysfunction have all been associated with increased risk of postoperative dementia.[179] In one study of 998 successive preoperative patients, Smith and associates found that the more severe the executive dysfunction, the greater the risk of postoperative delirium.[180]

In short, rates of delirium are high among patients with cardiovascular disease. Acute MI, cardiac surgery, and cardiac failure requiring IABP support are each associated with high rates of delirium, and a number of risk factors for delirium have been established in the cardiac population.

Delirium and Medical Outcome

To our knowledge, there have been no studies investigating the outcome of delirium specifically in cardiac patients. However, a number of studies have examined the effects of delirium on the medical outcome of general hospital patients. Studies of ICU patients have found that delirium significantly increases length of stay (LOS) in the ICU,[182–185] overall length of hospitalization,[181,183,185] and amount of time on a ventilator[184]; one such study found that when other factors (e.g., severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration) were controlled, delirium was the strongest independent determinant of hospital LOS.[181]

In addition to increased LOS in the ICU and hospital, delirium can significantly affect other important outcome measures. Delirium has been associated (independent of disease severity, age, and other medical and demographic factors) with significantly greater rates of functional decline during hospitalization, increased rates of admission to long-term care after admission, and reduced ability to perform activities of daily living compared with patients without delirium.[185–188]

Finally, and perhaps most important, delirium appears to be independently associated with increased mortality. Delirium is associated with high rates of in-hospital mortality.[185,188,189] Furthermore, prospective studies have found that delirium predicts mortality at 1,[190] 2,[191] and 3[192] years after discharge in elderly patients. In one study, each additional day the patient spent in delirium was associated with a 20% increased risk of prolonged hospitalization and a 10% increased risk of death.[193] These effects of delirium on life span are independent of medical co-morbidity, functional status, and baseline cognitive status.

In short, delirium is common among cardiac patients in the general hospital, including post-MI patients, patients undergoing cardiac surgery, and severely ill patients on IABP therapy. Multiple risk factors are associated with delirium in cardiac patients, and the causes for any particular patient's delirium are often multiple. Although the effects of delirium on outcome have not been studied specifically in cardiac patients, in the general medical population, delirium has been associated with increased LOS, worsened functional outcome, and increased mortality. Still needed are studies that examine the effects of delirium treatment on long-term outcome of cardiac patients in particular.

Differential Diagnosis of Delirium in the Cardiac Patient

A wide variety of medical conditions and medications can cause or exacerbate delirium, and it is helpful for the psychiatrist to use mnemonics (such as VINDICTIVE MAD,[148] cited in Chapter 10) to allow for a systematic approach to delirium. In the delirious cardiac patient, a number of specific causes should be carefully considered (Table 23–3). CNS hypoperfusion is a common mechanism of delirium in the cardiac population; this can result from poor cardiac output caused by CHF or myocardial ischemia, from co-morbid carotid disease, from CNS bleeding (in the setting of anticoagulation), or from relative hypotension.

The phenomenon of relative hypotension deserves special mention. Patients with baseline uncontrolled hypertension who are admitted with myocardial ischemia or another cardiac event are often placed on one or more antihypertensives, and blood pressure is run "low," with systolic blood pressure typically between 100 and 120 mm Hg. Such patients are likely to have significant baseline hypertension, which may lead to stiffening of cerebral vessels with impaired ability to autoregulate. When these patients' blood pressure is lowered to "normal" (significantly below their baseline blood pressure), cerebral hypoperfusion and ischemia may result, leading to delirium.

Other common causes of delirium in the cardiac patient include hypoxia during CHF, hypertensive encephalopathy, electrolyte abnormalities (e.g., hyponatremia in the

TABLE 23–3 Selected Causes of Delirium Among Cardiac Patients in the General Hospital

Central Nervous System Hypoperfusion
Myocardial infarction/ischemia
Cerebrovascular accident (ischemic or hemorrhagic)
Hypovolemia (due to dehydration or bleeding)
Relative hypotension
Other Central Nervous System Disorders
Dementia (of any type)
Major depressive disorder
Other General Medical Conditions
Electrolyte abnormalities (especially sodium with diuretic administration)
Thyroid abnormalities
Hypertensive encephalopathy
Hypoxia (during pulmonary edema)
Infections (e.g., pneumonia, urinary tract infections)
Alcohol withdrawal
Cardiopulmonary bypass
Medication-Related Causes
Digoxin toxicity
Narcotic analgesics
Benzodiazepines
Anticholinergic medications
H_2-blockers

context of diuretic therapy), and medication effects (e.g., digoxin toxicity). The general hospital psychiatrist should rule out each of these potential etiologies of delirium in the cardiac patient.

Psychopharmacologic Issues in the Delirious Cardiac Patient

As noted in the American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Delirium*,[194,195] the use of medications is an important component of a multipronged approach to the psychiatric management and treatment of delirium; such an approach also includes monitoring and ensuring safety, educating the patient and family regarding the illness, and implementing environmental and supportive interventions (e.g., placing the patient near the nursing station and frequently reorienting the patient). This chapter will not discuss the treatment of delirium in depth (see Chapter 10), but it will touch on the topics relevant to the delirious cardiac patient.

In general, psychotropic agents are used for the supportive treatment of delirium. They can reduce agitation and psychotic symptoms and may help normalize the sleep–wake cycle. They usually are not the primary treatment or antidote for delirium (i.e., determining and specifically treating the etiology of the delirium), but they can reduce the risk of patient harm and alleviate patient distress until the etiology is identified and effectively treated.

Antipsychotics are the symptomatic treatment of choice for most delirious patients. These agents effectively reduce agitation and provide sedation for the delirious patient; moreover, they are generally quite safe. The greatest experience has been with haloperidol. This agent can be given orally or intramuscularly, but the IV form is both more rapidly acting and much less associated with the development of extrapyramidal symptoms (EPS); prospective study[196] and clinical experience have found the rate of EPS with IV haloperidol to be minimal. Haloperidol generally has no significant effects on heart rate, blood pressure, or respiratory status, and it has essentially no anticholinergic effects.

Haloperidol has, however, been associated with the development of torsades de pointes (TDP), a malignant polymorphic ventricular arrhythmia that can occur with medications that lengthen the cardiac QTc interval. More than two dozen cases of TDP have been reported with haloperidol,[197–199] and rates of TDP from haloperidol in the treatment of delirious patients have ranged from 0.36% to 3.5%.[197,200] TDP appears more common at high doses (> 35 mg per day) of haloperidol, though it has also occurred at low doses.[197] Because hypokalemia and hypomagnesemia have been associated with the development of TDP, it is recommended that patients receiving IV haloperidol have these electrolytes monitored and repleted as needed. IV droperidol has also been used effectively in the treatment of delirium, though concerns about its propensity to cause TDP have significantly reduced its availability and use.

More recently, atypical antipsychotics, especially risperidone[201,202] and olanzapine,[203] have been used in the treatment of delirium. These agents are also well tolerated; risperidone and quetiapine can cause orthostatic hypotension, and olanzapine has mild anticholinergic effects, but in general, these agents have little effect on heart rate, blood pressure, or respiratory status and can be safely used in cardiac patients.

Several studies have evaluated the use of atypical antipsychotics in delirious patients. In a small prospective study, Mittal and co-workers found that cognitive and behavioral symptoms of delirium improved with risperidone.[204] A double-blind study of haloperidol and risperidone found no difference in the response rates of delirious patients.[205] Another observational study of 64 patients found risperidone to be clinically effective in 90% of delirium cases.[206]

Comparative studies of olanzapine and haloperidol have shown similar improvements in symptoms of delirium with some increased sedation in patients treated with olanzapine.[207,208] Furthermore, quetiapine has been reported to be a safe and effective treatment of delirium in multiple studies (retrospective, case series, and open prospective).[209,210] Finally, aripiprazole has also been reported to be of benefit in treating delirium in a case series.[211]

Studies comparing haloperidol and atypical antipsychotics have not identified any clinical advantages to use of an atypical agent over use of haloperidol.[211,212] However, EPS have been seen less often after use of atypical agents than with haloperidol—although studies evaluating adverse effects are limited in scope and size.[213] No study has examined the efficacy or tolerability of atypical antipsychotics in the specific population of cardiac patients.

There have been concerns about the potential for atypical antipsychotics to cause QTc prolongation (potentially predisposing to TDP), especially in patients with cardiac disease. To address this, a study of the effects of a number of antipsychotics on the QTc of 154 subjects was undertaken.[214] In the study six antipsychotics (thioridazine, haloperidol, ziprasidone, risperidone, quetiapine, and olanzapine) were orally administered to the highest dose tolerated. Thioridazine (the antipsychotic most associated with TDP with oral admistration[215]) and ziprasidone were associated with the greatest QT prolongation, whereas olanzapine and haloperidol had the least. It is difficult to extrapolate the results of this study to delirious cardiac patients, however, because the subjects were largely healthy young men without co-morbid medical illness.

Furthermore, the Food and Drug Administration recently issued a black box warning about the increased risk of sudden death associated with the use of all antipsychotic medications in demented elderly patients. Psychiatrists treating delirium in such patients must be thoughtful in balancing the risks of a persistent delirium with the risk highlighted by the black box warning.[216]

Recently, several studies have evaluated the efficacy of antipsychotic medications preoperatively to reduce the risk of patients developing delirium. A small, randomized, placebo-controlled trial found that haloperidol prophylaxis in patients undergoing gastrointestinal surgery reduced the postoperative incidence of delirium.[217] Delirium prophylaxis with atypical antipsychotics has also been studied. In a study by Prakanrattana and associates, 126 patients receiving cardiac surgery on bypass were randomized to receive risperidone or placebo after awakening postoperatively.[218] The delirium incidence (but not other postoperative outcomes) was significantly lower in the risperidone group

as compared with the placebo group. Lastly, a randomized, placebo-controlled study of olanzapine in orthopedic surgery found that patients treated with olanzapine had a lower incidence of postoperative delirium.[219] Treatment of cardiac patients with delirium with benzodiazepine monotherapy is generally contraindicated because these agents can worsen confusion or cause paradoxical disinhibition, especially in elderly, demented, or brain-injured patients. However, benzodiazepines are the treatment of choice in delirium secondary to alcohol or benzodiazepine withdrawal and in delirious patients unable to tolerate high doses of antipsychotics (or who have significant cardiovascular side effects such as hypotension). Benzodiazepines may be used in combination with antipsychotics in the symptomatic treatment of delirium.

Other agents may be used to treat certain delirious states in cardiac patients. For example, physostigmine can be used to treat delirium resulting from anticholinergic toxicity,[220] naloxone can be used to treat delirium caused by opioid intoxication, and IV thiamine can be administered to those with Wernicke's encephalopathy.

The Practical Management of the Delirious Cardiac Patient

As with other conditions involving cardiac patients, the management of delirium involves careful diagnosis and the consideration of co-morbid conditions. Once diagnosis and etiology have been established, the general hospital psychiatrist can then implement optimal behavioral and nonpharmacologic strategies and intelligently use psychotropic agents that reduce medical risk while effectively decreasing symptoms:

Make an informed diagnosis of delirium, and carefully consider potential etiologies. Delirium is characterized by an acute onset, disorientation, poor attention, fluctuation of levels of consciousness, and alterations in sleep–wake cycle. Psychotic symptoms, anxiety, worry, and reports of depressed mood may or may not be present. A careful review of the chart and cognitive evaluation (that considers orientation, attention, and executive function) can allow the consultant to use these factors to distinguish delirium from other psychiatric illnesses. Once a diagnosis has been made, the psychiatrist should work to consider all possible causes of delirium. The cause of delirium is frequently multifactorial; therefore the identification of one potential contributing factor of delirium should not preclude the search for further potential abnormalities leading to an acute confusional state. The consultant should pay special attention to the initiation and termination of medications and their relationship to the onset of delirium; a careful review of nursing medication sheets often reveals a wealth of information that can provide important answers regarding a delirium of unknown etiology.

Aggressively treat all potential etiologies of delirium. Treating the core etiology of delirium is the only way to definitively reverse delirium; all other behavioral and pharmacologic remedies are symptomatic treatments that reduce risk and increase comfort until the primary etiologies of the delirium resolve. Therefore treatment of urinary tract infections, vitamin B_{12} deficiency, mild metabolic abnormalities, and other seemingly minor contributing factors to delirium is absolutely crucial.

Use nonpharmacologic strategies to minimize confusion and ensure safety. Having the patient situated near the nursing station or in other areas where the patient can be frequently monitored can reduce the risk of falls, wandering, or other dangerous actions. Placing the patient in a room with a window and a clock—to help orient patients to day–night cycles—can also be useful. The use of Posey vests, sitters, or locked restraints may be required when a delirious patient's inability to safely navigate places him or her at risk; in almost all cases, medication should be given in combination with physical restraint to reduce discomfort and risk of harm while in restraints. The presence of reassuring family members or friends at the bedside can mitigate paranoia and agitation, whereas visitors that overstimulate the patient may worsen symptoms. The consultant may recommend that the team either encourage or dissuade interaction with certain visitors depending on the response of the patient's symptoms to the visitors.

Use antipsychotic medications to reduce agitation and psychotic symptoms and regulate the sleep–wake cycle. IV haloperidol is often the drug of choice for agitated, paranoid, or hyperactive patients with delirium. As noted previously, this agent is associated with low rates of EPS, and it has little effect on heart rate or blood pressure. It is rapidly effective in the IV form. Cardiac patients may be at increased risk for TDP, and therefore risk factors for this arrhythmia (e.g., prolonged QTc interval and electrolyte abnormalities) must be considered before its use. The protocol used at the MGH (Table 23–4) for the use of IV haloperidol

TABLE 23–4 Massachusetts General Hospital Protocol for IV Haloperidol in Agitated Delirious Patients

Check pre-haloperidol QTc interval.
If QTc > 450 ms, proceed with care.
If QTc > 500 ms, consider other options.
Check potassium and magnesium, and correct abnormalities.
Aim for potassium > 4 mEq/L, magnesium > 2 mEq/L.
Give dose of haloperidol (0.5–10 mg) based on level of agitation and patient's age and size.
Goal is to have patient calm and awake.
Haloperidol precipitates with phenytoin and heparin; flush line before giving haloperidol if these agents have been used in the same intravenous tubing.
Wait 20-30 minutes. If patient remains agitated, double dose.
Continue to double dose every 30 minutes until patient is calm.
Follow QTc interval to ensure that QTc is not prolonging.
If QTc increases by 25% or becomes >500, consider alternative treatments.
Once effective dose has been determined, use that dose for future episodes of agitation.
Depending on likely course of delirium, may schedule haloperidol or give on as-needed basis.
For example, may divide previous effective dose over next 24 hours, giving every 6 hours.
Or may simply give effective dose as needed for agitation.
Consider small dose at night to regulate sleep–wake cycle in all delirious patients.

considers these risk factors for TDP and uses a progressive dosing schedule. An initial dose (from 0.5 to 10 mg based on the age and size of patient and the extent of agitation) is selected and administered to the patient. If the patient is not calm within 20 to 30 minutes, the dose is doubled and continues to be doubled every 20 to 30 minutes until the patient is calm. This effective dose is then used when and if the patient again becomes agitated. Though most patients require standard doses of haloperidol (2 to 10 mg), some patients have required (and safely received) thousands of milligrams for agitation.[221]

If an agitated, delirious patient is or becomes unable to receive IV haloperidol (e.g., because of QTc prolongation), there are a number of other options. Sublingual olanzapine wafers are also fast-acting and effective in the treatment of delirium. Mildly agitated patients willing to take oral medications can be given oral atypical antipsychotics, such as risperidone, olanzapine, or quetiapine. Finally, patients whose agitation requires rapidly acting IV medication and who cannot receive IV antipsychotics may be given narcotics (e.g., morphine) or benzodiazepines (e.g., lorazepam) parenterally when immediate sedation is required; though these agents may worsen confusion, they are effective in the short term, when sedation is urgently needed. IV benzodiazepines are also the agents of choice in delirium tremens caused by benzodiazepine or alcohol withdrawal.

Once the agitated delirious patient has been safely and adequately sedated, there is often a question of whether to schedule antipsychotic medication or to use it on an as-needed basis for agitation. Such a decision may depend on the likely duration of the delirium, if this can be determined. For example, if the delirium is secondary to CNS hypoperfusion in a patient with low cardiac output on an IABP, such delirium may well be prolonged, and scheduling of an antipsychotic would be reasonable. In contrast, delirium in an elderly cardiac patient resulting from narcotic administration may be short-lived once the narcotic has been eliminated, and standing antipsychotics may not be needed. In most cases of delirium, we have found that it is often reasonable to schedule a low dose of IV haloperidol or an oral atypical antipsychotic at bedtime to help regulate the sleep–wake cycle, which is often seriously perturbed in delirious patients. We have found that by ensuring adequate sleep at appropriate hours, delirious cardiac patients have the best possible chance to recover.

CASE 3

Mr. C, a 64-year-old man with three-vessel CAD and no significant psychiatric history, was admitted for CABG. Though he was alert, oriented, pleasant, and cooperative before his surgery, he became angry and threatening 2 days later, reporting that the nurses were the "minions of the devil" and that he needed to leave the hospital immediately; notes revealed that he had not slept for 24 hours. Psychiatry was urgently consulted for "psychosis and capacity to leave against medical advice."

The psychiatrist found Mr. C sitting on his bed, wearing only his pajama top. He angrily reported that the nurses were stealing money from him and had injected "poisons" into him. He was disoriented to time and place, and he was unable to attend to conversation for more than a few seconds. He had pulled off his telemetry leads and not allowed the nurses to check his vital signs. The psychiatrist was able to get Mr. C to agree to stay for the moment, and after confirming a normal postoperative QTc interval and normal electrolyte levels, he persuaded Mr. C to accept an injection of 3 mg IV haloperidol. After 20 minutes Mr. C became sedated, and he fell asleep after 45 minutes.

When Mr. C's leads were reattached and vital signs checked, he was noted to have new-onset atrial fibrillation with a rate of 119. His heart rate was slowed with the use of β-blockers, and he returned to normal sinus rhythm within 12 hours. He received two further doses of IV haloperidol, and 25 mg of quetiapine each night. His delirium slowly resolved over the next 6 days, coinciding with resolution of his atrial fibrillation and with treatment of a urinary tract infection, and the quetiapine was discontinued on his discharge to a cardiac rehabilitation facility.

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Sexual Disorders and Sexual Dysfunction

24

Linda C. Shafer, M.D.

A comprehensive psychiatric evaluation of any patient in the general hospital setting should include close attention to complaints, impairments, and deviations of sexual function. Although on occasion, sexual problems are the primary reason for consultation (particularly among patients admitted to urologic or gynecologic services), more often they may provide important clues about an underlying medical or psychologic condition. Consider the "difficult" patient on obstetrics who repeatedly refuses gynecologic exams, the formerly mild-mannered elderly gentleman who now shouts obscenities and gropes at nurses, or the sexually-provocative patient who evokes strong reactions from the medical team. Could the patient on obstetrics have a history of sexual trauma, the elderly man a frontal lobe tumor, or the provocative patient a personality disorder? These are a few of many examples that serve to highlight the role that understanding sexuality plays in caring for patients both compassionately and effectively.

The consulting psychiatrist should also be reminded of the importance that being able to maintain a healthy sexual life holds for many patients, regardless of the reason for hospitalization. Sexuality may take on even greater significance for patients suffering from illness that directly impairs sexual function, because of the difficulties both real and perceived. Psychiatric consultants should be alerted to high rates of sexual problems in patients with chronic diseases (especially cardiovascular disease, cancer, diabetes, neurologic problems, end-stage renal disease, and pain). Many chronic diseases result in depression, which in turn contributes to decreased sexual desire. Moreover, psychological reactions to existing illnesses run the gamut, from fear that sex can kill (post–myocardial infarction) to distress over low sexual self-image (post–disfiguring surgery), to avoidance of sex, to fear of pain during sex, to fear that sexual advances will be rejected, all leading to decreased sexual intimacy.[1]

When offering suggestions for patient management, such as prescribing a new psychotropic medication, care should be taken to minimize or treat sexual side effects as much as is possible. This may also help to improve patient rapport and compliance. In cases where sexual dysfunction appears to have a psychological component, or where longer-term behavioral, psychotherapeutic, or pharmacologic therapy may be warranted, referral for outpatient psychiatric care can be arranged.

The purpose of this chapter is two fold. The first aim is to assist the consulting psychiatrist in developing an approach to assessing sexual issues (including creation of a differential diagnosis and a management plan) as they may appear in the inpatient setting. The second aim is to educate the consulting psychiatrist on sexual disorders of primary psychological and mixed psychological and organic origins, so that appropriate outpatient care can be arranged, if necessary. In this way, the transition from inpatient care to outpatient follow-up can be optimized.

EPIDEMIOLOGY AND RISK FACTORS

Sexual disorders are extremely common. It has been estimated that 43% of women and 31% of men in the United States suffer from sexual dysfunction.[2] In addition, lack of sexual satisfaction is associated with significant emotional (including depression and marital conflict) and physical (e.g., cardiovascular disease and diabetes mellitus) problems.[2,3]

Sexual disorders affect individuals across the epidemiologic spectrum, and risk factors for them have been identified. Overall, the prevalence of sexual dysfunction is greater in women than it is in men. Sexual dysfunction increases with age, regardless of gender. Men and women with higher levels of education have fewer sexual problems and less anxiety about sexual issues.[2,3] Co-existing psychiatric or medical conditions (including diabetes mellitus, cardiovascular disease, other genitourinary disease) are associated with a decline in sexual function in both men and women, as is diminished general health status.[2–4] It has been estimated, for example, that 10% to 54% of patients do not resume sexual activity after myocardial infarction (MI); 45% to 100% of patients with uremia or who are undergoing hemodialysis experience low sexual desire; and 26% to 50% of patients with untreated depression experience erectile dysfunction (ED).[5]

Among those with obesity and a sedentary lifestyle, weight loss and increased physical activity are associated with improved sexual function.[6–8] The association between race and sexual dysfunction is more variable.[2,9] There is a strong association between ED and vascular diseases.[10] In fact, ED may be the initial complaint in patients with underlying cardiovascular disease.[11] Recent evidence suggests an increased risk of ED among individuals who possess specific genetic mutations (e.g., polymorphisms in genes for nitric oxide synthase and Rho kinase) in molecular pathways responsible for resisting endothelial dysfunction.[12] Sexual trauma for both sexes is associated with long-term negative changes in sexual function.[13] A strong association exists between paraphilias and childhood attention-deficit/hyperactivity disorder (ADHD), substance abuse, major depression or dysthymia, and phobic disorder.[14,15] The prototypical paraphiliac is young, white, and male.

PATHOPHYSIOLOGY

The ability to maintain adequate sexual function depends on complex interactions among the brain, peripheral nerves, hormones, and the vascular system. Disease states in these systems are associated with sexual dysfunction. However, no single comprehensive view has been established.

Brain regions involved in sexual arousal include the anterior cingulate gyrus, prefrontal cortex, thalamus, temporo-occipital lobes, hypothalamus, and amygdala.[16] The neurotransmitters dopamine and norepinephrine appear to stimulate sexual function, whereas serotonin may inhibit orgasm. Testosterone, estrogen, progesterone, oxytocin, and melanocortin hormones have a positive effect on sex, but prolactin is an inhibitor.[17,18]

Recent data suggest a central role for nitric oxide (NO) at the vascular level. In women, NO is thought to control vaginal smooth muscle tone; higher levels of NO are associated with increased vaginal lubrication. In men, NO allows for increased intrapenile blood flow, which facilitates erection. NO acts via the generation of cyclic guanosine monophosphate (cGMP), which has vasodilatory properties. Phosphodiesterase type-5 (PDE-5) inhibitors (the prototype of which is sildenafil) act to inhibit the degradation of cGMP, which prolongs the effects of NO.[19] Cholinergic fibers, prostaglandin E, vasoactive intestinal peptide (VIP), and possibly neuropeptide Y (NPY) and substance P may also improve vasocongestion.[20]

Sexual dysfunction may be best understood by having knowledge of the stages of the normal sexual response; these vary with age and physical status. Medications, diseases, injuries, and psychological conditions can affect the sexual response in any of its component phases, and can lead to different dysfunctional syndromes (Table 24–1).[21] Three major models of the human sexual response have been proposed.

Masters and Johnson[22,23] developed the first model of the human sexual response, consisting of a linear progression through four distinct phases: (1) excitement (arousal), (2) plateau (maximal arousal before orgasm), (3) orgasm (rhythmic muscular contractions), and (4) resolution (return to baseline). Following resolution a refractory period exists in men.

Kaplan[24] modified the Masters and Johnson model by introducing a desire stage; this model emphasized the importance of neuropsychological input in the human sexual response. The Kaplan model consisted of three stages: (1) desire; (2) excitement/arousal (including an increase in peripheral blood flow); and (3) orgasm (muscular contraction).

Basson,[25] who recognized the complexity of the female sexual response, more recently proposed a biopsychosocial model of female sexuality that consisted of four overlapping components: (1) biology, (2) psychology, (3) sociocultural factors, and (4) interpersonal relationships. Notably, this conceptualization suggested that women may be receptive to, and satisfied with, sex even in the absence of intrinsic sexual desire if other conditions were met (such as emotional closeness). These other factors could then potentially stimulate direct sexual desire. The fact that physical measurements of female arousal (such as increased vaginal secretions) are poorly correlated with sexual satisfaction lends support for Basson's view.

Aging is associated with changes in the normal human sexual response. Men are slower to achieve erections and require more direct stimulation of the penis to achieve erections. Women have decreased levels of estrogen, which leads to decreased vaginal lubrication and narrowing of the vagina. Testosterone levels in both sexes decline with age, which may result in decreased libido.[26]

TABLE 24–1 Classification of Sexual Dysfunctions

IMPAIRED SEXUAL RESPONSE PHASE	FEMALE	MALE
Desire	Hypoactive sexual desire Sexual aversion	Hypoactive sexual desire Sexual aversion
Excitement (arousal, vascular)	Sexual arousal disorder	Erectile disorder
Orgasm (muscular)	Orgasmic disorder	Orgasmic disorder Premature ejaculation
Sexual pain	Dyspareunia Vaginismus	Dyspareunia

CLINICAL FEATURES AND DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)[27] classifies sexual disorders into four major categories. *Sexual dysfunction* is characterized by disturbances in sexual desire and/or psychophysiologic changes in the sexual response cycle. *Paraphilias* are characterized by recurrent, intense sexual urges that involve unusual objects or activities. *Gender identity disorders* involve persistent cross-gender identification and discomfort with one's assigned sex. *Sexual disorders not otherwise specified* are used to code disorders that are not classifiable into any of the other categories. All sexual disorders must cause clinically significant distress or an impairment of social function before a diagnosis can be made. Disorders are classified as *primary*, when there has never been a period of satisfactory function, or *secondary*, when the difficulty occurs after adequate function had been obtained.[27]

The diagnosis of a sexual problem relies upon a thorough medical and sexual history. Physical examination and laboratory investigations may be crucial to identification of organic causes of sexual dysfunction. Primary psychiatric illness may present with sexual complaints (Table 24–2).[27] However, most sexual disorders have both an organic and a psychological component. Physical disorders, surgical conditions (Table 24–3),[21,28] medications, and use or abuse of drugs (Table 24–4)[29] can affect sexual function directly or cause secondary psychological reactions that lead to a sexual problem. Psychological factors may predispose, precipitate, or maintain a sexual disorder (Table 24–5).[30,31]

APPROACH TO SEXUAL HISTORY-TAKING

The sexual history provides an invaluable opportunity to uncover sexual problems. Because patients are often embarrassed to discuss their sexuality with physicians or view sex

TABLE 24–2 Psychiatric Differential Diagnosis of Sexual Dysfunction

PSYCHIATRIC DISORDER	SEXUAL COMPLAINT
Depression (major depression or dysthymic disorder)	Low libido, erectile dysfunction
Bipolar disorder (manic phase)	Increased libido
Generalized anxiety disorder, panic disorder, posttraumatic stress disorder	Low libido, erectile dysfunction, lack of vaginal lubrication, anorgasmia
Obsessive–compulsive disorder	Low libido, erectile dysfunction, lack of vaginal lubrication, anorgasmia, "anti-fantasies" focusing on the negative aspects of a partner
Schizophrenia	Low desire, bizarre sexual desires
Paraphilias	Deviant sexual arousal
Gender identity disorder	Dissatisfaction with one's own sexual preference or phenotype
Personality disorder (passive–aggressive, obsessive–compulsive, histrionic)	Low libido, erectile dysfunction, premature ejaculation, anorgasmia
Marital dysfunction/ interpersonal problems	Varied
Fears of intimacy/ commitment	Varied, deep intrapsychic issues

as outside the realm of medicine, and because physicians are often reluctant to broach the topic of sex for fear of offending their patients, the need to make sexual history-taking a routine part of practice is paramount. Physicians should always attempt to be sensitive and nonjudgmental in their interviewing technique, moving from general topics to more specific ones. Questions about sexual function may follow naturally from aspects of the medical history (such as introduction of a new medication, or investigation of a chief complaint that involves a gynecologic or urologic problem).

Screening questions include: Are you sexually active? If so, with men, women, or both? Is there anything you would like to change about your sex life? Have there been any changes in your sex life? Are you satisfied with your present sex life? To maximize its effectiveness the sexual history may be tailored to the patient's needs and goals.[32] Physicians should recognize that paraphiliacs are often secretive about their activities, in part because of legal and societal implications. Patients should be reassured about the confidentiality of their interaction (except in cases where their behavior requires mandatory legal reporting, e.g., as with child abuse).

In taking a sexual history, the consulting psychiatrist should recognize that chronic illness often contributes to sexual dysfunction, whether by direct physical damage or associated psychological effects. Patients with cancer, end-stage renal disease, coronary artery disease, multiple sclerosis, and diabetes are all at increased risk of sexual problems. To explore the role physiologic illness may play in sexual dysfunction, consultants should ask questions about diseases, procedures, and medications that might affect hormone balance, disrupt normal anatomic genitalia, cause CNS dysfunction, damage vascular or peripheral nerve supply to sexual organs, or contribute to pain during sexual activity.[1]

Physical Examination and Laboratory Investigation

Though history-taking is often the most important tool in the diagnosis of sexual disorders, the physical examination may reveal a clear medical or surgical basis for sexual dysfunction. Special attention should be paid to the endocrine, neurologic, vascular, urologic, and gynecologic systems. Similarly, laboratory studies may be indicated, depending on the degree to which an organic cause is suspected.[5,16,18] There is no "routine sexual panel."

Screening tests can be guided by the history and physical examination. Tests for systemic illness include: complete blood count (CBC), urinalysis, creatinine, lipid profile, thyroid function studies, and fasting blood sugar (FBS). Endocrine studies (including testosterone, prolactin, luteinizing hormone [LH], and follicular stimulating hormone [FSH]), can be performed to assess low libido and ED. An estrogen level and microscopic examination of a vaginal smear can be used to assess vaginal dryness. Cervical culture and pap smear can be performed to investigate a diagnosis of dyspareunia. The nocturnal penile tumescence (NPT) test is valuable in the assessment of ED. If NPT occurs regularly (as measured by a RigiScan monitor), problems with erection are unlikely to be organic. Penile plethysmography is used to assess paraphilias by measurement of an individual's sexual arousal in response to visual and auditory stimuli.[33]

DIAGNOSTIC CRITERIA OF SPECIFIC SEXUAL DISORDERS

Male Disorders of Sexual Function

Male Erectile Disorder. Erectile dysfunction ("impotence") is defined as the inability of a male to maintain an erection sufficient to engage in intercourse; it is considered a problem if it occurs in more than 25% of attempts. Roughly 20 to 30 million American men suffer from ED; this symptom accounts for more than 500,000 ambulatory care visits to health care professionals annually. A number of risk factors for ED have been identified (Table 24–6). Between 50% and 85% of cases of ED have an organic basis. Primary (life-long) ED occurs in 1% of men under the age of 35 years. Secondary (acquired) ED occurs in 40% of men over the age of 60 years; this figure increases to 73% in men who are 80 years old. ED may be generalized (i.e., it occurs in all circumstances) or situational (i.e., it is limited to certain types of stimulation, situations, and partners). ED may be a symptom of a generalized vascular disease and should prompt further investigation.[2,10,34,35] Bicycle

TABLE 24–3 Medical and Surgical Conditions Causing Sexual Dysfunctions

ORGANIC DISORDERS	SEXUAL IMPAIRMENT
Endocrine	
Hypothyroidism, adrenal dysfunction, hypogonadism, diabetes mellitus	Low libido, impotence, decreased vaginal lubrication, early impotence
Vascular	
Hypertension, atherosclerosis, stroke, venous insufficiency, sickle cell disorder	Impotence, ejaculation and libido intact
Neurologic	
Spinal cord damage, diabetic neuropathy, herniated lumbar disc, alcoholic neuropathy, multiple sclerosis, temporal lobe epilepsy	Sexual disorder – early sign, low libido (or high libido), impotence, impaired orgasm
Local genital disease	
Male: Priapism, Peyronie's disease, urethritis, prostatitis, hydrocele	Low libido, impotence
Female: Imperforate hymen, vaginitis, pelvic inflammatory disease, endometriosis	Vaginismus, dyspareunia, low libido, decreased arousal
Systemic debilitating disease	
Renal, pulmonary, or hepatic diseases, advanced malignancies, infections	Low libido, impotence, decreased arousal
Surgical postoperative states	
Male: Prostatectomy (radical perineal), abdominal-perineal bowel resection	Impotence, no loss of libido, ejaculatory impairment
Female: Episiotomy, vaginal repair of prolapse, oophorectomy	Dyspareunia, vaginismus, decreased lubrication
Male and Female: Amputation (leg), colostomy, and ileostomy	Mechanical difficulties in sex, low self-image, fear of odor

riding has also been linked to penile numbness (associated with perineal nerve damage) and to ED (due to decreased oxygen pressure in the pudendal arteries).[36] Depression is a common comorbidity in patients with ED.

Male Orgasmic Disorder. This disorder ("retarded ejaculation") is defined as a persistent delay or absence of orgasm following normal sexual excitement. It is infrequent, with a lifetime prevalence of 2%; it occurs in men who are usually under the age of 35 years and who are sexually inexperienced. Retarded ejaculation is usually restricted to failure to reach orgasm in the vagina during intercourse. Orgasm can usually occur with masturbation or from a partner's manual or oral stimulation. The condition must be differentiated from retrograde ejaculation, where the bladder neck does not close off properly during orgasm, causing semen to spurt backward into the bladder. One must rule out retarded ejaculation in a couple who presents with infertility of unknown cause. The male may not have admitted his lack of ejaculation to his partner. Compared to men with other sexual dysfunctions, men with male orgasmic disorder have lower levels of relationship satisfaction, greater levels of distress, higher levels of health-related problems, and lower levels of self-reported sexual arousal despite strong penile response during psychophysiologic testing.[37,38]

Premature Ejaculation. This disorder is defined as recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it (most often less than 2 minutes after penetration or on fewer than 10 thrusts). The lifetime prevalence of premature ejaculation is 15%. Premature ejaculation is the most common male sexual disorder, affecting 30% of men. Prolonged periods of no sexual activity make premature ejaculation worse. If the problem is chronic and untreated, secondary impotence often occurs.[39]

Female Disorders of Sexual Function

Female Sexual Arousal Disorder. This disorder is defined as a persistent inability to attain or maintain an adequate lubrication–swelling response of sexual excitement. The lifetime prevalence is 60%. This condition is linked to problems with sexual desire. A lack of vaginal lubrication may lead to dyspareunia.[40–45]

Female Orgasmic Disorder. This disorder is defined as a recurrent delay in, or absence of, orgasm following a normal sexual excitement phase. Some women who can have orgasm with direct clitoral stimulation find it impossible to reach orgasm during intercourse. This is a normal variant of sensitivity that requires the pairing of direct clitoral contact with intercourse. Female orgasmic disorder has a lifetime prevalence of 35%. Approximately 5% to 8% of afflicted individuals are totally anorgasmic. Moreover, 30% to 40% of afflicted individuals are unable to achieve orgasm without clitoral stimulation during intercourse. The ability to reach orgasm increases with sexual experience. Claims that stimulation of the Grafenberg spot, or G-spot, in a region in the anterior wall of the vagina will cause orgasm and female ejaculation have never been substantiated. Premature ejaculation in the male may contribute to female orgasmic dysfunction.[41–45]

TABLE 24–4 Drugs and Medicines that Cause Sexual Dysfunction

DRUG	SEXUAL SIDE EFFECT
Cardiovascular	
Methyldopa	Low libido, impotence, anorgasmia
Thiazide diuretics	Low libido, impotence, decreased lubrication
Clonidine	Impotence, anorgasmia
Propranolol, metoprolol	Low libido, impotence
Digoxin	Gynecomastia, low libido, impotence
Clofibrate	Low libido, impotence
Psychotropics	
Sedatives	
Alcohol	Higher doses cause sexual problems
Barbiturates	Impotence
Anxiolytics	
Alprazolam, diazepam	Low libido, delayed ejaculation
Antipsychotics	
Thioridazine	Retarded or retrograde ejaculation
Haloperidol	Low libido, impotence, anorgasmia
Risperidone	Impotence
Antidepressants	
MAOIs (phenelzine)	Impotence, retarded ejaculation, anorgasmia
TCAs (imipramine)	Low libido, impotence, retarded ejaculation
SSRIs	
Fluoxetine, sertraline	Low libido, impotence, retarded ejaculation
Atypical (trazodone)	Priapism, retarded or retrograde ejaculation
Lithium	Low libido, impotence
Hormones	
Estrogen	Low libido in men
Progesterone	Low libido, impotence
Gastrointestinal	
Cimetidine	Low libido, impotence
Methantheline bromide	Impotence
Opiates	Orgasmic dysfunction
Anticonvulsants	Low libido, impotence, priapism

MAOI, Monoamine oxidase inhibitor; *SSRI*, selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant.

Vaginismus. This disorder is defined as recurrent involuntary spasm of the musculature of the outer third of the vagina, interfering with sexual intercourse. The frequency of this disorder is unknown, but it probably accounts for less than 10% of female sexual disorders. The diagnosis is often made on routine gynecologic examination when contraction of the vaginal outlet occurs as either the examining finger or the speculum is introduced. There is a high incidence of associated pelvic pathology. Life-long vaginismus has an abrupt onset, at the first attempt at penetration, and has a chronic course. Acquired vaginismus may occur suddenly, following a sexual trauma or a medical condition.[46]

TABLE 24–5 Psychological Causes of Sexual Dysfunction

Predisposing factors
Lack of information/experience
Unrealistic expectations
Negative family attitudes to sex
Sexual trauma: rape, incest
Precipitating factors
Childbirth
Infidelity
Dysfunction in the partner
Maintaining factors
Interpersonal issues
Family stress
Work stress
Financial problems
Depression
Performance anxiety
Gender identity conflicts

TABLE 24–6 Risk Factors Associated with Erectile Dysfunction

Hypertension
Diabetes mellitus
Smoking
Coronary artery disease
Peripheral vascular disorders
Blood lipid abnormalities
Peyronie's disease
Priapism
Pelvic trauma or surgery
Renal failure and dialysis
Hypogonadism
Alcoholism
Depression
Lack of sexual knowledge
Poor sexual technique
Interpersonal problems

Sexual Dysfunction Disorders Affecting Both Genders

Hypoactive Sexual Desire Disorder. This disorder is defined as a recurrent deficit or absence of sexual fantasies or a desire for sexual activity (taking into account factors affecting sexual function). The incidence of this disorder has increased from 37% in the early 1970s to 55% in the early 1980s. The lifetime prevalence of this condition is 40% in women and 30% in men.[47,48]

Dyspareunia. This disorder is defined as persistent genital pain associated with sexual intercourse. The prevalence of dyspareunia is 15% in females and 5% in males. Patients with dyspareunia often seek out medical treatment, but the physical examination is generally unremarkable, without genital abnormalities. If pain is caused solely by vaginismus or by a lack of lubrication, the diagnosis of dyspareunia is not made.[49]

Sexual Aversion Disorder. This disorder is defined as a persistent extreme aversion to genital sexual contact with a sexual partner. The exact incidence is unknown, but the condition is common. Primary sexual aversion is higher in men, but secondary aversion is higher in women. The syndrome is associated with phobic avoidance of sexual activity and/or the thought of sexual activity. One fourth of those with this condition also meet criteria for panic disorder. Affected individuals engage in intercourse once or twice a year. Patients tend to respond naturally to sexual relations if they can get past their high anxiety and initial dread.[50]

Paraphilias

Paraphilias. Most paraphilias are thought to have a psychological basis. Individuals with paraphilias have difficulty forming more socialized sexual relationships. Paraphilias may involve a conditioned response in which nonsexual objects become sexually arousing when paired with a pleasurable activity (masturbation). The diagnostic criteria and clinical features of the major paraphilias are summarized in Table 24–7.[27]

Gender Identity Disorder

Gender Identity Disorder. The onset of this disorder may be as early as 4 years of age, but the diagnosis cannot be made until adolescence or adulthood. In adolescents and adults, the disturbance is manifested by a variety of symptoms, such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., requests for hormones or surgery), or a belief in being born the wrong sex. By late adolescence or adulthood, 75% of boys with a history of gender identity disorder as a child will have a homosexual or bisexual orientation. Children with gender identity disorder may have co-existing separation anxiety, generalized anxiety, and depression, whereas adolescents are at risk for depression, suicidal ideation, and suicide attempts. Adults with the condition often have co-existing anxiety and depression. Adult males may have a history of transvestic fetishism as well as other paraphilias. Associated personality disorders are common in male patients. One in 30,000 males and 1 in 100,000 females have sex-reassignment surgery.[51]

DIFFERENTIAL DIAGNOSIS OF SEXUAL DISORDERS

The differential diagnosis of sexual disorders includes medical and surgical conditions (see Table 24–3),[21,28] adverse effects of medications (see Table 24–4),[29] and other psychiatric disorders (see Table 24–2).[27] Before a primary sexual disorder is diagnosed, it is important to identify potentially treatable conditions (both organic and psychiatric) that manifest as problems with sexual function. For example, treatment of depression may improve erectile function. Although paraphilias often have a psychological basis, an organic cause should be considered if the behavior begins in middle age or later; there is regression from previously normal sexuality; there is excessive aggression; there are reports of auras or seizure-like symptoms before or during the sexual behavior; there is an abnormal body habitus; or there is an abnormal neurologic examination. See Table 24–8 for the psychiatric differential diagnosis of paraphilias.[27] Patients who present with gender identity disorder generally have normal physical findings and normal laboratory studies. The differential diagnosis includes nonconformity

TABLE 24–7 Diagnostic Criteria of Specific Paraphilias

DISORDER	DEFINITION	FEATURES
Exhibitionism	Exposure of genitals to unsuspecting strangers in public.	Primary intent is to evoke shock or fear in victims. Offenders are usually male.
Fetishism	Sexual arousal using nonliving objects (e.g., female lingerie).	Masturbation occurs while holding the fetish object. The sexual partner may wear the object.
Frotteurism	Sexual arousal by touching and rubbing against a nonconsenting person.	The behavior occurs in a crowded public place from which the offender can escape arrest.
Pedophilia	Sexual activity with a prepubescent child. The patient must be at least 16 years of age and be 5 years older than the victim.	Pedophilia is the most common paraphilia. Most of the victims are girls. Victims are often relatives. Most pedophiles are heterosexual.
Sexual masochism	Sexual pleasure comes from physical or mental abuse or humiliation.	A dangerous form of hypoxyphilia, where oxygen deprivation enhances arousal, and accidental deaths can occur.
Sexual sadism	Sexual arousal is derived from causing mental or physical suffering to another person.	Sexual sadism is mostly seen in men. It can progress to rape. 50% of those afflicted are alcoholic.
Transvestic fetishism	Cross-dressing in heterosexual males for sexual arousal.	The wife (partner) may be aware of the activity and help in the selection of clothes or insist on treatment.
Voyeurism	Sexual arousal by watching an unsuspecting person who is naked, disrobing, or engaging in sexual activity.	Most commonly occurs in men, but it can occur in women. Masturbation commonly occurs. A variant is telephone sex.
Paraphilia not otherwise specified	Paraphilias that do not meet criteria for any of the previous categories.	Categories include necrophilia (corpses), zoophilia (animals), urophilia (urine), and coprophilia (feces).

TABLE 24–8 Psychiatric Differential Diagnosis of Paraphilias

Mental retardation
Dementia
Substance intoxication
Manic episode (bipolar disorder)
Schizophrenia
Obsessive–compulsive disorder
Gender identity disorder
Personality disorder
Sexual dysfunction
Nonparaphiliac compulsive sexual behaviors
Compulsive use of erotic videos, magazines, or cybersex
Uncontrolled masturbation
Unrestrained use of prostitutes
Numerous brief, superficial sexual affairs
Hypersexuality/sexual addiction

to stereotypical sex role behaviors, transvestic fetishism (cross-dressing), and schizophrenia (e.g., with the delusion that one belongs to the other sex).

TREATMENT

Organically-Based Treatment

The essence of treatment for sexual disorders involves the treatment of preexisting illnesses (e.g., diabetes); discontinuation or substitution of offending medications; reduction of alcohol, smoking, or both; increase in exercise; improvement in diet; and addition of medications for psychiatric conditions (e.g., depression). Although many medications for the treatment of hypertension inhibit sexual function, the angiotensin II–receptor blockers (e.g., losartan), are not associated with sexual side effects and may actually help prevent or correct sexual problems (such as sexual dissatisfaction, low frequency of sex, ED).[52] Any hormone deficiency should be corrected (e.g., addition of testosterone for hypogonadism, thyroid hormone for hypothyroidism, estrogen/testosterone for postmenopausal females, or bromocriptine for elevated prolactin after neuroimaging of the pituitary). Many medical illnesses are associated with physiologic and psychological impairments that when treated improve sexual function; selected examples are shown in Table 24–9.[5]

Psychotropic Medication–Induced Sexual Dysfunction

Antidepressants

Sexual dysfunction is a commonly reported side effect of selective serotonin reuptake inhibitors (SSRIs). According to some estimates, as many as 30% to 40% of SSRI users experience anorgasmia, 10% to 20% of patients experience decreased libido or ED, and 30% to 50% experience low desire.[5,53] Strategies to treat SSRI-induced sexual dysfunction are presented in Table 24–10.[53–62] Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) also cause sexual problems. Because of their sexual side effects, the SSRIs have been used with success to treat premature ejaculation and reduce compulsive sexual acts associated with Alzheimer's disease,[63] paraphiliac behavior,[64] and sexual obsessions in obsessive–compulsive disorder (OCD) spectrum patients.[65]

Antipsychotics

Typical antipsychotics (e.g., haloperidol and thioridazine) as well as atypical agents (e.g., risperidone and clozapine) are all associated with sexual dysfunction. Hyperprolactinemia may play a causal role. Most second-generation antipsychotics (e.g., olanzapine, quetiapine, aripiprazole, and ziprasidone) are associated with fewer sexual side effects.[66] Antipsychotics have also been used to dampen sexually inappropriate behaviors and paraphilias.[67]

Premature Ejaculation

There is no Food and Drug Administration (FDA)-approved treatment for premature ejaculation. However, the SSRIs (e.g., fluoxetine, sertraline, and paroxetine), used continuously or intermittently (2 to 12 hours before sex), can cause delayed or retarded ejaculation, which can treat premature ejaculation. Low doses may be effective. Clomipramine (a TCA) may be more effective in delaying

TABLE 24–9 Specific Treatments for Sexual Dysfunction Attributable to Medical Illness

DISEASE	ASSOCIATED IMPAIRMENT CAUSING SEXUAL DYSFUNCTION	TREATMENT
Coronary artery disease	Fear of recurrent MI	Reassure, exercise
	Fear of nitrate-PDE-5 interaction	Switch from nitrate to trimetazidine (not FDA-approved)
	Concurrent depression	Treat depression
Renal failure	Low testosterone (men)	Consider testosterone
	Hyperprolactinemia	Try bromocriptine, 25(OH)D
	Low zinc levels	Consider zinc replacement
	Anemia	Erythropoietin
	Uremic menorrhagia	Consider cyclic or daily progesterone
	Concurrent depression	Treat depression
	Estrogen deficiency	Local estrogen therapy
Urinary incontinence	Urinary leakage during sex	Consider surgery
Diabetes	Hyperglycemia	Improve glycemic control
Elevated prolactin	Hyperprolactinemia	Treat underlying cause
Adrenal disease	Diminished adrenal hormones	Consider DHEA

TABLE 24–10 Treatment Strategies for SSRI-Induced Sexual Dysfunction

STRATEGY	COMMENTS
Decrease the dose	May diminish antidepressant effect Consider in patients on high doses
Switch SSRIs	Paroxetine linked to highest rates of sexual dysfunction Fluvoxamine may have fewer sexual side effects No clear evidence to support this strategy
Switch to a non-SSRI agent	Data support bupropion, mirtazapine, duloxetine, nefazodone Consider transdermal selegiline Not FDA-approved: tianeptine, reboxetine, moclobemide Venlafaxine and desvenlafaxine *not* superior to SSRIs
Add "antidote" drug	Best evidence to support PDE-5 inhibitors (sildenafil, tadalafil, vardenafil), next bupropion, then buspirone (high dose) PDE-5 inhibitors not only improve erectile dysfunction but also arousal and orgasm even in some women on SSRIs Small studies support maca root (herbal agent) Consider amantadine, dextroamphetamine, methylphenidate, ginkgo biloba, granisetron, cyproheptadine, yohimbine, atomoxetine (data mixed)
Take a drug holiday	Limited studies show no clear benefit to this approach May precipitate withdrawal and encourage noncompliance
Await spontaneous remission	Rarely occurs

ejaculation than the SSRIs.[68] Dapoxetine, an SSRI in phase III clinical trials with a rapid onset and short half-life, is being studied as an on-demand treatment for premature ejaculation.[69] Topical anesthetic creams (such as lidocaine derivatives) appear to be successful in slowing ejaculation without inducing the systemic side effects of antidepressants; however, they can cause local skin irritation and penile numbing that sometimes leads to erectile problems. The most popular of these agents is EMLA cream, a combination of lidocaine and prilocaine.[70] When the premature ejaculation is secondary to ED, PDE-5 inhibitors should be used to treat ED first.

Erectile Dysfunction

The mainstay of treatment for ED is the use of oral PDE-5 inhibitors (e.g., sildenafil, vardenafil, and tadalafil), which can help men with a wide range of conditions; they are easy to use, and have few adverse effects (Table 24–11).[19,61,71,72] The PDE-5 inhibitors are effective in the treatment of antidepressant-induced ED and retarded ejaculation. Of note, the PDE-5 inhibitors are metabolized by P450 3A4 and 2C9 isoenzyme systems. Patients who take potent inhibitors (including grapefruit juice, cimetidine, ketoconazole, erythromycin, and ritonavir) of these P450 isoenzyme systems, should have a lower starting dose of a PDE-5 inhibitor. Statins may also help improve the efficacy of PDE-5 inhibitors.

Other oral agents are used to treat ED. Yohimbine (Yocon), an α_2-adrenergic inhibitor, has been available for many years and it may be useful in the treatment of psychogenic ED; however, its efficacy is uncertain. Phentolamine (Vasomax) is an α-blocker (not yet FDA-approved), that may produce erections by dilation of blood vessels. Apomorphine (Uprima) is a centrally acting D_1/D_2 dopamine receptor agonist administered sublingually (not yet FDA-approved). Although efficacious in the stimulation of erections, the drug is limited by its side effects, especially nausea and vomiting.[19] Centrally acting melanocortin receptor agonists (in development as an intranasal preparation) appear to be effective, but side effects (flushing, nausea) may limit their utility.[73] The amino acid L-arginine (an NO precursor) appears promising in men.

Second-line treatments for ED include use of intrapenile injection therapy, intraurethral suppository therapy, and vacuum-assisted devices (Table 24–12). The third-line treatment for ED is surgical implantation of an inflatable or malleable rod or penile prosthesis. Endarterectomy may correct ED in certain patients with underlying vascular disease.[74]

Female Sexual Dysfunction

The only approved medical–surgical intervention for the treatment of female sexual dysfunction is EROS-CTD, a clitoral suction device, which is used to increase vasocongestion and engorge the clitoris for better sexual arousal and orgasm. Numerous drug trials are being done using medications approved for male sexual dysfunction (PDE-5 inhibitors), hormone-based therapies, and novel agents. In general, PDE-5 inhibitors are not effective in improving female sexual function, but they may benefit some women who exhibit greatly diminished genital vasocongestion.[75] PDE-5 inhibitors also appear to be effective for women with SSRI-induced sexual dysfunction.

Testosterone (in a variety of forms), in combination with estrogen (Estratest), has been shown to improve libido, sexual arousal, and the frequency of sexual fantasies in surgically and naturally postmenopausal women.[76] However, it requires a relatively high dose, and because long-term estrogen use (including combination with progestin) is associated with risks, it is not routinely recommended. Recently, transdermal testosterone was shown to improve sexual function in postmenopausal women *not* taking estrogen, but long-term safety data are not available.[77] Tibolone, a steroid hormone with estrogenic, androgenic,

TABLE 24–11 First-Line Treatment for Erectile Dysfunction: Comparison of PDE-5 Inhibitors

MEDICATION	DOSE	ONSET	DURATION	FOOD INTERACTION	ADVANTAGES	SIDE-EFFECTS	CONTRAINDICATIONS
Sildenafil (Viagra)	25-100 mg Max - one dose per day	30-60 min	4 hrs (up to 12 hrs)	Delayed absorption with high-fat foods	50%-85% efficacy	Headache, low BP, flushing, dyspepsia, vasodilation, diarrhea, visual changes (blue tinge to vision) Non-arteritic anterior ischemic optic neuropathy (NAION)	Active caronary artery disease, hypotension No nitrates for 24 hrs after dose Caution with α-blockers
Vardenafil (Levitra)	2.5-20 mg Max -one dose QD	15-30 min	4 hrs (up to 12 hrs)	Delayed absorption with high-fat foods	75% efficacy No visual side-effects	Headache, low BP, flushing, dyspepsia, vasodilation, diarrhea Non-arteritic anterior ischemic optic neuropathy (NAION)	Active CAD, hypotension May prolong QTc May increase liver function tests Avoid nitrates for 24 hrs after dose Avoid α-blockers (Hytrin and Cardura); use cautiously with Flomax or Uroxotra
Uroxatral	5-20 mg	30-45 min	24-36 hrs	None	75% efficacy No visual side-effects Can be taken with food	Headache, low BP, flushing, dyspepsia, vasodilation, diarrhea Non-arteritic anterior ischemic optic neuropathy (NAION)	Active CAD, hypotension Avoid nitrates for 48 hrs after dose Avoid α-blockers (Hytrin and Cardura); use cautiously with Flomax or Uroxatral

CAD, Coronary artery disease; *QTc*, corrected QT interval; *LFTs*, liver function tests.

TABLE 24–12 Second-Line Treatments for Erectile Dysfunction

TREATMENT	EFFECTS	ADVANTAGES	DISADVANTAGES
Intraurethral suppository: MUSE (alprostadil)	Prostaglandin E_1 gel delivered by applicator into meatus of penis Induces vasodilation to cause erection	60% efficacy Less penile fibrosis and priapism than with penile injections Can be used twice daily	Not recommended with pregnant partners Mild penile/urethral pain
Penile self-injection: alprostadil (Caverject and Edex)	Prostaglandin E_1 injected into base of penis Induces vasodilation to cause erection	50%-87% efficacy Few systemic side effects	Can cause penile pain, priapism, fibrosis Not recommended for daily use
Vacuum constriction device (pump)	Creates vacuum to draw blood into penile cavernosa Elastic band holds blood in penis	67% efficacy No systemic side effects Safe if erection not maintained more than 1 hour	May not be acceptable to partner Erection hinged at base; does not allow for external ejaculation

and progestogenic metabolites, has been shown to increase vaginal lubrication, arousability, and sexual desire, but not the frequency of sexual intercourse or orgasm. It is also associated with an increased risk of stroke in women with osteoporosis over age 60 years.[78,79]

Bupropion (a dopamine and noradrenergic agonist) may increase arousability and sexual response in women. As in men, trials of yohimbine, apomorphine, and melanocortin agonists are ongoing. L-Arginine may also enhance female sexual function.[44]

Paraphilias

Pharmacologic therapy for paraphilias is aimed at suppression of compulsive sexual behavior. The antiandrogen drugs, cyproterone (CPA) and medroxyprogesterone acetate (MPA, Depo-Provera), which act by competitive inhibition of androgen receptors, are used to reduce aberrant sexual tendencies by decreasing androgen levels (not yet FDA-approved). Treatment with leuprolide (approved for prostate cancer) and triptorelin (not yet FDA-approved), synthetic gonadotropin-releasing hormone analogues, decrease testosterone to chemically castrating levels (after an initial transient increase) and may completely abolish deviant sexual tendencies. The SSRIs and clomipramine may lower aberrant sexual urges by decreasing the compulsivity/impulsivity of the act and by decreasing aggressive behaviors. Antipsychotics have also been used to treat paraphilias.[80,81]

Gender Identity Disorder

The major treatment for gender identity disorder is sex-reassignment surgery. Hormone therapy may be necessary to suppress original sex characteristics (i.e., with luteinizing hormone–releasing hormone (LHRH) agonists, CPA, estrogens, and testosterone).

Psychologically-Based Treatments

Sexual Dysfunction

General principles of treatment include improving communication (verbally and physically) between partners, encouraging experimentation, decreasing the pressure of performance by changing the goal of sexual activity away from erection or orgasm to feeling good about oneself, and relieving the pressure of the moment (by suggesting there is always another day to try). The PLISSIT model provides a useful framework for approaching treatment of sexual problems and can be tailored to the desired level of intervention. The stages are (1) P: permission; (2) LI: limited information; (3) SS: specific suggestions; and (4) IT: intensive therapy. Permission-giving involves reassuring the patient about sexual activity, alleviating guilt about activities the patient feels are "bad" or "dirty," and reinforcing the normal range of sexual activities. Limited information includes providing basic knowledge about anatomy and physiology and correcting myths and misconceptions. Specific suggestions include techniques of behavioral sex therapy (Table 24–13). Intensive therapy may be useful for patients with chronic sexual problems, complex psychologic issues, or both. Whereas the first three stages (P, LI, SS) may be implemented by any health care provider, the last stage (IT) usual requires an expert with special training in sex therapy.[21,28,82]

Paraphilias

Paraphilias are often refractory to treatment, and recidivism is high, but several nonpharmacologic modalities have been used with varying success. Insight-oriented or supportive psychotherapy is relatively ineffective. Cognitive-behavioral therapy (CBT) can be used to help patients identify aberrant sexual tendencies, alter their behavior, and avoid sexual triggers to prevent relapse. Aversive therapy, via conditioning with ammonia, is used to reduce paraphiliac behavior. Orgasmic reconditioning is used to teach the paraphiliac how to become aroused by more acceptable mental images. Social skills training (individual or group) is used to help the paraphiliac form better interpersonal relationships. Surveillance systems (using family members to help monitor patient behavior) may be helpful. Lifelong maintenance is required.[83]

Gender Identity Disorder

Individual psychotherapy is useful both in helping patients understand their gender dysphoria and in addressing other psychiatric issues. A thorough psychologic evaluation is generally required before sex reassignment surgery can be performed. Marital and family therapy can help with adjustment to a new gender.[84]

TABLE 24–13 Specific Behavioral Techniques of Sex Therapy

SEXUAL DISORDER	SUGGESTIONS
Hypoactive sexual disorder	Sensate focus exercises (nondemand pleasuring techniques) to enhance enjoyment without pressure
	Erotic material, masturbation training
Sexual aversion disorder	Same as for hypoactive sexual disorder For phobic/panic symptoms, use antianxiety/antidepressant medications
Female sexual arousal disorder	Lubrication—saliva, KY jelly for vaginal dryness
Male erectile disorder	Sensate focus exercises (nondemand pleasuring techniques)
	Use female superior position (heterosexual couple) for nondemanding intercourse
	Female manually stimulates penis and if erection is obtained she inserts the penis into the vagina and begins movement
	Learn ways to satisfy partner without penile/vaginal intercourse
Female orgasmic disorder	Self-stimulation
	Use of fantasy materials
	Kegel vaginal exercises (contraction of pubococcygeus muscles)
	Use of controlled intercourse in female superior position
	"Bridge technique"—male stimulates female's clitoris manually after insertion of the penis into the vagina
Male orgasmic disorder (during intercourse)	Female stimulates male manually until orgasm becomes inevitable Insert penis into vagina and begin thrusting
Premature ejaculation	Increased frequency of sex
	"Squeeze technique"—female manually stimulates penis until ejaculation is approaching, then the female squeezes the penis with her thumb on the frenulum; pressure is applied until the male no longer feels the urge to ejaculate (15-60 sec); use the female superior position with gradual thrusting and the "squeeze" technique as excitement intensifies
	"Stop–start technique"—female stimulates the male to the point of ejaculation then stops the stimulation; she resumes the stimulation for several stop–start procedures, until ejaculation is allowed to occur
Dyspareunia	Treat any underlying gynecological problem first
	Treat insufficient lubrication
Vaginismus	The female is encouraged to accept larger and larger objects into her vagina (e.g., her fingers, her partner's fingers, Hegar graduated vaginal dilators, syringe containers of different sizes)
	Recommend the use of the female superior position allowing the female to gradually insert the erect penis into the vagina
	Use extra lubricant (KY jelly)
	Practice Kegel vaginal exercises to develop a sense of control

CONCLUSION

Sexual problems are common in the general population, and in medically ill, hospitalized patients, the prevalence is even greater. Even when a sexual problem is not the primary reason for consultation, the consulting psychiatrist should feel comfortable and well-equipped to take a sexual history as a routine part of the evaluation. Although time and privacy are important limitations in the inpatient setting, the sexual history may reveal an unrecognized sexual concern; uncover an underlying medical or psychiatric illness; or at the very least help better understand the *patient* in a functional context, and in turn, improve the patient–doctor relationship.

With our population growing older, the potential for sexual problems is on the rise. Patients both in and out of the hospital are living with complex medical problems and taking multiple medications. At the same time, with the shifting focus of medicine from improving not only the length of life but also the *quality* of life, physician responsibility to recognize and treat sexual problems is ever greater. Consulting psychiatrists can be helpful in discerning the biological, psychological, and social factors that contribute to a sexual problem. Recognizing the sexual side effects of psychotropics and other medications is a key part of the evaluation. Fortunately, many effective treatment strategies now exist (e.g., use of PDE-5 inhibitors for SSRI-induced sexual dysfunction). With increasing understanding of the biological basis for sexual dysfunction, the opportunity to treat sexual problems should only continue to expand.

Some sexual problems may be the result of an acute illness or require only short-term treatment or medication adjustment. By seeing patients in the hospital setting and getting an appreciation of the psychological and physical

limitations that patients face, consultant psychiatrists may offer creative solutions to facilitate a sexual life. The inpatient setting also provides a unique opportunity to get multiple specialists involved as necessary (e.g., urologist, gynecologist, and endocrinologist) to provide comprehensive care. Ultimately, the consultant psychiatrist may play a pivotal role in triaging the patient to an outpatient provider for longer-term management.

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Organ Failure and Transplantation

25

Owen S. Surman, M.D.
Laura M. Prager, M.D.

ADVANCES IN TRANSPLANTATION BIOLOGY

The past 4 decades have seen dramatic growth in organ transplantation. Kidney transplantation, an uncommon event in the mid 1960s, is now a routine operation. With the advent of cyclosporine, tacrolimus, and other immunosuppressive treatments for graft rejection, transplantation (of livers, hearts, and lungs) became practical in the 1980s; excellent survival statistics now accompany such procedures. Solid organ transplantation is the focus of this chapter. Bone marrow transplantation is beyond the scope of this chapter.[1]

PROCEDURAL LIMITATIONS

Although a variety of factors affect the efficacy of organ transplantation, the most pressing challenge remains the shortage of available deceased-donor and living-donor organs. Rejection and the complications of antirejection therapy continue to limit successful transplantation. Exciting developments are on the horizon. Steroid-sparing approaches using sirolimus show promise in pancreatic islet cell transplantation research. Work proceeds on animal models of xenotransplantation, even though the potential for interspecies spread of infection remains a major concern. Tissue engineering is at an early, but promising, stage of scientific discovery. Immunologic tolerance is essential to transplantation, and one new strategy is to irradiate the bone marrow of transplant recipients and to perform transplantation of donor marrow as a means of producing temporary immunologic chimerism. This protocol has had initial success in clinical trials with combined bone marrow and renal transplantation for patients with myeloma kidney.[2]

In some nations, societal limits have restricted access to deceased donor organs.[3] Japan, for one, will permit family consent for deceased organ availability beginning in July 2010. Asystolic cadaveric organ donation offers an alternative for renal allografts[4]; however, other organs are less able to withstand ischemic injury. Kidney donation from living donors is common in many countries, and participation of unrelated living donors is now a common and accepted practice in the United States. Unfortunately, the scarcity of kidneys has stimulated a burgeoning black market in illicit sale of organs from poor third-world donors, who risk their health as victims of organ trafficking.[5]

Living donors can be a source of transplanted organs under some circumstances. Parent-to-child liver transplantation is frequently performed using the left lateral lobe, and living-related or living-unrelated lobar-lung transplantation is another option, with a lung lobe donated by each of two living donors. Transplantation of the right hepatic lobe from a living adult donor to a recipient has proved lifesaving for liver transplant candidates, who face a 20% risk of dying before obtaining a liver from a cadaveric source. The greater morbidity of this type of surgery for liver donors has become a source of ethical deliberation.[6] Risk of mortality has decreased with operative experience and improvement in criteria for donor selection and perioperative care. Complications include biliary stricture, bile leaks, secondary biliary cirrhosis, pulmonary embolism, bleeding, pain, and prolonged recovery time. Posttraumatic stress disorder (PTSD) has been reported in one study of living partial-liver donors in Japan.[7] State regulations for partial-liver transplantation from living donors have been developed under the auspices of the New York State Department of Public Health,[8] and there are clear national guidelines from the Center for Medicare and Medicaid Services (CMS).[9] The National Organ Transplant Act endorses ethical practices related to organ donation and prohibits the sale of organs.

THE NEED FOR PSYCHIATRIC INTERVENTION

Patient selection and organ donor selection require psychiatric input. In some centers, a psychiatrist works with each specific transplantation team. However, many transplantation centers rely on general hospital psychiatric consultation services, and in some centers, psychologists and social workers are involved in the psychosocial screening of recipients and donors.

Perioperative psychiatric support of transplant candidates requires an appreciation of the special needs of patients with end-stage organ failure.[10] Psychiatrists are asked to predict the likelihood of patient compliance after transplantation and to treat preoperative and postoperative psychiatric syndromes. Postoperative sequelae unique to transplantation are a consequence of allograft rejection and the use of immunosuppressive agents. Many clinicians refer to the patient's rollercoaster-like experience of transplantation, replete with promise and uncertainty.

ORGAN FAILURE

Common Features

Functional decline and subsequent loss of previous social roles are inevitable sequelae of end-organ failure. Such conditions predispose to adjustment disorders, anxiety syndromes, and depression. Loss of mental acuity, which may progress to frank encephalopathy, may also accompany organ failure.

End-Stage Renal Disease

Renal failure may have a systemic or a local cause. Systemic diseases include diabetes mellitus (DM), hypertension, and collagen vascular diseases. Patients with DM often bear the added burden of retinopathy, sensory deficits, neuropathy, and gastrointestinal dysmotility. Chronic lithium therapy can cause renal failure. Hereditary causes of renal failure, such as polycystic kidney disease, can have the added complication of reducing family donor availability. Patients with familial syndromes are sometimes burdened with concern about the emergence of the disorder among younger family members. Their acceptance of treatment for renal failure may be affected by adverse experiences of other afflicted family members.

The availability of dialysis is the feature that most clearly distinguishes renal failure from other types of end-organ disease. Hemodialysis is performed at most acute care centers, typically three times weekly in approximately 4-hour sessions. Patients can also undergo hemodialysis at chronic care centers or even receive home-based treatments. The scheduling of treatments has a significant impact on work and family life. Continuous ambulatory peritoneal dialysis can be performed intermittently, typically four times daily or continuously throughout the night. To avoid peritonitis, patients must be capable of meticulous self-care. Mood disorders, cognitive impairment, environmental stress, and noncompliance, among other things, can impair adherence to a careful regimen. All of these may be indications for referral for psychiatric or social service assistance.

Depression, a common complication of dialysis treatment, emerges more frequently among those with a higher level of morbidity. Some researchers have attempted to standardize measures for medical impairment in this population. An example of this is the end-stage renal disease (ESRD) severity index.[11] Some studies suggest that depression increases the mortality rate among dialysands.[12] Alterations of endocrine function (especially from hyperparathyroidism), anemia, metabolic stress, and cognitive function contribute to the depression associated with renal failure.[13]

Encephalopathy is a common consequence of uremia and an indication for hemodialysis; it is often confused with depression by nonpsychiatric physicians. Neuropsychiatric syndromes have included dialysis disequilibrium and dialysis dementia, which is obviated by removal of aluminum hemodialysis.[13] Seizures are common in patients with uremia; complex partial seizures often result in behavioral changes (e.g., agitation and catatonia) that respond to anticonvulsant therapy.[14,15] Encephalopathy may also occur in response to activation of cytokines as part of the immunologic activation by synthetic dialysis membranes.[16]

Psychopharmacologic care of the patient with renal failure requires dosage adjustments of standard anxiolytics, antidepressants, and neuroleptics, as described by Bennett and associates.[17] Depression is best managed with selective serotonin-reuptake inhibitors (SSRIs), bupropion, and psychostimulants.[13,18] Short-acting anxiolytics are generally preferable to longer-acting ones to minimize the buildup of metabolites. Monitoring the blood levels of anticonvulsants can be complicated by low values that may result from changes in protein binding. Unbound or free levels of phenytoin and carbamazepine are more valuable measurements. Lithium carbonate is readily dialyzed; therefore, it should be administered after dialysis treatments. Some patients require continued administration on the days they do not receive dialysis. Frequent monitoring (especially at the outset of treatment) is essential to detect and avoid toxicity. Monthly levels, drawn before hemodialysis, are advisable once a satisfactory dosing schedule has been established. Deferoxamine, an iron-binding and aluminum-binding agent, should be administered when aluminum encephalopathy is suspected.[13]

Psychotherapy can be challenging with patients in renal failure. Insight-oriented psychotherapeutic strategies may be destabilizing for those who rely on denial and who lack a sense of control[19]; cognitive therapy and other active, ego-supportive approaches may be more helpful. Hypnotherapy can be beneficial for patients with needle phobias and other forms of anxiety.

Dialysis patients sometimes choose to terminate treatment, particularly in the face of what they feel is an unacceptable reduction in their quality of life.[20,21] In such instances, the psychiatrist may be called on to assess the patient's capacity to refuse treatment. As the following case example illustrates, careful psychiatric diagnostic evaluation and treatment can have a significant, sometimes life-changing, impact on the patient's course.

CASE 1

Mr. A, 40-year-old man with DM, was referred for psychiatric evaluation of depression because he wanted to discontinue hemodialysis. There was no personal or family history of depression. He reported a depressed mood in association with chronic pain from diabetic neuropathy and from the severe headaches that often followed hemodialysis sessions. Mr. A agreed to a trial of an antidepressant and an analgesic after hemodialysis. His pain remitted, his mood lifted, and he subsequently chose to undergo renal transplantation.

On occasion, a patient has the capacity to refuse treatment, wishes to withdraw from therapy, and demonstrates a full understanding of the impact of such a choice. In these cases, it may be necessary for the psychiatrist to support the team and the patient's family while dialysis is discontinued.

Quality of Life and Choice of Renal Failure Therapy

The choice between dialysis and transplantation for patients with ESRD varies with the medical circumstances. Patients with DM are less tolerant of hemodialysis

and are at risk for acceleration of retinopathy. Patients older than 60 years who are on chronic hemodialysis are also at increased risk for mortality and morbidity. Historically, some centers have had a bias toward either dialytic or transplantation-based treatment of patients with ESRD.[22]

Waiting time varies among organ procurement centers in the 11 designated regions functioning under the auspices of the United Network of Organ Sharing (UNOS), and it is not unusual for patients in New England, for example, to wait 4 or 5 years to obtain a deceased-donor kidney. Those with financial means can be listed at more than one center, but transplantation will not improve quality of life for those patients unable even to secure funding for the required, expensive immunosuppressant medication. Patients may have difficulty gaining access to an established transplantation center for perioperative and postoperative care. Likewise, for a patient with advanced atherosclerosis, a successful vascular anastomosis and transplantation may not be possible. For diabetic patients and those older than 60 years, "extended donor organs" derived from older deceased donors whose kidneys do not meet standard UNOS criteria can be another option. Combined pancreas and kidney transplantation, although associated with an increased risk for postoperative morbidity, offers an advantage because the need for insulin therapy is eliminated.

In 1985, Evans and associates[23] reported that 80% of 144 kidney transplant recipients and 48% to 60% of 715 dialysis patients were functioning at a near-normal level. Overall, transplant patients do better than patients receiving dialysis. Improvements in dialysis technique and the availability of erythropoietin to combat the anemia of renal failure have done much to improve the circumstances of those who have high levels of preformed antibody or who are otherwise unsuited for transplantation.

Organ Donation

Further discussion of organ donation and its psychiatric implications is provided later in this chapter. Criteria for unrelated organ donation have traditionally included documentation of a close bond between the donor and the recipient, altruistic intent on the part of the donor, and lack of coercion (as evidenced during medical evaluation and a standard psychiatric interview). Liberalization of organ donor criteria now allows for selective participation of Good Samaritan donors. A new challenge has arisen as some recipients turn toward one or another form of public solicitation. Some make their needs known in newsletters at places of worship. A website (MatchingDonors.com) offers Internet exposure for a fee; many centers choose not to accept such arrangements.

Organ donation depends on the willing participation of the donor, the recipient, and the surgical team. Transplantation surgeons must decide on their level of acceptance before operating on a healthy individual for purposes of organ donation, and centers vary regarding the inclusion of living-donor surgery of any type. Historically, UNOS has prohibited financial remuneration of a donor by a recipient.[24] The World Health Organization has also taken a strong stand against the sale of organs. But medical ethics evolve with changing social mores, and recently UNOS has allowed donors to receive reimbursement for specific expenses related to organ donation, such as travel costs. Psychiatric evaluation of donors often reveals new information about donors that may inform the selection process.

CASE 2

Ms. B, a 32-year-old woman, wanted to be a kidney donor for her divorced boyfriend's ex-wife, whose renal failure had been caused by systemic lupus erythematosus. Psychiatric evaluation revealed that the intended donor was guilt ridden about the recipient's circumstances. No established bond existed between the two women. The potential donor was "the other woman," a role in which she had been cast. Ms. B. gave a history of physical abuse by her mother and sexual abuse by her mother's three marital partners. She acknowledged a feeling of universal love and a wish to please others. She seemed accepting and possibly relieved when the psychiatrist rejected her candidacy as a donor. She also pointed out the parallels between her current situation and her past traumas.

At some centers, family members and close friends of the recipient are included in a pretransplantation family meeting attended by the recipient's nephrologists, nurse coordinator, social worker, a transplantation psychiatrist, a financial coordinator, and a representative from the tissue-typing laboratory. Current practice requires that transplant recipients and donors receive informed consent from the multidisciplinary care team. Donors who have completed a separate selection process can participate with the (intended) recipient in family meetings joined by a designated donor psychiatrist, social worker, and nurse coordinator. This attention to providing separate teams for evaluation of donor and recipient is a CMS-established protocol change.

Allograft survival statistics have improved substantially, granting a living-donor kidney transplant a half-life of 16 years. To deal with the critical shortage of kidneys, a donor-swap program is available in the New England region and through some other organ procurement organizations. In this program, two donors, each of whom is blood type–incompatible with an intended recipient, can exchange roles, thereby allowing the two recipients to obtain a kidney. In all instances of living-donor participation, it must be understood that the donor is a patient with rights to medical care independent of the recipient's need or institutional priorities.[24]

End-Stage Heart Disease

Among those who undergo heart transplantation, the leading preoperative diagnoses are coronary artery disease and cardiomyopathy. Before transplantation, prolonged intensive care unit (ICU) stays are the rule, because medical selection criteria are based on urgency. Many relatively high-functioning younger patients, who risk death from arrhythmia, have lengthier waits as outpatients.

Pretransplantation stress is similar to the stress associated with increased cardiac vulnerability in the general population. Major factors include the adverse impact of role loss and of separation from family.[25,26] Recently, attention has been paid to the favorable impact of positive affect on autonomic regulatory balance and heart rate variability.[27] Fear that transplantation may not be forthcoming or effective also causes anticipatory bereavement.

As with other types of organ failure for which there is no sustaining maintenance therapy, a patient approaching heart transplantation may express a willingness to proceed because there is no other choice. The anger and anxiety that frequently accompany this predicament are also associated with cardiovascular morbidity.[28] Encephalopathy may develop secondary to decreased cerebral blood flow, metabolic disorders, and medication effects (e.g., of lidocaine and β-blocking agents).[29]

Prolonged ICU stays and their attendant stress call for creative management strategies. Psychopharmacologic support may include use of anxiolytics and antidepressants (e.g., those with a low risk for cardiotoxicity). Tricyclic antidepressants (TCAs) are disadvantageous in this population before transplantation surgery because of their potential for causing arrhythmias and orthostatic hypotension. Constipation, a frequent side effect of TCAs, may also increase cardiovascular risk by creating the need for Valsalva maneuvers.[30] Use of bupropion or an SSRI is preferred, with appropriate regard for their potential drug–drug interactions related to their cytochrome P450 isoenzyme effects.

CASE 3

Mr. C, a middle-aged man with a highly counter-dependent style, became depressed after learning that his status on the transplant list had fallen because other patients were more acutely ill. Although he confided that he planned to forgo transplantation and leave the ICU, he agreed to a trial of bupropion. Within 3 days, his mood improved and he again elected to undergo transplantation. When pruritus developed, Mr. C agreed to add diphenhydramine to his regimen rather than discontinue bupropion. His transplantation proceeded uneventfully, and he required no postoperative antidepressant therapy.

Delirium is a common and demanding complication for those who require placement of an intraaortic balloon pump. Hypotension and microembolic events may be responsible, although cytokine activation might play a role. Use of IV haloperidol is a first-line approach to the management of agitated delirium. Adequate analgesia also is essential for patients with severe angina; additional support from a hospital-based pain management team may be required.

Hypnotherapy and other cognitively based strategies can enhance the patient's adaptive response. For example, one young mother used self-hypnosis to master lonely nights in the ICU; she imagined that the beeping of her monitor represented the sound of a spaceship on which she journeyed each night with her children. Another patient, a middle-aged policeman with intractable chest pain, found relief in frequent images of fishing with a brother who resided out of state. Another man who proved especially intolerant of medical dependency was able to use a hypnotic suggestion that he had a double. While engaged in a more active fantasy of managing his horse farm, he could imagine that it was his double that lay in the hospital as a passive recipient of life-saving care.

End-Stage Liver Disease

The most frequent causes of liver failure in the United States are alcoholic cirrhosis and alcoholic hepatitis; other causes include infectious and autoimmune hepatitis, primary biliary cirrhosis, and sclerosing cholangitis. Hepatocellular carcinoma is also an indication for transplantation when the disease is confined to the liver. Acuity is the deciding factor in the allocation of livers. The current Model for End-Stage Liver Disease (MELD) system gives priority to ICU-based patients and to medically stable outpatients with good-prognosis hepatocellular carcinoma.[31,32] There are strict criteria for deceased-donor liver transplantation in the setting of hepatocellular carcinoma, and the shortage of organs has virtually eliminated liver transplantation as a palliative approach.

At the time of evaluation and listing for transplantation, patients with liver failure have less than a year to live. Recurrent esophageal bleeding, tense ascites, recurrent encephalopathy, nutritional impairment, coagulopathy, and jaundice are common findings. Sleep apnea, another complication of end-stage liver disease, is presumably related to accumulation of abdominal ascites.[33]

The principal cause of hepatic encephalopathy is absorption of toxic metabolites from the intestine. The presence of false neurotransmitters may also result in central nervous system depression. Grading of hepatic encephalopathy has traditionally been accomplished with the Parsons-Smith criteria.[34] Some critically ill patients present in frank stupor and may not recall their preoperative course. Subtler cognitive dysfunction may be evident on a standard mental status examination or notation of odd behavior patterns. It is especially important for the consultant to learn about premorbid function because patients with so-called subclinical hepatic encephalopathy[35] are likely to improve after transplantation. Neurologic improvement after transplantation may be slow for some patients, but, in general, transplantation is associated with a significant improvement in the recipient's quality of life.[36]

Medical management is the primary approach to these patients. Control of bleeding and infection, reduction of protein intake, and administration of lactulose constitute the standard approach. Use of anxiolytics and sedatives must be used carefully because most are hepatically metabolized and may precipitate obtundation even when used in relatively modest doses.[36]

Patient Selection and End-Stage Alcoholic Liver Disease

There is considerable variation in both screening methods and acceptance criteria for transplant candidates between centers. Type of psychosocial assessment, degree of reliance on standardized testing, and level of training and experience of mental health professionals differ.[10,37–39]

Other factors that may influence a center's decision include the patient's age and body mass index. Delisting criteria for patients whose medical prognosis has deteriorated during the wait for a liver are not standardized.[10,40]

As in the case of heart and lung transplantation, many patients awaiting liver transplant die before an organ becomes available, so the principal consideration in patient selection is capacity to benefit.[41] The steady attrition of candidates for solid organs leads inevitably to utilitarian considerations.[42] In 1991, Moss and Siegler[43] argued that patients with end-stage alcoholic liver disease (ESALD) should be accountable for their histories of substance abuse, even if assignment of fault to such patients leads to second-class status. A risk of such logic is the possibility that patients will become hostages to their past and be excluded by third-party payers from reimbursement of transplantation.[44] Unequal access within a specific category, independent of prognosis, is a form of discrimination incompatible with federal guidelines for the disabled.[45] Predicting the risk for relapse has become the principal challenge in regard to patient selection. Absence of reliable biological markers for active alcohol abuse and difficulty in obtaining reliable historical data from patients and families intent on obtaining advanced medical care for a loved one complicate the picture.

CASE 4

Ms. D, a middle-aged woman who presented for liver transplantation, had generalized anxiety. Postoperatively, she was tremulous and encephalopathic. Alcohol withdrawal was considered, but her husband steadfastly swore that his wife did not drink. Her condition continued to deteriorate, and she developed hyperbilirubinemia. In a visit to the transplantation unit, her husband confided that at home he had unexpectedly discovered a medicine bottle filled with hard liquor, suggesting a history of surreptitious drinking. She went on to retransplantation and again developed malignant hyperbilirubinemia of unknown cause, which proved fatal.

Beresford and colleagues[46] advocated a system of inclusion based on Valliant's prognostic criteria. They assessed the extent to which patients and their families recognized alcohol dependence, the current degree of social stability, and the prospect and degree of lifestyle change conducive to long-term sobriety. Yates and co-workers[47] assessed prognosis with attention to the amount of alcohol consumed and the frequency and success of prior rehabilitation efforts.

Reported rates of recidivism have varied after transplantation for ESALD. For example, Knechtle and colleagues[48] proceeded with liver transplantation in those whose families advocated for transplantation despite failure of the patient to meet criteria for abstinence. This cohort of patients did as well as those with established sobriety, but long-term data from this study are not available. However, subsequent studies demonstrated that patient and graft survival for appropriately selected members of this patient population are comparable to those of other groups with liver failure.[49,50]

Candidates for liver transplantation for ESALD should acknowledge their history of substance abuse, agree to lifelong sobriety, and participate in an active treatment program before undergoing transplantation.[10] Important risk factors are shorter periods of sobriety, polysubstance abuse, history of multiple rehabilitation attempts, history of alcohol dependency, and family history of alcohol abuse.[10] Many centers provide written criteria and require that patients commit themselves to sobriety by signing a formal contract, with the understanding that alcoholism is a relapsing illness. Patients should be advised and encouraged to acknowledge relapse after transplantation, so that effective treatment can be initiated in a timely fashion. Some centers also include random testing.

Patients with opioid addictions have done well on methadone maintenance. Attempts to wean patients from methadone often prove destabilizing, although some centers persist in excluding patients on methadone mainenance.[51,52] Carefully screened patients with bipolar disorder or psychotic disorders can do well after transplantation. It is essential to determine that the condition is manageable before proceeding with transplantation and to arrange for reliable long-term psychiatric follow-up care in the community.[10]

Organ Donorship

The demand for cadaveric livers has led to a number of innovative procedures, including split-liver transplantation and reduced-size grafts for pediatric recipients. The ethics of partial hepatectomy from parent donors to critically ill offspring was initially explored by Singer and associates in 1989[53]; their approach is now widely accepted. Nonetheless, postoperative risks are greater for liver donors than for kidney donors. Right hepatic lobe adult-to-adult transplantation, which places the living donor at still greater risk, initially proceeded without the level of thoughtful deliberation that had marked the introduction of parent-to-child partial liver transplantation.[6] With increased experience, there has been a reduction in operative complications and recognition that donor safety comes first.[54]

Confounding the problem of selection and informed consent is the determination of donors who have made up their mind to proceed. Donor candidates sometimes engage in "impression management," and outright deception has been known to occur.[55] Communication psychologists have referred to the concept of *strategic trajectory*, wherein the intended donor filters new information through a preestablished set of expectations. This is a useful concept in regard to preoperative teaching and informed consent.[56] Current best practices provide the donor with opportunity to hear about the potential risks of organ donation, as well as about the benefits shared with the recipient, from the perspective of an independent donor advocate and from the designated donor surgeon, medical specialist, social worker, coordinator, and psychiatrist.

Psychopharmacologic care of the patient with end-stage liver disease has limitations imposed by the metabolism of psychoactive medications and by the role of hepatic enzymes. Preoperative anxiety and agitation can be treated with low doses of short-acting benzodiazepines. In the presence of hepatic encephalopathy, oxazepam is preferred because it does not require oxidative metabolism.

Lorazepam is a safe agent in low dosage for nocturnal sedation. Although insomnia is frequent in this patient population, it must be treated gently.

Antidepressants can be helpful in the management of liver transplant patients and in those awaiting transplant who contend with hepatitis C infection and who become depressed as a side effect of interferon therapy.[57,58] Bupropion is preferred because of its stimulating effect, but SSRIs are also effective. All antidepressants carry a small risk for hepatotoxicity. Duloxetine (Cymbalta) carries a black box warning against use in the setting of hepatic impairment.

End-Stage Lung Disease

Lung transplantation is a therapeutic option for many patients with end-stage pulmonary failure. Afflicted patients may suffer from obstructive lung disease (e.g., chronic obstructive pulmonary disease or α_1-antitrypsin deficiency), restrictive lung disease (e.g., idiopathic pulmonary fibrosis), septic lung disease (e.g., cystic fibrosis or bronchiectasis), or pulmonary vascular disease (that results in pulmonary hypertension). As lung transplantation is a therapy of last resort, all candidates must accept that they have a limited life expectancy without surgery, and deem that the benefits of transplantation outweigh the risks.

Unfortunately, the number of candidates for lung transplantation exceeds the number of available cadaveric donor organs. Therefore, the waiting list for lung transplantation can be several years long, even though ranking is now based on severity of illness as reflected in a calculated lung allocation score. When pulmonary failure develops, unlike in the case of other solid organs, there is no machine that can provide satisfactory support for patients who are awaiting transplantation. In fact, ventilator dependence can be a contraindication to transplantation. Most candidates, therefore, wait at home, often at some distance from the transplantation center.

A joint statement by the International Society of Heart and Lung Transplantation, the American Society of Transplant Physicians, the American Thoracic Society, the European Respiratory Society, and the Thoracic Society of Australia and New Zealand offers general guidelines for consideration of lung transplant candidates.[59] Shared guidelines for contraindications to transplantation include, in addition to active medical problems (such as malignancy and human immunodeficiency virus infection), many psychosocial parameters. Active cigarette smoking and alcohol or recreational drug abuse are absolute contraindications to lung transplantation. Other disabling psychological symptoms (e.g., ongoing suicidal or homicidal ideation, a history of suicide attempts or chronic self-injurious behaviors, poor compliance with medication regimens, acute psychosis, an eating disorder, and dementia) are relative contraindications to transplantation.

Because of the scarcity of cadaveric organs, many centers now offer the option of living-donor lobar-lung transplantation to suitable recipients. Such recipients are typically young people with cystic fibrosis who are usually small in stature, and, therefore, a single lobe from two individuals of average size will provide sufficient pulmonary capacity. Donors must have the same blood type as the recipient, but they do not have to be biologically related. Potential donors must undergo a comprehensive psychological evaluation as well as a medical work-up (both by evaluators who are not active members of the transplantation team) to determine motivation and to ensure autonomy, informed consent, and the absence of coercion.

Many psychiatric disorders occur in patients with pulmonary failure. Almost all candidates referred for lung transplantation suffer some degree of anxiety, as most people become anxious in the setting of increasing shortness of breath. Candidates for transplantation often describe both anticipatory anxiety (particularly in the setting of planned exertion) and panic attacks, despite oxygen supplementation. This is consistent with the study by Pollack and co-workers,[60] which showed a 17% incidence of panic disorder among 115 patients referred for pulmonary function testing. Adjustment disorder with depressive features is also common in this population, as patients struggle to cope with their progressive inability to perform even simple activities of daily living. In the setting of chronic, debilitating illness, pulmonary patients may develop major depression that requires aggressive psychopharmacologic intervention as well as supportive therapy. Those who are extremely ill may become delirious from hypoxia or hypercapnia. In addition, the medications used to treat the complications of pulmonary disease may precipitate psychiatric problems.

CASE 5

Ms. E, a 21-year-old married woman with pulmonary fibrosis, was referred by her pulmonologist for lung transplantation. She had no other medical problems and had no formal psychiatric history. A college graduate, she had worked full time for several years. During the year before her evaluation, she had to work fewer hours because of worsening pulmonary function. Although she described herself as "even-keeled," she had become increasingly anxious as her pulmonary function worsened. Even when her pulmonologist started her on continuous oxygen treatment, she remained anxious. At the time of her evaluation, she felt overwhelmed and was having panic attacks, particularly when she anticipated leaving her apartment to go to work. She also had trouble socializing with her husband and her friends. Her discomfort was such that she considered leaving her job. Panic disorder secondary to pulmonary decline was diagnosed, and an SSRI and a benzodiazepine (in a low dose) were prescribed. She did extremely well on this regimen, began a pulmonary rehabilitation program, kept her job, and resumed her social life with her friends.

As with other solid organ transplant patients, lung transplant patients are maintained on immunosuppressive drugs (including cyclosporine, FK-506 [tacrolimus], and prednisone) for the remainder of their lives; each can produce a variety of neuropsychiatric disorders (such as mood disorders, psychosis, and leukoencephalopathy).[10] Because of their immunosuppression, these patients are vulnerable to infections (such as by cytomegalovirus, *Aspergillus*, *Nocardia*, *Listeria*, *Cryptococcus*, and nontubercular *Mycobacterium*) that can also cause neuropsychiatric signs and symptoms.

CASE 6

Mr. F, a 60-year-old married man with no psychiatric history, became quite depressed and developed suicidal thoughts several months after single-lung transplantation for chronic obstructive pulmonary disease. He suffered from anhedonia and felt sleepy all the time (despite receiving adequate rest at night). His medications included cyclosporine and antihypertensives. His prednisone had been tapered slowly down to 15 mg/day. He took no pain medications or sedative–hypnotics. He denied any acute psychosocial stressors. Cyclosporine was discontinued, and tacrolimus was begun. His mood improved within several weeks and he felt more alert and awake; he began to participate once again in the activities of his household.

PREOPERATIVE CONSIDERATIONS

Psychiatric Concerns

Hope versus Loss

Typically, the first psychiatric encounter with the transplant patient occurs at the initial medical evaluation for transplantation candidacy. For many, transplantation represents hope for autonomy and prolongation of life; it also implies the terminal nature of their organ failure. While the patient tries to accept the need for transplantation, grief (which varies in intensity with the severity of organ failure and with styles of adaptive function) is manifest.

Preparation for Living versus Dying

Christopherson[61] described the challenge to families who simultaneously prepare for the alternative outcomes of survival and death for loved ones facing heart transplantation. Our group reported the case of a successful liver transplant candidate whose family was making funeral arrangements when he was placed on the list.[62]

False Starts

Patients awaiting transplantation experience considerable stress. For the cardiac patient waiting in the ICU, the wait for a heart is like the watched pot that never boils. For outpatients waiting years for lung transplantation, there is the feeling of having been forgotten. For some, the long preparation for transplantation is followed by a call to the hospital for an organ that never materializes. These false starts are expectedly unsettling.

Survivor Guilt and Its Variations

Transplantation candidates commonly express guilt about their need for an organ—a need that can only be filled by another person's death. Patients with familial disorders may also be sensitive to a loved one's inability to obtain a successful allograft. Patients who have experienced organ failure often have an opportunity to bond with other candidates undergoing similar evaluations and therapy. As transplantation becomes available, some patients feel sadness for those who continue to wait for a graft, guilt because they received the organ first, or unhappiness and disillusionment because their suffering continues as a result of postoperative complications. At the time of the transplantation evaluation, patients often feel guilty about the stress that their illness imposes on family members.

Depression

Premorbid depression has long been thought to predispose to postoperative morbidity.[63] Patients with a premorbid history of depressive disorder require a treatment plan to safeguard against the risk for postoperative depression that is associated with noncompliance with medication requirements and postoperative follow-up visits.[10]

Anxiety

Transplant recipients often experience some degree of preoperative anxiety, which rapidly resolves with postoperative return of end-organ function. For some solid-organ recipients, the hope for an organ may give way to anxiety when a graft finally becomes available. On rare occasions, such anxiety may lead a patient to refuse an organ. Emergency psychiatric consultation may prove helpful.

Some patients approach surgery with minimal apprehension. Frank denial can be a problem for the individual who mistakenly expects that transplantation will be immediately beneficial and uneventful. Psychiatric intervention is recommended for the patient with debilitating anxiety, with unrealistic expectations, or with premorbid anxiety disorders or phobias specific to the planned procedure.[10]

Personality Impairment

Trust is essential to successful organ transplantation because of the need for the patient to work closely with members of a treatment team around life and death issues. Patients with personality disorders present with a pattern of strained relationships and are at higher risk for transplantation complications. Fortunately, most transplantation procedures occur in a time frame that allows the team to establish a therapeutic alliance. Overall, the best predictor of postoperative compliance is preoperative compliance.[10]

Informed Consent

Teaching and informed consent are the cornerstones of preoperative care. In addition to a declaration of clinical goals and methods for their accomplishment, preoperative discussions between the patient and the transplant team form the basis of a bond that will ultimately allow continued communication during the difficult times that inevitably follow solid-organ transplantation. The opportunity to shape expectations is especially important. Transplant patients need to understand that hospital care may be prolonged and that recurrent admissions may be necessitated by rejection, infection, and other posttransplantation complications. The need for indwelling catheters, drains, and special diets must be addressed and an approach to postoperative pain established. Transplant recipients need to manage complicated medication regimens, frequent postoperative clinic visits, and the financial demands of transplantation. The process of selection, the contemplated waiting time for transplant, and the rules governing status on the list should be carefully explained. Young people especially must be made aware of the cosmetic impact associated with the use of high dosages of steroids after transplantation,

including the likelihood of weight gain and the potential for DM, cataract formation, mood swings, irritability, impaired concentration, and tremor. Potential complications must be presented with sensitivity. It may seem kind to withhold information, but patients who were uninformed and who then suffer adverse postoperative effects experience failed expectation and regret about undergoing transplantation. Observation by the team in the course of teaching and informed consent provide important information about mental status and coping styles.[10]

Teaching Venues

For most solid-organ transplantation evaluations, the patient undergoes a standard series of visits with surgery, nursing, psychiatry, social services, anesthesiology, and other medical and paramedical subspecialties as indicated. Some insurance plans allow inpatient admission to facilitate evaluation, and others require that this process occur on an outpatient basis. Our institution sometimes uses a family meeting format for interviewing kidney transplantation patients before placing their name on the cadaveric organ list or proceeding with living-donor evaluation.

The psychosocial interview complements the process of informed consent and provides an excellent opportunity to instruct patients in relaxation techniques, to counsel them about mobilizing an effective support network, and to inform them about the potential for postoperative mental status change and how it is best addressed. The psychiatrist, consulting psychologist, and social worker are in the optimal position to reinforce adaptive skills and to assist in cognitive reframing and use of behavioral techniques for the enhancement of perceived control and well-being. Several studies have demonstrated the favorable postoperative impact of preoperative psychological interventions.[64,65]

Patient–patient interactions provide a valuable adjunct to preoperative teaching. Many successful transplant recipients enjoy the opportunity to give something back by sharing their experience with new transplant candidates. Patient groups are similarly effective. They may rely on lay leadership or on a skilled group therapist. The format may include didactic teaching sessions to which members of the surgical team are invited. Some groups include patients and family members. Printed materials and audiovisual presentations are a useful educational supplement.

Psychotherapy

Indications

Patients with Axis I or Axis II disorders should be encouraged to receive psychiatric care in preparation for transplantation. Ongoing treatment is crucial, particularly when compliance is a concern or the patient is experiencing debilitating emotional symptoms. Patients who are psychologically asymptomatic or who have mild adjustment disorders are best advised to mobilize whatever resources they find most beneficial. This may include supportive counseling for the patient and family, religious involvement, or community-based support.

The pretransplantation psychiatric evaluation provides a format for brief therapy. It often is useful to tell patients that the purpose of the psychiatric interview is to teach, to form a basis for subsequent *ad hoc* psychiatric referrals, and to ascertain whether any special needs must be addressed for transplantation to be successful. Patients should be advised that the object is to see whether they can realistically benefit from a transplant, and whether there are specific circumstances that need to be addressed before transplantation can proceed. Even this one-time psychiatric interview may provide a unique opportunity for listening and debriefing. While underscoring the hope of transplantation, the therapeutic psychological encounter allows recognition of loss and expression of grief. Patients who express feelings of guilt about the need for a cadaveric organ are best reminded of the inevitability of death and of the relief many bereaved families experience when informed of the opportunity for organ donation. Some patients may require reassurance about body image after transplantation. Above all, the pretransplantation interview is an excellent opportunity to strengthen the therapeutic alliance.

The preoperative transplantation patient is like a cryptographer in search of clues that will aid him or her in mastering unforeseen events. In an early study, Schachter and Singer[66] found that experimental participants responded differentially to injected adrenaline depending on their exposure to waiting room "stooges" who were either irritable or elated. This is not to say that one should deny pain or tell patients how to feel, but that patients can be taught how to cope within the range of experiences typically encountered in the transplantation setting. Egbert and associates[67] demonstrated that patients undergoing abdominal surgery had greater postoperative comfort and required fewer narcotics when they were taught before their operation about the normalcy of postoperative pain and were encouraged to ask for pain medication as needed. Similarly, one can instruct patients about the risk for postoperative delirium, while emphasizing that some degree of confusion is frequent, that this is temporary, and that it will respond to appropriate adjustments in medication.

Phobic disorders relevant to the surgical setting should be identified and plans made to effect desensitization. Postnoxious desensitization, in which individuals are encouraged to fantasize acquisition of a desired goal and then to work backward in their imagination to gain mastery of the steps required for goal attainment, has been described.[68]

Psychotherapy is demanding for clinicians who serve these patients. The consultant visits the ICU each time with the realization that the patient's room may be empty and the bed neatly remade (or occupied by a new patient). The effort to diminish one's own sense of loss may deter even a seasoned consultant from making an emotional commitment. Such countertransference reactions, when acknowledged, add to the psychiatric consultant's appreciation of the level of stress encountered by a patient's relatives and friends and by other members of the transplantation team.

Psychopharmacologic Treatment

Psychopharmacologic care of the transplantation patient has been reviewed in depth by Trzepacz and associates.[57,69,70] Judicious use of antidepressants, anxiolytics, and antipsychotics can be lifesaving. The pretransplantation evaluation

provides an excellent chance to learn which agents have been helpful and which have not. Some patients give histories of intolerance to benzodiazepines or neuroleptics; this information may prove invaluable on subsequent admissions if the patient's ability to communicate effectively is compromised.

In general, it is essential to tailor psychopharmacologic management to the demands of organ failure and to maintain a close liaison with other medical subspecialists involved in the patient's care. Cassem's[71] dictum, "start low and go slow," is valuable and helps avoid the pitfalls of oversedation and iatrogenesis.

Special Services

Social Service Intervention

It is most helpful to work with a medical social worker who is familiar with the demands of transplantation and who is available to attend work rounds on a weekly basis. The social worker is an invaluable source of patient and family support and plays a pivotal role in ensuring that the patient will be able to access needed health care perioperatively.

Recreation Therapy and Audiovisual Material

Patients who wait for weeks in the hospital require support and distraction. Activities (such as card games, board games, and crafts) may prove useful. One heart transplant patient who enjoyed oil painting was able to overcome his depression by producing canvases that he offered for sale to the staff.

Relaxation videotapes may be made available through a closed-circuit teaching channel. Some hospitals use teaching films for patients and their potential donors when they come to family meetings before transplantation selection. Movies, music, and books on tape may reduce tension during prolonged hospital stays. Complementary medicine procedures, such as therapeutic touch, may also prove effective.

PATIENT SELECTION

Tragic Choices

Tragic Choices, Calabrese and Bobbit's[72] landmark work in medical ethics, is an apt phrase for the challenge posed by the limitation in resources for solid-organ transplantation. Ethical models applied to this task are inevitably in conflict if each is taken to its logical endpoint.[72] Assignment may be made on a basis that is relatively egalitarian or utilitarian. If the decision to transplant is primarily driven by patient demand, candidates with unacceptably high risk are included, and the pool of recipients is larger than if the decision were made on the basis of potential outcome and societal benefit.[42] If wait time is the predominant consideration in listing for transplant, patients in most acute need will not survive long enough to receive an organ, and patients who are relatively healthy will decline in health status before they reach the top of the list.

A rational approach to solid-organ transplantation is necessarily multicameral.[73] Current selection procedures are based on acuity of illness. However, special consideration among renal transplant recipients is given to patients who are sensitized with high levels of preformed antibody. Availability of a six-antigen match is considered a priority, independent of other factors. Transplantation is prioritized for patients willing to accept a kidney from older donors whose kidneys would customarily be discarded because of age.

Outcome data are important in patient selection, but some high-risk candidates are accepted. For example, the 1-year survival rate for early retransplantation of a failed hepatic allograft is comparable to the results with a primary liver transplant. In the setting of later retransplantation, results are 15% to 40% worse than with primary transplantation, especially in the setting of infection with hepatitis C virus. Many centers perform second transplantations.[74] Multiple organ recipients are another subgroup at high risk. Some centers offer transplantation to Jehovah's Witnesses, despite the religious prohibition of the use of blood products. Recipients who belong to this group may elect to accept blood or plasma, and church elders can sometimes participate to the advantage of the patient and the surgical team. Among lung transplant recipients, ventilator support can be a contraindication to transplantation, whereas heart and liver candidates are given priority listing when on a ventilator, unless the likelihood of a successful outcome is poor because of additional complications, such as active infection or renal failure.

Prioritization in solid-organ transplantation has varied over time, beginning with the more selective or para-judicial lifeboat ethics philosophy of the 1960s and continuing to our current, more egalitarian approach. It is principally, however, a societal consideration. Individual transplantation centers may vary in their assessment of a given candidate, but the decision to transplant is driven by a medical model.[41,75,76] The team must determine who will benefit in the context of currently accepted norms for selection.[10]

Psychiatrist's Role

The psychiatrist is charged with the task of determining whether the patient is sufficiently able, motivated, and possessed of sufficient social supports to follow through with the demands of transplantation. Unfortunately, we lack valid and reliable predictive data. Freeman and co-workers[77] used the determination "reservation about suitability for transplantation" for 19 of 70 patients who were psychiatrically screened for heart transplantation. Fourteen of their patients who met *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (DSM-III), criteria for a psychiatric disorder had postoperative surgical or psychiatric complications. Levenson and Olbrisch[37,38,78] showed that transplantation centers differ in their acceptance of patients who manifest psychiatric symptoms or syndromes. Some groups do not accept patients with active schizophrenia. Most centers deny patients with active substance abuse, dementia, current suicidality, multiple past suicide attempts, or severe mental retardation. Mild mental retardation, affective disorder, and commission of a felony are other considerations that may be exclusionary, especially in cardiac and lung transplantation programs, which tend to be more selective. In an attempt to standardize patient evaluation and selection, Olbrisch developed the psychosocial assessment of candidates for transplantation (PACT), which rates each of four categories along a five-point

semantic differential: social support, psychological health, lifestyle factors, and understanding of transplantation and follow-up.[79] Transplantation centers tolerate potentially high risk patients based on factors that include size of the center and total volume of cases, outcome statistics, and availability of psychiatric consultation. Experience dictates that solid-organ transplantation has proved successful in selected patients with schizophrenia, major depression, personality disorder, substance abuse, and moderate mental retardation.[42]

Through active participation with the transplantation unit, the psychiatrist learns about specific concerns that team members bring to the selection process. Patient compliance is an obvious concern; the social worth of the candidate is another.[80] Some patients who come to transplantation evaluation pose a measure of social risk, as in the case of an antisocial patient or the patient whose care will require extensive and expensive resources. Team members may also be overly invested when they have participated in the long-term care of a patient who has experienced multiple setbacks or rejection of a previous allograft. The psychiatrist plays an important role as educator, sharing current practice standards in psychiatric care and participating in ethical review of complex clinical events.

Nonadherence

Nonadherence is an important source of secondary graft failure.[81] Nonadherence may be evident in various forms, including missed appointments, failure to report important clinical changes in a timely fashion, dietary abuse, and missed medications. Unexpectedly low blood levels of cyclosporine or of other required medications might signal failure to take prescribed doses. Patients with recurrent rejection who stabilize with surprising rapidity after hospital admission and routine monitoring of medications are very likely nonadherers.

Other factors that predispose patients to nonadherence include depression, substance abuse, cognitive impairment, and personality disorder. Patients are at increased risk when they live at a distance from the transplantation center, and when there is insufficient social and financial support. Youth is another risk factor; young people may be more prone to denial and more reactive to the cosmetic complications of immunosuppressant medications.[82]

Although it is difficult to predict with certainty in individual cases, the patient's history of adherence is a valuable clue to future performance.[10] When possible, patients who are at risk by virtue of psychiatric history or social turmoil should have an extended period of follow-up, with the understanding that documentation of compliance must precede transplantation. All reasonable efforts should be undertaken to treat ongoing psychiatric impairment and to improve social support. Frequent posttransplantation clinic visits may reduce risk of nonadherence among high-risk patients.

ORGAN DONATION

Types of Donation

In the United States, the principal source of organs available for transplantation is cadaveric, brain-dead donors with a heartbeat. Hospitals have site-specific criteria for determination of brain death that usually include both diagnostic tests (such as an apnea test, electroencephalography, transcranial Doppler, and a cerebral blood-flow scan) and clinical signs (such as fixed and dilated pupils, absent reflexes, unresponsiveness to external stimuli, and apnea).

UNOS is the nonprofit agency endowed by the United States Congress that regulates the distribution of organs for transplantation. One of its branches, the Organ Procurement and Transplant Network, divides the country into 11 geographic regions in which the allocation of organs proceeds according to local need and priority. Each region has its own organ procurement organization. The radius of distribution for each type of organ depends on how vulnerable each type is to ischemic injury. Donor hearts are limited to a 500-mile radius. Kidneys can be transported across the continent because they can tolerate up to 48 hours of hypothermic perfusion. Lungs can tolerate only 6 hours outside the body.

The length of time candidates spend on the waiting list for transplantation differs between geographic regions. Furthermore, the waiting list for each organ type is arranged according to different models. For kidney transplantation, the time the candidate has spent waiting is the primary determining factor. However, full compatibility of human leukocyte antigens between donor and candidate confers priority for potential candidates for kidney transplantation. For heart, lung, and liver candidates, acuity of illness confers priority on the list. Pediatric candidates have priority on the waiting list for both kidneys and livers.

Many transplantation centers support a coordinator for organ donation who usually is a registered nurse. That person serves as a liaison between the transplantation team and the local organ procurement organization and also educates the hospital staff and the patients about organ donation and transplantation.

Mechanisms for Increased Organ Donation

The mismatch between the number of persons requiring organ transplantation and the number of available cadaveric organs has prompted investigation into other opportunities for organs, such as extending the age limit on donors, donors without a heartbeat, and living donors. Efforts have also been made to educate the public about the need for organs and to ask patients and relatives to consider the issue and to state their wishes prior to death. In the United States, the required consent law protects individuals; all potential organ donors must have provided clear consent for organ donation. In Spain, Belgium, and Singapore, the rule of presumed consent applies: all persons are presumed to be organ donors unless they have specifically refused to donate.

Deceased donors are identified by neurologic criteria of brain death. In contrast, the non–heart-beating donor has suffered irreversible cardiac or respiratory failure. Weber and co-workers[83] demonstrated no difference in outcome for 122 kidney transplants regardless of whether the transplanted organ was from a heart-beating or non–heart-beating donor. Notwithstanding initial controversy about the use of non–heart-beating donors, the current demand for organs

has led to increased use of this approach in kidney transplantation and frequently, albeit less frequently, in liver transplantation.

The participation of living organ donors was discussed earlier. The mortality rate for nephrectomy is 0.03%, and the risk for morbidity ranges from 1% to 10%.[84] The mortality rate for partial hepatectomy is approximately 0.2%.[8] Estimates of morbidity have varied but are currently considered to be in the range of 25% to 30%. To date, no deaths have been associated with living-donor lobar-lung donation, although the morbidity rate has been estimated to be as high as 61% at some centers.[85] A recent study of medical and psychological sequelae of living-donor lobar-lung donation suggests that these living donors feel positively about their donation despite experiencing a subjective decline in exercise tolerance.[86]

A qualitative study of kidney donors by Fellner and Marshall[87] reported on the psychological benefit experienced by a majority of participants. A sobering finding was the tendency of donor candidates to minimize risk, an observation that led the authors to question the meaningfulness of informed consent. Donors often want to get on with the process and put it behind them. One technique for dealing with this strategic trajectory (see Organ Donorship, earlier) is to enlist the donor in the evaluation process and share the challenge inherent in successful informed consent with the donor candidate. The intent is to tear down the barrier of formality and invite the donor metaphorically to the other side of the treatment setting. Development of rapport is often sufficient to counter resistance and allow the donor to be forthcoming about perceived coercion or ambivalence. Simmons demonstrated the potential benefits of donor participation as well as some of the caveats, such as the need to be mindful of the "black sheep" donor whose participation was probably an attempt to gain favor through an aura of altruism.[73]

A shortcoming in the history of living-donor organ donation in the United States has been the lack of a medical registry. We are now accumulating sufficient data to know that kidney donors experience good health relative to the general public.[88] Likewise, living-donor lobar-lung donors demonstrate pulmonary function tests within the normal range after lobectomy, despite volume loss of approximately 20% of the total.[86]

Evaluation of the potential donor must ensure autonomy, lack of coercion, absence of psychiatric contraindication or active substance abuse, sufficient social support, and medical coverage in the event of postoperative complication. There must be full disclosure about the details of perioperative procedures, required recovery time, postoperative physical limitations, and the required length of time before resumption of driving and a return to active employment or full-time childcare. Pain, potential length of disability, appearance of the operative incision, and potential risk of graft loss must be discussed. Families and patients can put considerable pressure on individual family members or friends to donate. In some instances, patients or family members have offered a financial incentive to donation or have threatened to withdraw financial support if the potential donor backs out. Sometimes the spouse or significant other of the potential donor objects to donation and withdraws emotional support or even leaves the relationship altogether. The potential donor should always be informed that, should he or she choose not to donate, the transplantation team will protect his confidences and not reveal the reason for refusing him as a candidate.

POSTOPERATIVE PSYCHIATRIC CONSIDERATIONS

Improvement in Psychological Function

Improved neuropsychiatric function after transplant surgery accompanies the reversal of end-organ failure; at times it is associated with a sense of rebirth. Improvement in anxiety, depression, and cognition typically occurs most rapidly after renal transplantation, and it is often evident within the first 2 days after transplantation because blood urea nitrogen and creatinine levels decrease. Riether and associates found marked improvement in depression and anxiety within the first 3 months after heart transplantation.[89] Liver recipients improve more slowly, but some patients have shown marked progress in well-being as early as 2 to 3 weeks after transplantation. Increased psychological adjustment and improved quality of life after liver transplantation have been well documented and are attributable in part to change in neuropsychiatric function.[35]

Organic Brain Syndromes

Intraoperative cerebral ischemia may occur among heart transplant patients because of decreased perfusion resulting from hemorrhagic or embolic phenomena. Psychotic reactions are most likely to occur within the first 48 hours after surgery. Hotson and Enzmann pointed out that when psychotic manifestations are delayed by 2 to 5 days with rapid response to neuroleptic treatment and environmental support, the cause is more likely to be multifactorial.[90]

Factors contributing to postoperative delirium include endocrinopathy, electrolyte abnormality, hypovitaminosis, infection, bleeding, drug or medication withdrawal, cerebrovascular abnormality, drug–drug interactions, and adverse medications effects.[10] For a complete discussion of the cause and treatment of delirium, see Fricchione and co-workers.[91] Sources of drug toxicity include anesthetic agents, analgesics (including normeperidine toxicity), and prednisone, which may cause sleep impairment, emotional lability, and perceptual abnormalities. Affective psychosis was a more frequent finding in the earlier years of transplantation, when rapid dosage reduction of prednisone was not yet standard. Both cyclosporine and tacrolimus may be associated with neurologic complications (including seizures, delirium, headache, coma, cortical blindness); another complication, central pontine myelinolysis, can occur as a locked-in syndrome.[10,92,93]

Development of leukoencephalopathy can be identified by fluid-attenuated inversion recovery (FLAIR).[94] Switching calcineurin agent (cyclosporine or tacrolimus) is often efficacious. Hypertension, renal dysfunction, and tremor may serve as clues to calcineurin toxicity. This may result from drug–drug interactions secondary to cytochrome

P450 enzyme inhibitors (such as erythromycin, ketoconazole, and diltiazem).[10] Calcineurin toxicity has also been described as a consequence of genetic polymorphism in P-glycoprotein.[95]

Herbal Toxicity

Herbal agents may be a cause of drug–drug interaction and allograft loss, or may be a cause of direct renal, hepatic, or cardiac toxicity.[10,96]

Anxiety

Anxiety in the early postoperative period can result from failed expectations or from repeated and disabling major complications. Decreasing amounts of medical supervision or change from one-to-one nursing in the ICU to shared nursing on the transplantation floor may also precipitate increased anxiety.

Patients who undergo IV pulses of corticosteroids may experience mood swings or anxiety that typically subsides within a day or two of completion of rescue therapy. Increasing tremor signals cyclosporine toxicity. OKT3, a monoclonal antibody used for acute rejection, may be associated with severe headache, joint pains, and other anxiety-generating systemic effects.

Posttransplantation biopsy procedures are another source of stress. Renal and hepatic biopsies are performed on an *ad hoc* basis. Routine endocardial biopsy and bronchoscopy, however, are ordered for heart and lung transplant recipients.

Delays in hospital discharge frequently cause frustration and anxiety. Psychiatric consultation may be required, however, for the patient who insists that discharge is premature. This behavior may result from fear associated with unresolved symptoms or with transition from the close in-hospital monitoring by the surgical team to the less restrictive and possibly less supportive home environment.

Body Image Distortions

Cushingoid changes from prednisone are especially troublesome for young patients undergoing transplantation. One young liver transplant patient chose to undergo a series of cosmetic surgeries in young adulthood to rid her of unwanted adipose tissue. She was not obese, but she was dissatisfied with her appearance. Prednisone can increase body hair, and cyclosporine may also be associated with hirsutism. Common warts, which can flourish in immunosuppressed individuals, may also prove disfiguring and uncomfortable.

Castelnuovo-Tedesco[97] and others have been especially interested in the psychological impact of the transplant recipient's incorporation of a body part from the donor. Perhaps the most dramatic account was that of a Ku Klux Klan grand dragon who joined the National Association for the Advancement of Colored People on learning that his donor was an African American.[98] Some patients comment on changes in their food choices and wonder whether the donor's lifestyle may have been contributory. A middle-aged heart–lung recipient who determined the identity of her cadaveric donor told a national television audience, during an appearance on the Phil Donahue Show, that her subsequent vigor led to an affair with a postadolescent man whose age was similar to that of her donor.

One of the most unusual cases we have encountered was of a 43-year-old heart-transplant recipient who reported a recurrent dream in which he was driven by starvation to strip and chew the flesh of his own arm. Preoperatively, he had expressed anxiety about the prospect of receiving a cadaveric organ. Several months after his operation, a discussion of the dream led to a statement that it sounded like cannibalism. "Yes," he responded, "when I was in the Army working in the motor pool, there was a sign that said, 'Do not cannibalize!'" He explained that it had been an unsanctioned practice to take working parts from other vehicles to service ones in need of repair.

Depression

Postoperative depression may arise as a recurrence of affective illness. Steroid-induced depression is common and tends to be accompanied by irritability that is less evident to the patient than to the family and to the attending surgical staff. Rejection is another common cause of depression, and it may be related to the fear of graft loss, to cytokine production, or to end-organ dysfunction.

Also important for the transplant psychiatrist is awareness of the link between depression and infection.[10] Psychiatric consultation may sometimes precede a request for infectious disease consultation because mood changes may foreshadow a fever spike or evidence of systemic illness. Cytomegalovirus infection is especially common after transplantation, and it is associated with a significant increase in first-time psychiatric consultation.[99] Typically, these patients do not express hopelessness or suicidal ideation, but other neurovegetative signs such as appetite reduction, lethargy, and psychological withdrawal are common.

Psychological Rejection

Viederman[100] and others have raised the possibility of psychologically induced allograft rejection. This concept is interesting but speculative. More likely, psychologically based rejection results from noncompliance caused by depression, memory impairment, substance abuse, or adjustment reaction related to psychosocial stress, or by altered body image. Medication costs thousands of dollars annually, and nonadherence may follow loss of third-party funding or other adverse economic developments.

POSTOPERATIVE PSYCHIATRIC INTERVENTION

Long-Term Care

Transplant patients are often told that they will end up with a new set of medical problems once end-organ replacement has occurred. Morbidity may occur as a function of rejection, medication side effects, and progression of systemic disease. The care of transplantation patients is thus a

long-term prospect, and the consulting psychiatrist may be reconsulted at intervals, especially for those who are most ill or least able to adapt.

Patients who are at highest risk psychologically should have follow-up plans created before the operative intervention. Patients with affective disorders, schizophrenia, substance abuse, or moderate mental retardation can be managed with supportive counseling, psychopharmacologic care, and implementation of social resources.

Psychotherapeutic Interventions

Psychotherapy may include the reframing of expectations. For example, a patient who is recovering from a prolonged ICU stay will need help with assessment of his or her progress, which may be measured by absence of a monitor, reduction of IV lines, and signs of early mobilization. Guilt and shame may follow an encounter with delirium or result from the preoperative wish for a donor organ. Patients can be helped to understand that these experiences are common. Daily visits to delirious or acutely depressed patients are advisable and may be a source of relief to the patient, the family, and the surgical staff.

Behavioral interventions may be designed with the nursing staff, to assist in the management of excessive dependency, hostility, or resistance. Group therapy is of value for many patients and family members and may be conducted by the psychiatrist, social worker, psychologist, or psychiatric nurse clinician.

Psychopharmacologic Intervention

Treatment with antipsychotics requires modification of immunosuppressant protocols (when feasible), correction of metabolic abnormalities, and treatment of bleeding, infection, and rejection. Complex partial seizures should be considered as a cause of psychosis, but care must be taken in the choice of anticonvulsants. Anticonvulsants such as phenytoin, valproate, and carbamazepine are P450 enzyme inducers and may decrease levels of immunosuppressants. It is best to follow the serum level of calcineurin inhibitors to avoid risk for rejection. Haloperidol and atypical antipsychotic agents are effective in management of agitated delirious states. Care must be taken to observe for Q-T prolongation. Antipsychotic agents of the traditional or atypical (second-generation) variety are known to be associated with an increased risk for sudden death from arrhythmia, especially in older patients. An algorithm for use of IV haloperidol has been presented by Fricchione and co-workers.[91]

Use of antidepressants and anxiolytics should be accompanied by the precautions addressed earlier. A full range of agents, as well as electroconvulsive therapy, can be used after surgery. TCAs are often preferred for diabetics with peripheral neuropathy, or for management of migraine or insomnia in those patients who are not at cardiovascular risk. In the setting of hepatic dysfunction, serum levels should be followed. For the most part, bupropion and SSRIs are better tolerated. Monoamine oxidase inhibitors are best avoided, but we have encountered one heart transplant patient whose resistant depression responded only to tranylcypromine.

Posttraumatic Stress Disorder

Occasionally, a patient with recurrent nightmares and the spontaneous recollection of medically traumatic events associated with transplantation is encountered. The prevalence of posttraumatic stress disorder (PTSD) in transplant recipients is not known. Fukunishi and colleagues[7] documented PTSD in 4 of 40 donors who underwent right lobe hepatectomy; although this is an isolated report, transplantation psychiatrists should be mindful of the potential.

CONCLUSION

Psychiatric consultation on the transplantation unit is highly rewarding and places the psychiatrist in a pivotal role as a member of a multidisciplinary team. The transplantation unit is a challenging setting in which a full range of psychiatric skills and sensitivity is employed. The dearth of available organs necessitates a thoughtful and constructive approach to candidate selection. The participation of living donors is a unique circumstance that is worthy of both celebration and support. Transplant patients approach operative intervention carrying the burden of progressive organ failure and its attendant neuropsychiatric complications. The postoperative course of transplant patients is associated with improved quality of life and a requirement for long-term care.

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Patients with Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

BJ Beck, M.S.N., M.D.
Oliver Freudenreich, M.D.
Jonathan L. Worth, M.D.

Human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) are prevalent in disenfranchised populations, including addicts, gay men, sex workers, ethnic minorities, and the seriously mentally ill, who may have particular difficulty advocating for and accessing adequate care.[1] Not only is HIV infection more prevalent among the mentally ill,[2–4] but psychiatric illnesses are more prevalent in those who are HIV positive.[5–7] Personality disorders are overrepresented in the HIV-positive population as well,[8–10] possibly because certain traits (such as impulsivity, reckless disregard for safety, affective instability, or chronic feelings of emptiness) can predispose persons to risky behavior and to HIV infection.

As recently as the 1990s, HIV infection was a terminal illness. However, the advent of highly effective antiretroviral medication regimens has made HIV a manageable, chronic illness for many,[11,12] although it sometimes is associated with a high medication side-effects burden.[13] The emerging cohort of aging and elderly persons infected with HIV for many years[14] has now created the challenge of managing chronic diseases not necessarily related to HIV itself.[15] Unfortunately, poorly treatable cognitive impairment from HIV, age-related processes, and the possible interplay of the two,[16] have resulted in a growing number of infected persons with varying degrees of cognitive impairment including dementia.[17] Despite much progress, complacency, stigma, secrecy, and shame continue to interfere with HIV detection.[18] Culture, lifestyle, and socioeconomic barriers to prevention and to appropriate HIV care persist.[19]

HIV is a blood-borne, sexually transmitted retrovirus that contains RNA as its genetic material and the enzyme reverse transcriptase, which facilitates the (reverse) transcription of RNA to double-stranded DNA in infected human cells. This virion-derived DNA moves to the host cell nucleus, where it randomly integrates into host chromosomes, catalyzed by the virion-encoded enzyme, integrase. Once within the host chromosome, the pro-viral DNA can remain inactive (latent), or it can express a range of genetic activity, including functional virus production. Such now-functional viruses can go on to infect other cells, preferentially the CD4 subpopulation of T-lymphocytes, thereby causing severe (primarily cell-mediated) immune dysfunction for which the virus and the resulting syndrome were named. Immunodeficiency, a predilection for certain opportunistic infections, and AIDS-defining conditions correlate with a decline in CD4 lymphocyte count[20] (Table 26–1). This infection cycle repeats billions of times, the host mounts an immune response, and a set point (or dynamic equilibrium) is eventually reached. The set point varies from person to person, and it has been found to be of prognostic significance.[21,22] Notably, the virus also invades the central nervous system (CNS) early, possibly within hours to days of the initial infection.[23,24]

Although the science behind HIV infection and its treatment is changing at a rapid pace, the general tenets of this chapter should provide a consistent framework for the safe and comprehensive psychiatric evaluation and care of adults at risk for, or infected with, HIV/AIDS. Four general questions help set the context for such an evaluation: At what stage of HIV infection is the patient in terms of symptomatic disease and CD4 lymphocyte count? Is there evidence of HIV-associated CNS infection? Does the patient have a premorbid psychiatric history? How did the patient become infected with HIV? The important implications of the first three questions might seem more obvious and should be clear by the completion of the chapter. The fourth question is often a highly personal story, one that reveals the patient as a person. The answer to this question foreshadows how the patient will relate to illness and to medical care. This knowledge informs not only the psychiatrist's evaluation but also the patient's individualized treatment and management plans.

EPIDEMIOLOGY

Despite the existence of effective therapies, HIV/AIDS remains a terminal illness in much of the world; it cuts across all ages and socioeconomic groups, each with specific characteristics and considerations.[19] The numbers in the Global Summary published in December of 2007 by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[25] are the result of a revised statistical model

TABLE 26–1 AIDS-Defining Conditions that Emerge with Advancing Immunosuppression

CD4 CELL COUNT (CELLS/mm³)	CONDITION
200–500	Thrush
	Kaposi's sarcoma
	Tuberculosis reactivation
	Herpes zoster
	Herpes simplex
	Bacterial sinusitis/pneumonia
100–200	*Pneumocystis jerovicii* pneumonia
50–100	Systemic fungal infections
	Primary tuberculosis
	Cerebral toxoplasmosis
	Progressive multi-focal leukoencephalopathy
	Peripheral neuropathy
	Cervical carcinoma
0–50	Cytomegalovirus disease
	Disseminated *Mycobacterium avium-intracellulare complex*
	Non-Hodgkin's lymphoma
	Central nervous system lymphoma
	HIV-associated dementia

Modified from APA: Practice guideline for the treatment of patients with HIV/AIDS, *Am J Psychiatry* 157S:1–62, 2000.

and improved assessment processes in certain large regions (e.g., India, sub-Saharan Africa). Although the reported global prevalence is somewhat lower (33.2 million in 2007, versus 39.5 million reported in 2006[26]), this is more likely the result of the model, and not an actual change in prevalence. Women make up half of the infected adults worldwide, and roughly 2.5 million children younger than 15 years are infected.

The report estimates that there has been a gradual decrease in the incidence of new infections since a peak in 1998, with a 2007 incidence of roughly 2.5 million, with 420,000 of those new cases diagnosed in children younger than 15 years. This incidence is only partially offset by the (declining) total number of AIDS deaths (2.1 million in 2007), which means the number of persons living with HIV will continue to rise, although the prevalence (measured over a growing global population) has stabilized. Sub-Saharan Africa remains the most heavily infected region, accounting for 67% of all people living with HIV, for 72% of all AIDS deaths,[27] and for 68% of all new cases in 2007.[25] Still, this is significantly improved from the late 1990s, when 95% of all infected people lived in this region.[28]

In the United States, among the most heavily infected industrialized nations, more than a million people are infected with the virus, with an estimated 55,400 new infections yearly between 2003 and 2006, and possibly more (56,300) by some estimates.[29] The incidence is thought to have peaked in the mid-1980s, falling off sharply in the early 1990s, with a lower spike in 1997 followed by a fairly stable, though unacceptably high, incidence (55,000 to 56,000) of new infections in the third decade of the disease in this country. The advent of highly active antiretroviral therapy (HAART) in 1996 has decreased the incidence of AIDS onset and AIDS-related deaths, so more people in the United States are living with HIV infection than ever before.

A disproportionate number of the newly infected in the United States are ethnic and racial minorities (primarily African American and Hispanic[30]; less so Asian and Pacific Islanders[31]), and heterosexual women.[29,32] However, outbreaks of other sexually transmitted diseases (STDs) in gay men raise the specter of a possible HIV resurgence in this population and suggest that the success of HAART may have led to complacency and the resumption of unsafe sexual practices in men who have sex with men (MSM),[33,34] to some degree fueled by the recreational use of methamphetamine (crystal meth).[35] Up to 30% of patients with HIV disease are also infected with hepatitis C virus (HCV). These co-infected patients are rather different from HIV mono-infected patients with regard to risk factors and psychiatric illnesses: most patients have acquired HCV from injection drug use, which is the main mode of transmission for HCV.

HIV INFECTION AND THE CENTRAL NERVOUS SYSTEM

Within days of the initial infection, the virus is transported to the brain by monocytes that then differentiate into macrophages. These infected but not dead macrophages may be activated randomly, leading over time to excessive secretion of normal inflammatory substances and cell death without neuronal infection. That is, HIV infection causes neuronal destruction without infecting neurons.[36] The CNS appears to be an independent reservoir of HIV replication; CSF viral load does not consistently correlate with plasma levels.[37,38] HIV in the CNS might also have different characteristics, such as mutations with increased viral resistance or neurotoxicity, than those of the peripherally observed virus. Current antiretrovirals have variable blood–brain barrier (BBB) penetrance, they may be less potent inhibitors of viral replication within the CNS, and some are themselves neurotoxic. The optimal antiretroviral drug regimen to combat HIV in the brain remains to be determined, but peripheral suppression of viral replication will need to be coupled with neuroprotection. New therapies might target regulatory human genes involved in viral replication,[39] the identification and exploitation of brain HIV-inhibitory factors,[24] and the enhancement of intrinsic brain defenses that favor neuroprotective, as opposed to neurotoxic, responses to the virus.[24]

Although early studies concentrated on sampling and volume of the frontal cortex, it is now apparent that HIV infection does not uniformly affect the brain; instead, it has a predilection for subcortical structures, such as the hippocampus and basal ganglia, with lower concentrations in the cerebellum and mid-frontal cortices.[40,41] This distribution, further differentiation of viral burden within particular basal ganglia regions, and concomitant structural changes in the brain (including ventricular enlargement, hippocampal atrophy, decreased basal ganglia volume, and white matter lesions), might explain the more characteristic cognitive and behavioral impairments associated with

HIV infection of the CNS.[36,42,43] These types of lesions in the base of the skull are better visualized by brain magnetic resonance imaging (MRI) than by computed tomography (CT) scanning.

When evaluating neurocognitive impairment in the HIV-positive patient, HIV infection of the CNS should always be a diagnosis of exclusion, made only after a thorough investigation of other possible etiologies for neurocognitive impairment, especially if symptoms are new or of acute onset.[44,45] Opportunistic infection, neoplasm, other systemic illness, medication side effects, drug–drug interactions, use of recreational drugs, withdrawal syndromes, and metabolic and nutritional derangements should be considered. Primary psychiatric disease should be at the bottom of the list, especially if there is not a significant preinfection history.[20,46–48]

Although neuropsychologic testing might not be specific,[41] it helps to localize and quantify impairments. Recommended neuropsychological tests include an HIV-specific test battery based on measures found by the AIDS Clinical Trials Group (ACTG) and the Multicenter AIDS Cohort Study to be sensitive to HIV-related cognitive deficits. These measures include Trail Making A and B, WAIS-R (Wechsler Adult Intelligence Scale—Revised) digit span and digit symbol, grooved pegboard, finger tapping, Stroop color and word test, FAS test of verbal fluency, Odd Man Out test, and computer-based measures of complex reaction time.[49–52] Other measures are added as clinically indicated. Test battery times less than 60 minutes are less likely to produce patient fatigue, which confounds test interpretation and creates significant patient frustration or humiliation.

MEDICATIONS FOR HIV INFECTION

There are several classes of antiretroviral medications: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors, and fusion and entry inhibitors.[53] Drugs in the first four classes all interfere with viral replication inside infected host cells. By contrast, the next wave of drug development has targeted the prevention of viral entry into the host cell.[54] Antiretroviral medications are generally used in combinations of one or more drugs from more than one class. Single-drug therapy is discouraged because of the rapid development of resistance that can spread to an entire class of medications, thus limiting the prospects for further effective treatment. The most commonly recommended initial regimen (i.e., for the antiretroviral-naive patient) includes two NRTIs plus either an NNRTI or a PI, preferably with ritonavir boosting (i.e., addition of low-dose ritonavir to another PI). The different classes of medication differ in their therapeutic mechanisms and side-effect profiles (Table 26–2).

Nucleoside (and Nucleotide) Reverse Transcriptase Inhibitors

Nucleoside reverse transcriptase inhibitors are nucleoside analogues that inhibit the action of the enzyme reverse transcriptase. This enzyme inhibition slows or prevents viral replication. Most of the NRTIs require multiple daily doses, do not interact with other drugs, and can be taken with or without food. Didanosine (ddI), however, can decrease the absorption of other antiretrovirals if they are taken together, and it must be taken on an empty stomach. All NRTIs have been associated, albeit rarely, with a fatal syndrome of lactic acidosis and hepatic steatosis. Tenofovir is a nucleo*tide* reverse transcriptase inhibitor, a subclass distinguished by fewer chemical steps to intracellular activity and a negative charge that effectively keeps the compound in the cell and active longer, allowing once-daily administration.[54] The first antiretroviral drugs to be used, NRTIs remain the backbone of current HIV multidrug regimens.

Nonnucleoside Reverse Transcriptase Inhibitors

Like the NRTIs, the NNRTIs also interfere with reverse transcriptase. The NNRTIs have been shown to be active against viral strains of HIV that are resistant to NRTIs and PIs. However, if NNRTIs are used alone or with a single NRTI, resistance develops quickly, and it usually generalizes to the whole class (i.e., to all the NNRTIs). The NNRTIs can also cause a rash early on; it is thought to be more common and severe (including onset of Stevens–Johnson syndrome) with nevirapine. Drug interactions with PIs and other drugs can occur because of their metabolism by the cytochrome P450 (CYP) hepatic isoenzyme system. Efavirenz is an NNRTI noteworthy for its greater potential (as compared to other drugs in this class) for neuropsychiatric side effects (e.g., somnolence, agitation, insomnia, abnormal dreams, impaired concentration and attention, psychosis, and suicidality). Such side effects are thought to be related to plasma level and are pharmacogenetically predisposed.[55,56]

Protease Inhibitors

Protease inhibitors interfere with viral replication, maturation, and new infection of cells by inhibiting the enzymatic cleavage of necessary viral protein precursors. Like the NNRTIs, PIs are metabolized by CYP enzymes, leading to drug interactions. PIs can cause gastrointestinal (GI) side effects and liver transaminase elevations. In addition, PIs can worsen or cause diabetes, insulin resistance, lipodystrophy, and hyperlipidemia. They have also been associated with increased bleeding in hemophiliacs and an increased risk of myocardial infarction.[57]

Integrase Inhibitors

Integrase is the viral enzyme that catalyzes the integration of virally derived DNA into the host cell DNA in the nucleus, forming a provirus that can be activated to produce viral proteins. Raltegravir, the first approved integrase inhibitor, is a useful addition to therapy in the setting of multidrug resistance. However, it must be supported by other agents because of the high propensity for genetic mutations leading to raltegravir resistance.[58] A trial with treatment-naive HIV-1–infected patients demonstrated more-rapid decline in viral load (as compared to efavirenz) and suggests that there may be a future role for integrase inhibitors in initial therapy regimens.[59]

TABLE 26–2 Side Effects Profile of Antiretrovirals

AGENT	MAJOR SIDE EFFECTS
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Zidovudine (Retrovir, AZT, ZDV)	Depressed bone marrow/anemia, neutropenia, GI symptoms, HA, insomnia
Didanosine (Videx, ddI)	Pancreatitis, peripheral neuropathy, GI symptoms
Zalcitabine (Hivid, ddc)	Peripheral neuropathy, stomatitis
Stavudine (Zerit, d4T)	Peripheral neuropathy, pancreatitis, lactic acidosis
Lamivudine (Epivir, 3TC)	Minimal
Abacavir (Ziagen, ABC)	Hypersensitivity (HLA-B*5701 pre-treatment screening)
Tenofovir (Viread, TDF)	Renal toxicity
Emtricitabine (Emtriva, FTC)	Minimal
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Nevirapine (Viramune, NVP)	Rash (Stevens–Johnson syndrome), severe liver toxicity
Delavirdine (Rescriptor, DLV)	Rash
Efavirenz (Sustiva, EFV)	CNS symptoms, false-positive urine drug test for cannabis
Etravirine (Intelence, ETR)	Rash, GI symptoms
Protease Inhibitors (PI)	
Saquinavir (Invirase, SQV)	GI symptoms, paresthesias, hepatitis, HA, lipodystrophy; increased TGC, cholesterol, glucose, transaminases (liver enzymes)
Ritonavir (Norvir, RTV)	GI symptoms, paresthesias, hepatitis, asthma, lipodystrophy; increased TGC, cholesterol, glucose
Indinavir (Crixivan, IDV)	HA, asthma, blurred vision, dizziness, metallic taste, thrombocytopenia, increased glucose, nephrolithiasis, GI symptoms, lipodystrophy, rash, increased TGC and cholesterol
Nelfinavir (Viracept, NFV)	GI symptoms, lipodystrophy; increased TGC, cholesterol
Amprenavir (Agenerase, APV)/	GI symptoms, asthma, rash, HA
Fosamprenavir (Lexiva, FOS-APV)	GI symptoms, HA, depression, rash, fatigue, increased cholesterol/TGC/ glucose/transaminases
Lopinavir/Ritonavir (Kaletra, LPV/RTV)	GI symptoms, fatigue, HA, asthenia, lipodystrophy, pancreatitis; increased cholesterol, glucose, transaminases
Atazanavir (Reyataz, ATV)	GI symptoms, hyperbilirubinemia (25%-50%)
Tipranavir (Aptivus, TPV)	GI symptoms, rash (sulfa drug!)
Darunavir (Prezista, DRV)	GI symptoms
Fusion and Entry Inhibitors	
Enfuviritide (Fuzeon, T-20)	Skin irritation at injection site, bacterial pneumonia
Maraviroc (Selzentry, MVC)	Fever, cough, cold
Integrase Inhibitors	
Raltegravir (Isentress, RAL)	GI symptoms

From *APA HIV-Related Neuropsychiatric Complications and Treatment* (website). HIV-Psychotropic Drug Interactions and Toxicity, slide 22; http://www.avert.org/treatment.htm; http://www.fda.gov/oashi/aids/virals.html. Accessed February 11, 2010.
GI, Gastrointestinal; *HA*, headache; *TGC*, triglyceride.
Antiretroviral combination pills: Atripla = FTC + TDF + EFV; Combivir = AZT + 3TC; Epzicom = 3TC + ABC; Trizivir = AZT + 3TC + ABC; Truvada = FTC + TDF

Fusion and Entry Inhibitors

Once the viral protein gp120 forms a complex with the CD4 receptor, conformational changes expose viral gp120 areas for binding with host cell chemokine co-receptors CCR5 and CXCR4, a necessary step for viral entry into the host cell. Maraviroc is a new chemokine co-receptor antagonist (CCR5 antagonist) drug that blocks the binding of HIV to CCR5 co-receptors in CCR5-tropic (R5 virus) HIV-1 infection. Despite relatively persistent efficacy against multidrug-resistant strains, maraviroc resistance has been attributed to the emergence of CXCR4-tropic (X4 virus) strains.[60] Studies are also exploring the utility of using maraviroc in initial treatment regimens.[61]

Enfuvirtide, the first approved drug in this new class, interferes with viral fusion to the host cell membrane by inhibiting the necessary conformational change in a particular viral envelope protein (gp41) that would otherwise trigger the formation of a transmembrane pore through which the virus would enter the host cell. Administered subcutaneously, enfuvirtide requires twice-daily injections. It is commonly associated with injection-site reactions, an increased incidence of bacterial pneumonia, and rare hypersensitivity reactions.[53] Although resistance to enfuvirtide has also been reported, the drug is recommended for treatment-experienced patients who develop viral replication despite continuous antiretroviral therapy.[54]

Other Medications

HAART regimens are often complicated by the addition of antibiotics, antivirals, and antifungals used to prevent or treat opportunistic infections. Lipid-lowering drugs or oral hypoglycemic agents may be necessary to treat the antiretroviral-induced abnormalities in lipid metabolism and glucose control. Antiretroviral GI side effects can require the

addition of antidiarrheals, proton pump inhibitors, or H_2 blockers. Pain syndromes may require antiinflammatory or narcotic medications, as well as antiseizure medications or tricyclic antidepressants (TCAs). The not uncommon co-morbidity of HIV infection with heroin (or other opiate) addiction can require the addition of an opiate agonist (e.g., methadone), a partial agonist (e.g., buprenorphine), or (less preferable[62]) an antagonist (e.g., naltrexone) medication. Treatment for co-morbid alcohol dependence may also include use of naltrexone, disulfiram, or acamprosate.

HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND)[63]

In 1991, the American Academy of Neurology (AAN) developed criteria and nomenclature for the prevalent HIV-associated neurocognitive dysfunctions recognized at the time.[64] This system recognized HIV-associated dementia (HAD) (previously known as AIDS dementia complex) and minor cognitive–motor disorder (MCMD). HAD was further subdivided based on the presence of motor or behavioral features. This has been a useful organizational system to describe the greater (HAD) and lesser (MCMD) neurocognitive impairments associated with HIV.

However, since then, concurrent with the more standard use of increasingly effective antiretroviral therapies, there has been growing awareness of overlap between mild HAD with motor or behavioral symptoms and MCMD. This awareness, and the recognition that some infected patients without noticeable functional impairment do show deficits on neuropsychological testing, prompted leaders in the research field to develop new definitional criteria. This new nosology recognizes three conditions, including HAD, HIV-associated mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI).[63] Some decry this syndromic approach altogether and suggest that further research needs to provide cerebrospinal fluid (CSF) and MRI biomarkers of active HIV encephalitis, the putative etiology of HIV-associated neurocognitive symptoms.[65] The challenge, however, is to find such markers that remain relevant in the presence of HAART, because some researchers have discovered no correlation between markers and neurologic status in actively treated patients.[66]

HIV-Associated Dementia

HIV-associated dementia, a subcortical dementia similar to that seen in Huntington's disease,[41] is severe enough to cause functional impairment, and it has no other definable cause. HAD is an AIDS-defining condition with a prevalence in the United States of 21% to 25% before the advent of HAART; since then it has decreased to 7% to 10%. Associated with reduced white-matter volume, atrophy of the basal ganglia (reduced gray matter volume), and cell death, HAD is characterized by slowed information processing, deficits in attention and memory, and impairments in abstraction and fine motor skills.[36,41,67]

HIV-Associated Mild Neurocognitive Disorder

Mild neurocognitive disorder most closely relates to what has been called MCMD, a condition more common than HAD. The prevalence of MCMD prior to HAART was 25% in those with early symptomatic disease and 50% in those with AIDS.[68] With the advent of widely used HAART, those figures declined to 14% and 24.4%, respectively.[36]

By definition, MND involves mild to moderate cognitive impairment (1 standard deviation [SD] below demographically corrected norms), in at least two cognitive domains, that at least mildly interferes with daily activities.[63] For patients in cognitively taxing jobs, however, even "mild" problems may be significant enough to interfere with, and to preclude, continued employment.

Asymptomatic Neurocognitive Impairment

HIV-associated dementia and MCMD were clearly inadequate descriptors for the wide array of neuropsychological symptoms reported and observed in 22% to 30% of "asymptomatic" (i.e., subsyndromal) seropositive patients.[69] By definition, ANI also involves mild to moderate cognitive impairment (1 SD below demographically corrected norms) in at least two cognitive domains but without obvious impairment in daily function. It is extremely difficult to make the judgment that there are no obvious functional impairments without extensive third-person observation. Given the diagnostic ambiguity of this group, it is not clear whether the prevalence of subsyndromal (or "asymptomatic") symptoms has decreased with the advent of HAART. It may even be that this group has increased as HAART has changed the appearance of HAND.[70]

HAND in the Era of HAART

Diagnostic assignment for HAND fluctuates for roughly 20% of infected patients. For MND and ANI, it may be that neuronal dysfunction, rather than cell death, is the mediator. This is important because it suggests that the pathology may be treatable and that these syndromes are potentially reversible. Given that even mild functional impairment and subtle deficits might contribute to poor medication adherence, MND and ANI can contribute to worse overall prognosis. Because of the prevalence, prognostic implications, and possible reversibility, research and improved measurement efforts should focus on these less-severe forms of HAND.[36,42,67]

For patients with HAD, the fluctuation in neurocognitive status of some, versus the sustained deficits of others, might represent the array of individual experiences with the virus, treatment, other illnesses, and substance use.[71] Long-time survivors who have suffered high viral loads and poor immune function without benefit of HAART might have permanent neurocognitive deficits, which further interfere with treatment adherence, leading to a declining trajectory. This is in contrast to the patient with newly diagnosed HIV infection who might present with criteria for HAD but whose condition improves when effectively treated with HAART.[72,73] Substance use, head trauma, and co-infection with the neurotropic hepatitis C virus[74] also add to the neurotoxic insult of HIV and predispose to significant brain dysfunction.

DIFFERENTIAL DIAGNOSIS OF PSYCHIATRIC DISTRESS

Psychiatric symptoms are common in the HIV-infected population and can reach a level of severity to meet criteria for *Diagnostic and Statistical Manual for Mental Disorders*, 4th

edition (DSM-IV) disorders. Or, as with neurocognitive impairments, psychiatric symptoms may be subsyndromal; underlying causes should be identified and reversed when possible, although it might still be necessary to treat the psychiatric symptoms (Table 26–3[75]).

Mental Disorder Due to a General Medical Condition

Differential diagnosis should always begin with mental disorder due to a general medical condition.[44,46,76] HIV CNS infection, HAD, MND, and ANI should be considered, along with opportunistic infections[77] and neoplasms. Other considerations include side effects of medications including neurotoxic HIV medications, steroids, antibiotics, antifungals, over-the-counter (OTC) preparations, and herbal supplements; drug–drug interactions such as herbal and OTC preparations; alcohol and recreational drugs; substance intoxication or withdrawal.[47] Nutritional effects include nutritional deficits such as thiamine, folate, zinc, cobalamin (vitamin B_{12}), and pyridoxine (vitamin B_6); poor intake resulting from medication or disease-induced nausea, mood disorder, painful oral lesions, or addiction; poor absorption; abnormal losses such as from gastritis, diarrhea, vomiting, or nephropathy; or increased demand resulting from hypermetabolic state due to infection, stress, or neoplasm.[48] Metabolic derangements (e.g., electrolyte abnormalities), renal or hepatic dysfunction, and endocrinopathies (e.g., glucose intolerance, hyperadrenalism, hypocalcemia, or thyroid dysfunction)[78] can also cause psychiatric symptoms.

TABLE 26–3 Differential Diagnosis of Neuropsychiatric Symptoms in Patients with HIV Infection and AIDS

Psychiatric disorders
Psychoactive substance intoxication or withdrawal
Primary HIV-associated syndromes
- Seroconversion illness
- HIV CNS infection
- HIV-associated neurocognitive disorders (HAND)

CNS opportunistic infections
- Fungi: *Cryptococcus neoformans, Coccidioides immitis, Candida albicans, Histoplasma capsulatum, Aspergillus fumigatus*, and mucormycosis
- Protozoa/parasites: *Toxoplasma gondii* and amebas
- Viruses: CJ virus (progressive multifocal leukoencephalopathy [PML]), CMV, adenovirus type 2, herpes simplex virus, and varicella zoster virus
- Bacteria: *Mycobacterium avium-intracellulare, M. tuberculosis, Listeria monocytogenes*, gram-negative organisms, *Treponema pallidum,* and *Nocardia asteroides*

Other neurotropic infective agent
- Hepatitis C virus

Neoplasms
- Primary CNS non-Hodgkin's lymphoma
- Metastatic Kaposi's sarcoma (rare)
- Burkitt's lymphoma

Medication side effects
- Endocrinopathies and nutrient deficiencies
- Addison's disease (CMV, *Cryptococcus*, HIV-1, and ketoconazole)
- Hypothyroidism
- Vitamins A, B_6, B_{12}, and E deficiencies
- Hypogonadism

Anemia
Metabolic abnormalities: hypoxia; hepatic, renal, pulmonary, adrenal, and pancreatic insufficiency; hypomagnesemia; hypocalcemia; water intoxication, dehydration; hypernatremia; hyponatremia; alkalosis; and acidosis
Hypotension
Complex partial seizures
Head trauma
Non–HIV-related conditions

Adapted from: Querques J, Worth JL: HIV infection and AIDS. In Stern TA, Herman JB, editors: *Psychiatry update and board preparation*, New York, 2000, McGraw-Hill, p 208.

CJ, Creutzfeldt–Jakob disease; *CMV*, cytomegalovirus; *HIV*, human immunodeficiency virus.

Delirium

Delirium is a common neuropsychiatric complication in hospitalized patients with AIDS,[79] and it may be a predictor of significantly decreased survival.[80] In patients with asymptomatic HIV infection or CD4 lymphocyte counts greater than 500/μL, it is rare for an HIV-related condition to cause delirium; substance intoxication or withdrawal is a more likely cause. This includes drugs (such as steroids) used as alternative HIV therapies.

Among patients with symptomatic HIV infection or a CD4 lymphocyte count less than 500/μL, HIV-related conditions and iatrogenic causes (Table 26–4) should be high on the differential diagnosis for delirium and should be at the top of the list for patients at advanced stages of AIDS or when the CD4 lymphocyte count falls below 100/μL. There should be a continued high index of suspicion for substance intoxication and withdrawal. Seizure disorder should also be in the differential diagnosis because HIV-infected patients are at increased risk for new-onset seizures, especially partial complex seizures.[81,82]

A sudden change in mental status is not characteristic of HAD alone; more often it is a result of underlying causes. Patients with advanced HAD experience symptomatic worsening with mild states of delirium during the late afternoon when they are increasingly fatigued or during the night (i.e., sundowning).

The primary goal in the management of delirium is the identification and treatment of causative factors. The need for laboratory tests, including anatomic brain imaging, electroencephalogram (EEG), CSF examination, and blood tests, must be guided by history and clinical examination. If delirium is a treatment-emergent adverse effect, the suspected medication should be discontinued or an alternative agent substituted.

Depression

The most common psychiatric complication of HIV infection or AIDS, depression, should never be considered appropriate. When a person suffers from clinical depression (i.e., experiences sufficient symptoms to meet DSM-IV criteria), the patient deserves to be treated.[83–85] The same criteria for a diagnosis of depression in a person without HIV infection should be used in a person with HIV infection.

TABLE 26–4 Neuropsychiatric Side Effects of Medications Commonly Used in Patients with HIV Infection and AIDS

DRUG	SIDE EFFECTS
Nucleoside Reverse Transcriptase Inhibitors	
Zidovudine (AZT)	Headache, restlessness, agitation, insomnia, mania, depression, irritability, delirium, somnolence, peripheral neuropathy
Didanosine	Insomnia, mania, peripheral neuropathy
Zalcitabine	Peripheral neuropathy
Stavudine	Mania and peripheral neuropathy
Lamivudine	Similar to AZT
Abacavir	Headache
Emtricitabine	Headache
Tenofovir	Headache
Nonnucleoside Reverse Transcriptase Inhibitors	
Nevirapine	Headache
Delavirdine	Headache
Efavirenz	Abnormal dreams, agitation, insomnia, euphoria, depression and suicidality, somnolence, confusion, psychosis; false-positive urine drug test for cannabis Headache, fatigue
Etravirine	Headache
Protease Inhibitors	
Indinavir	Headache, asthenia, blurred vision, dizziness, insomnia
Ritonavir	Circumoral and peripheral paresthesias, asthenia, altered taste
Saquinavir	Headache
Nelfinavir	Headache and asthenia
Amprenavir/fosamprenavir	Headache
Lopinavir/ritonavir combination	Asthenia, headache, insomnia
Atazanavir	Headache
Darunavir	Headache
Tipranavir	Fatigue, headache
Fusion/Entry Inhibitors	
Enfuvirtide (T-20)	Fatigue
Maraviroc	Insomnia
Integrase Inhibitors	
Rategravir	Headache
Other Antivirals	
Acyclovir	Headache, agitation, insomnia, tearfulness, confusion, hyperesthesia, hyperacusis, depersonalization, hallucinations
Ganciclovir	Agitation, mania, psychosis, irritability, delirium
Antibacterials	
Cotrimoxazole	Headache, insomnia, depression, anorexia, apathy
Trimethoprim-sulfamethoxazole	Headache, insomnia, depression, anorexia, apathy, delirium, mutism, neuritis
Isoniazid	Agitation, depression, hallucinations, paranoia, impaired memory
Dapsone	Agitation, insomnia, mania, hallucinations
Antiparasitics	
Thiabendazole	Hallucinations and olfactory disturbance
Metronidazole	Agitation, depression, delirium, seizures (with IV administration)
Pentamidine	Hypoglycemia, hypotension, confusion, delirium, hallucinations
Antifungals	
Amphotericin B	Headache, agitation, anorexia, delirium, diplopia, lethargy, peripheral neuropathy
Ketoconazole	Headache, dizziness, photosensitivity
Flucytosine	Headache, delirium, cognitive impairment
Others	
Steroids	Euphoria, mania, depression, psychosis, confusion
Cytosine arabinoside	Delirium with cerebellar signs

Adapted from: Querques J, Worth JL: HIV infection and AIDS. In Stern TA, Herman JB, editors: *Psychiatry update and board preparation*, New York, 2000, McGraw-Hill, p 210; and U.S. Food and Drug Administration: *HIV and AIDS activities* (website). Available at http://www.fda.gov/oashi/aids/HIV.html. Accessed February 11, 2010.

As is the case with certain other medical illnesses, it may be hard to interpret the more somatic neurovegetative symptoms (such as fatigue, loss of appetite, altered sleep patterns, or difficulty with concentration).

Fatigue

Clinically impairing fatigue affects at least one third of patients with HIV/AIDS.[86] Although the etiology may be multifactorial, a search for remediable causes is an important first step. Pain and sleep deprivation contribute to fatigue in many patients. Importantly, fatigue is not pathognomonic for depression. In fact, fatigue is associated with advanced HIV disease. It can also be disproportional to apparent disease status. However, reports of depressed mood, poor interest, and guilt, along with feelings of hopelessness, helplessness, and worthlessness, can facilitate the diagnosis of depression.[87]

Bereavement

The patient with HIV infection or AIDS often suffers multiple losses (including friends, health, physical ability, career, income, housing, child custody, independence, or a sense of freedom or autonomy). Mood and related symptoms require careful evaluation in the setting of loss or bereavement. If the patient meets criteria for major depression and is not responding to supportive interventions, pharmacologic treatment is warranted.

Suicide

Suicidal thoughts should always be assessed; they are more prevalent in patients with asymptomatic HIV infection than in those with AIDS.[88] The incidence of suicide in patients with HIV infection or AIDS has decreased since the advent of HAART; it is now similar to that seen with other medical illnesses. The incidence of suicide in this population of HIV-infected persons and those with other medical illnesses, however, is still higher than in the general population. Risk factors include symptomatic depression, persistent pain, drug use (specifically injection drug use[89]) or alcohol use, domestic violence,[90] altered cognition (i.e., delirium or HAD), social isolation, multiple losses, hopelessness, and personality disorders.[20,91] Serious thoughts of self-harm usually indicate the need for inpatient care. Electroconvulsive therapy (ECT) may be a lifesaving procedure for patients who are severely depressed and suicidal, especially when they are medically compromised and unable to tolerate medications or the delay in their effectiveness.

Anxiety

Prevalent in HIV infection, anxiety runs the gamut from an acute response to a devastating diagnosis, to a full-blown anxiety disorder. Patients with a history of an anxiety disorder are at increased risk, as are those with few social supports and poor coping skills. In susceptible patients, onset or recrudescence of anxiety symptoms may be predictably related to disease milestones or to signs of disease progression such as initial diagnosis, declining CD4 count, increased viral load, onset of opportunistic infections, chronic pain or paresthesias, wasting, or physical changes that make the disease more public.[20,92] The somatic symptoms often associated with anxiety (e.g., tremor, muscle tension or spasm, shortness of breath, dizziness, headache, sweating, flushing, palpitations, nausea, vomiting, or diarrhea) need to be carefully investigated for possible medical causes, medication side effects, drug interactions, use of activating recreational drugs, or withdrawal from opiates or sedative–hypnotics.

Mania

Mania in the setting of a personal history of recurrent mood episodes is a core feature of bipolar disorder and is considered primary (idiopathic) mania. Without such a history or a strong family history of bipolar disorder, any first episode of mania in the setting of HIV infection should be considered secondary (organic) mania as a result of the physiologic effects of HIV CNS infection, opportunistic infections, neoplasm, medications, or use of substances of abuse.[93] Current or previous treatment with zidovudine (AZT), which penetrates the blood–brain barrier, seems to be protective, whereas less-penetrating medications, such as ddI and zalcitabine (ddC), have not shown such benefit. A positive correlation exists between the manifestation of HIV-associated mania and the eventual development of HAD, MND, or ANI, although mean survival is not adversely affected. HIV-associated structural brain lesions might not be more common in patients who develop mania.[94]

HIV-related secondary mania accounted for more than 40% of hospital admissions for acute mania in a 6-month period in Uganda, where HIV is very prevalent.[95] Review of this cohort confirmed earlier suggestions that HIV-related mania is clinically distinct from primary (bipolar) mania, in that HIV-related mania typically manifests with more irritability and psychosis rather than euphoria.[87] The manic HIV patients tended to be more aggressive, paranoid, and talkative. They also had more auditory and visual hallucinations, tended to be older, and were more cognitively impaired.

Psychosis

A preexisting psychotic disorder may be a risk factor for HIV infection, and it is positively associated with psychosis in HIV-positive patients. The literature somewhat suggests that a history of substance abuse, depressive episodes, or certain personality disorders might also correlate with the onset of psychotic symptoms in HIV-associated disease and that antiretroviral therapy may be protective against the development of psychosis.[96–98] Secondary causes include more immediate psychoactive substance use (particularly methamphetamine use), CNS HIV infection (usually a late-stage manifestation) or opportunistic infections, neoplasms, nutritional deficits, metabolic derangements, or delirium. There are also case reports of psychosis induced by antiretroviral medication (e.g., efavirenz[99]). HIV-infected patients with psychosis tend to exhibit greater cognitive impairment.[98]

Sleep

Sleep problems are highly prevalent (30% to 40%) in HIV infection for a variety of reasons.[99–101] They may be related to the stage of HIV disease, persistent pain (e.g., from peripheral sensory neuropathy), or psychosocial issues.[101] Other related medical conditions can include sleep apnea, congestive heart

failure, paroxysmal nocturnal dyspnea, gastroesophageal reflux, polyuria, or delirium. Related movement disorders associated with sleep include restless legs syndrome (RLS) and periodic limb movement disorder (PLMD).

Medications such as antivirals, interferon, psychostimulants, antidepressants, and bronchodilators and substances such as alcohol, caffeine, nicotine, cannabis, and opiates can interfere with restorative sleep. Psychiatric disorders such as depression, anxiety, adjustment disorders, acute stress, and coping with life events can also disrupt normal sleep. In addition, lack of structure (e.g., from unemployment), daytime napping, and other contributions to disordered sleep hygiene can lead to reversal of the sleep–wake cycle.

Few things in life seem better when one is sleep deprived. Insufficient or inefficient sleep negatively affects energy, mood, memory, cognition and cognitive speed, work performance, and quality, enjoyment, and safety. Insomnia and fatigue also appear to be associated with increased morbidity and disability. One fourth of patients try OTC sleep aids (e.g., diphenhydramine, valerian root, or melatonin), 27% use alcohol, and less than 15% take prescribed sedative–hypnotics.[102]

Substance Use

Although injection drug use is the second most common risk factor HIV infection in the United States,[103] other modes of drug use and alcohol abuse also increase the risk of infection through unsafe sexual practices, drug-induced hypersexuality, disinhibition, impulsiveness, altered cognition, impaired judgment, or prostitution to obtain drugs or money for drugs.[20] In the substance-abusing population, HIV infection is associated with youth, homelessness, being from an ethnic minority, and having a history of sexual victimization. Prior psychiatric illness is also common, with bipolar disorder, major depression, schizophrenia, and schizoaffective disorder being the most prevalent Axis I disorders. Antisocial and borderline personality disorders are the most common Axis II disorders.[104]

HIV infection tends to be diagnosed at a more advanced stage of the disease in injection drug users and may have a more rapid downhill course. Injection drug use is also seen as a bridge of infection through heterosexual and mother-to-child transmission. Continued drug use can speed the patient's decline in several ways: suppressed immune function, increased risk for infections (e.g., STDs, hepatitis C virus [HCV] infection, pneumonia, abscesses, endocarditis, and tuberculosis [TB]), drug interactions with antiretroviral agents, poor ability to adhere to complicated medical regimens, and chaotic lifestyles that make scheduled medical follow-up difficult.[105] This population has a high tolerance to medications and possibly a low tolerance to pain, discomfort, or inconvenience. It is also a population at risk for impaired cognitive function from neurotoxic substances, poor nutrition, metabolic encephalopathies, ischemia, stroke, seizures, and head trauma.

Pain

The evaluation of pain and its adequate treatment and management are essential in the care of patients with HIV infection or AIDS. Pain is a common reason for psychiatric consultation and, rather than death, is often what patients fear most.[106] Pain control is one of the cornerstones in the care of patients with end-stage AIDS. Pain syndromes, including neuropathy, myopathies, and headache, are common among patients with HIV infection, particularly those who have received certain older antiretroviral drugs (see later). The psychiatrist might need to intervene when hospital staff who care for a patient with a history of substance disorder fail to distinguish between the management of the patient's addiction and the adequate treatment of pain or fail to provide adequate pain relief to patients from a racial or ethnic minority.[107]

Peripheral sensory neuropathy, the most common pain syndrome in patients with HIV-associated disease, affects up to 35% of patients with AIDS.[108,109] Most commonly the neuropathy manifests as a distal, symmetric polyneuropathy that can be caused by HIV infection or particularly by the "d" antiretroviral drugs, ddI, ddC, and stavudine (d4T). The diagnosis is confirmed on the basis of the neurologic examination and laboratory tests, including an electromyogram and nerve conduction studies. Treatment includes a change in the antiretroviral regimen to avoid nerve-toxic agents and the avoidance of other aggravating factors such as alcohol. One study found lamotrigine to be effective.[110]

APPROACH TO PSYCHIATRIC CARE

Screening and Prevention

It is estimated that a quarter of those infected with HIV in the United States are unaware of their seropositivity, that the unaware are responsible for the majority of new infections, and that many would take steps to change their risky behavior if they were informed of their status.[111] In 2006, the Centers for Disease Control and Prevention (CDC) Division of HIV/AIDS Prevention took steps to address this by issuing new recommendations advocating for universal HIV screening in all health care settings: medical inpatient and outpatient, mental health, and substance abuse settings. The recommendations require no special patient consent for screening, which is performed once the patient is so notified, unless the patient specifically delines consent; this is universal opt-out screening.[112] However, many states still have statutes that require written informed consent.

Psychiatrists care for an at-risk population.[113] Knowledge about HIV status and transmission is essential, but not sufficient. The first step in prevention is the assessment of the patient for risk factors and behavior. Patients must be able to perceive themselves as at risk in order for counseling to be effective.[114] Prevention models with individual and groups of chronically mentally ill and substance-abusing patients must be specific and tailored to the population being addressed. Programs with counselors whose cultural backgrounds are similar to those of the patient population have proved most effective. Programs geared toward the injection drug use community have enlisted community members as prevention leaders.

Collaboration

Although a number of demonstration projects have shown the efficacy of wrap-around services for HIV-infected patients,[115,116] it is the exception rather than the

rule to have medical, mental health, and addiction services, including methadone maintenance, in one coordinated site.[117] More commonly, patients with multiple diagnoses have complicated treatment regimens and have multiple providers at diverse sites of care, a situation that can parallel the chaos in the rest of their lives. In the absence of single-site treatment, intensive management of care can keep all treaters informed, provide outreach to improve attendance at appointments, assist with concrete services (e.g., housing, transportation, and child care), and help devise and implement an individualized medication adherence plan. The consultation psychiatrist has a unique opportunity to facilitate communication and to coordinate care among members of the patient's care team.

Adherence

Adherence is the cornerstone of successful therapy for HIV infection. Missed doses lead to treatment resistance and sometimes resistance to whole classes of medication. This, in turn, is correlated with increased morbidity and mortality, as well as the development of more treatment-resistant viral strains. Active substance abuse, homelessness, a lack of social supports, domestic violence, personality disorders, and psychiatric illness, especially major depression,[118,119] have long been recognized as risk factors for poor adherence.[120] However, the presence of one or more of these factors is not justification for exclusion from antiretroviral therapy. Rather, these factors are challenges to be addressed in preparation for initiating HAART, which may be postponed for several months while active treatment is initiated for addictions or psychiatric problems, along with readiness for concurrent medications and education about adherence.[121,122] The patient hospitalized with HIV infection is a captive audience for the initiation or reinforcement of this preparation for HAART.[76]

Effective adherence programs are tailored to the patient in terms of language, education, culture, lifestyle, and personality. Individualized adherence programs capitalize on or enhance the patient's social supports (e.g., family, intimate partners, friends, and groups), cognitive abilities, and personality style. They require accessibility, flexibility, and positively framed incentives (i.e., rewards, not punishments).[76,123] Adherence is further promoted when the patient has a high level of satisfaction with the physician,[123] understands the importance of taking every dose, believes that missed doses lead to resistance, knows and recognizes each specific medication, and is informed of possible side effects.

Simplifying the regimen (e.g., reducing the number of doses and food restrictions) and minimizing the pill burden helps fit the regimen into the patient's lifestyle. Clearly written instructions are helpful, if the patient is literate. Tying pill-taking to daily routines, along with pill boxes, alarms, pagers, directly observed therapy, or other reminder systems, can also increase adherence. Patients who are comfortable taking medications in front of other people also have an easier time incorporating HAART into their lives.[124] Adherence to scheduled medical appointments is associated with optimal viral suppression and might warrant appropriate outreach efforts.[125]

Adherence is not static; it needs to be inquired about, and promoted by, each provider at every visit. Pill fatigue, complacency, transient or prolonged relapse of substance abuse or depression, onset of morphologic or metabolic side effects, onset or exacerbation of other medical conditions, hospitalization, or psychosocial stressors (e.g., financial, housing, insurance and changes, family or relationship issues, and travel) can interrupt or decrease the patient's previous level of adherence.

TREATMENT

Nonpharmacologic Treatments

Case Management

Case management is often necessary to help with basic needs such as food, shelter, transportation, child care, medical coverage, and other entitlements, which may be needed in this population and are powerful barriers to adequate treatment. In particular, patients with cognitive impairment (executive dysfunction and memory problems) are at risk for falling through the cracks unless appropriate help and supervision are provided.

Groups

Groups of various types, often provided in the community or by AIDS activist organizations, offer a supportive, social network and positive affiliations for members of an often disenfranchised and stigmatized population. Self-help, 12-step, and peer-counseling groups are examples of such community-based programs. Therapy groups and other more formalized groups[126] might focus on aspects of living with HIV infection (e.g., disclosure, adherence, and parenting), participant characteristics (e.g., women, particular ethnic minorities, gay men, and substance abusers), or mission (e.g., risk reduction or prevention).[20]

Individual Psychotherapy

Individual psychotherapy can help patients cope with HIV infection or AIDS-related issues and distress with approaches such as coping strategies, problem-solving, disclosure of HIV status, discrimination, relationships, sexuality, and bereavement. For patients whose infection was diagnosed more than a decade ago, issues of facing a foreshortened life span may be replaced by issues of living with a chronic illness.[127] There may be themes of remorse and longing for missed opportunities referent to this erroneous life view. The focus and goals of therapy may be specific to the stage of HIV-associated disease; late in the course of AIDS, therapy may focus on end-of-life issues (such as concerns about ongoing childcare and guardianship, coping with loss, progressive disability, and unremitting pain).

For specific diagnoses, including depression or anxiety disorders, proven therapies, such as interpersonal psychotherapy or cognitive-behavioral therapy (CBT), respectively, have been shown to be effective in this population.[126,128,129] Self-hypnosis, guided imagery, meditation, muscle relaxation, massage, yoga, aerobic exercise, or acupuncture may be therapeutic for selected patients.

Adherence to medications for HIV infection and psychotropic medications should be reinforced or explored.

It should be stressed that the therapist is a member of the patient's treatment team, and appropriate releases should be obtained to allow all team members to communicate and to coordinate care. The therapist, for instance, may spend more time with the patient and be the first clinician to suspect cognitive dysfunction that requires medical work-up and intervention.

Pharmacologic Treatment

Drug–Drug Interactions

Patients with HIV infection or AIDS may be taking HIV-related medications, psychotropic drugs, OTC and herbal preparations, alcohol or drugs of abuse, and drugs to treat those addictions. Such drug combinations are prone to interactions, overlapping side effects, and toxicities. Drug side effects, such as diarrhea (common to many antiretroviral agents), can decrease the absorption of other drugs. One drug can inhibit or promote the enzymatic degradation of another drug and cause toxicity or a subtherapeutic level, respectively. Some drugs can also switch from being potentiators to inhibitors or vice versa. A drug can induce or inhibit its own metabolism over time. Certain drugs can displace other drugs from plasma protein-binding sites, effectively increasing the concentration of the displaced drug. Potential drug interactions do not necessarily preclude the concomitant use of such medications but require a careful risk-to-benefit assessment, possible dose adjustment, periodic drug level monitoring, and monitoring for or treatment of side effects. Some general principles and frequently updated resources (Table 26–5) can aid in the safe pharmacologic treatment of these patients.

Effects on the CYP enzyme system in the liver account for many of the drug–drug interactions.[130] Of the key CYP isoenzymes involved in the metabolism of psychotropics and antiretrovirals (1A2, 2C9/19, 2D6, and 3A4), 3A4 and 2D6 account for the majority of the metabolism of psychiatric medications. Allelic differences cause 10% of whites and 1% of Asians to slowly metabolize 2D6 substrates,[131] and 20% of African Americans and Asians and 5% of whites slowly metabolize 2C19 substrates.[132,133] Medications can rely on more than one metabolic pathway, which acts as a safeguard against drug interactions. In vitro studies of drug metabolism do not adequately portray the human experience that is complicated by individual genetic and nutritional differences and multidrug and substance regimens.[130,131] As a rule of thumb, the PIs, followed by the NNRTIs, have the broadest effects on the CYP system; the NRTIs are mostly devoid of drug interactions. The PI ritonavir also induces glucuronyl transferase, a non-CYP metabolic enzyme.[130]

Antidepressants

Antidepressants are largely metabolized, though not exclusively, by 2D6 and 3A4. Ritonavir, and to a lesser extent indinavir, inhibit metabolism of 2D6 substrates; all of the PIs inhibit 3A4 metabolism to varying degrees.[134] Inhibition of the metabolism of the SSRIs, venlafaxine, and mirtazapine by ritonavir and indinavir increases the levels of the antidepressants, which might allow a therapeutic response at a low or moderate dose. Although high doses of the antidepressants could lead to serotonin syndrome[135] or other toxicities, a wide range of concentrations are generally well tolerated. Tricyclic antidepressants (TCAs), however, have a narrow therapeutic window; metabolic inhibition at 2D6, from PIs (or most SSRIs), can lead to serious toxicity, including death. Safe concurrent use of these medicines requires therapeutic drug monitoring of the TCA levels (to determine the appropropriate dose) and monitoring electrocardiograms (ECGs).[130]

Bupropion continues to be in a class by itself. Initially thought to be a substrate of 2D6, bupropion was considered contraindicated in patients taking PIs because of the potential for seizures. It turns out, however, that a

TABLE 26–5 Clinically Useful HIV/AIDS Resources on the Internet

PROGRAM	URL	COMMENTS
AIDS Clinical Trials Information Service (ACTIS)	www.actis.org	Provides quick and easy access to information on federally and privately funded clinical trials for adults and children
American Psychiatric Association AIDS Resource Center	www.psych.org/aids	Includes a searchable database of mental health resources, policy statements, training, and education information
HIV/AIDS Treatment Information Service	www.hivatis.org	Allows you to view and download HIV treatment guidelines, general HIV treatment information, and more
UCSF HIV InSite	http://hivinsite.ucsf.edu/medical	Includes a drug-interaction database by drug class, drug profiles, fact sheets, and links to treatment guidelines
United Nations Programme on HIV/AIDS	www.unaids.org	International epidemiology, news, and recommendations
United States FDA HIV/AIDS Program	http://www.fda.gov/oashi/aids/HIV.html	Includes information about approved antiretroviral drugs and treatment guidelines

little-studied isoenzyme, 2B6, is responsible for bupropion metabolism. Low doses and conservative titration are still recommended, but the actual risk seems much less than previously thought.[20,130] There has been one report of *in vitro* 2B6 inhibition by ritonavir, nelfinavir (PI), and efavirenz (NNRTI), causing significant interference with bupropion metabolism.[136] Whether this interference is significant *in vivo* is unclear. A prospective study that included the administration of bupropion to patients on PIs reported no serious adverse events and, specifically, no seizures.[137]

Nefazodone, no longer marketed under the trade name (i.e., Serzone) probably has no place as a newly started medication, but some patients may already be taking the generic form. It is a 3A4 substrate and inhibitor. When teamed with the PIs, a potentially dangerous synergistic inhibition diminishes the metabolism of other 3A4 substrates.[132,138,139] Use of this combination with astemizole, cisapride, or pimozide can cause cardiac arrhythmias; with benzodiazepines, respiratory depression can follow; with clozapine, seizures may be seen; with ergot alkaloids, systemic vasoconstriction can occur; and with sildenafil, priapism can arise.[130]

Citalopram and escitalopram have the least potential for clinically significant drug interactions.[138,139]

Psychostimulants, such as methylphenidate[140] and dextroamphetamine,[141] may be used to treat depression, to augment antidepressant therapy, or to treat the symptoms of fatigue and cognitive decline associated with HIV infection.[142] Methylphenidate can inhibit 2C9 and 2C19 metabolism, leading to increased levels of certain TCAs (i.e., desipramine, clomipramine, and imipramine), barbiturates, and warfarin. Dextroamphetamine, however, is a 2D6 substrate that neither inhibits nor induces the CYP isoenzymes, but it can compete at active sites.[20,130]

Benzodiazepines

Benzodiazepines are primarily 3A4 substrates, with the exception of lorazepam, oxazepam, and temazepam, which are metabolized by glucuronyl transferase. For this reason, these three exceptions are the drugs of choice when patients on (3A4-inhibiting) PIs require treatment with a benzodiazepine. Other benzodiazepines would be expected to have increased levels when co-administered with PIs, leading to possibly dangerous sedation or respiratory depression. However, use of these glucuronyl transferase substrates (e.g., lorazepam, oxazepam, and temazepam) with that enzyme's inducer, ritonavir, can require higher doses of benzodiazepines.[20,130] The NNRTIs efavirenz and nevirapine, along with the PI ritonavir, have the potential to induce the 3A isoenzymes. This 3A induction may be delayed and cause a drop in previously elevated benzodiazepine levels, resulting in decreased efficacy or withdrawal. This unpredictability precludes the regular use of such short-acting agents (e.g., alprazolam) because of the risk that withdrawal will precipitate seizures.[143]

Mood Stabilizers

Beyond optimizing the antiretroviral regimen, treatment of HIV-related secondary mania should be tailored to the patient's HIV status and general medical condition. In advanced HIV/AIDS, patients might find lithium or carbamazepine less tolerable. Valproate increases the risk of liver toxicity (especially in patients with chronic hepatitis C or other liver disease) and bone marrow suppression (especially in combination with zidovudine, whose levels may be increased via glucuronyl transferase inhibition[144]).

Although lithium does not interact with the CYP system, it should be avoided in HIV-positive patients with advanced illness because of its potential for toxicity with fluid and electrolyte shifts. Carbamazepine induces 3A4, lowering levels of the PIs and other antiretrovirals, a situation that could foster resistance, possibly to a whole class of medications.[130] It might be possible in certain instances to avert this resistance by using higher doses of the antiretroviral. However, carbamazepine is also relatively contraindicated in immune-suppressed patients because of its potential to cause leukopenia.[20] Lamotrigine bypasses the CYP system, but it is a glucuronyl transferase substrate and needs to be titrated slowly to reduce the risk of Stevens–Johnson syndrome.[130]

Neuroleptics

Plasma levels of clozapine, which has a complex metabolic pathway involving 1A2, 2C9/19, 3A4, and 2D6, can increase with concomitant use of PIs. Despite its relative contraindications given the potential for drug interactions and added bone marrow toxicity, clozapine may still be used, particularly because it is possible to monitor clozapine serum levels.[145] The rarely used pimozide, a 3A4 substrate, can cause fatal arrhythmias at high levels; therefore, it is contraindicated with the use of any 3A4 inhibitor and thus all PIs.[146]

Substance–Drug Interactions

Opiates also interface with hepatic metabolism, affecting and being affected by interactions with antiretroviral medications. Meperidine may be cleared more quickly, leaving a higher concentration of its neurotoxic metabolite that causes delirium and possibly seizures. Clearance of fentanyl, a 3A4 substrate, is decreased by ritonavir, which can cause nausea, dizziness, and possibly respiratory depression. Codeine and its derivatives are prodrugs that need to be converted to analgesics. PIs can block this conversion and make pain control more difficult. PIs can also induce withdrawal in heroin-addicted persons or patients on methadone maintenance. Conversely, ritonavir inhibits metabolism of ecstasy, ketamine, cocaine, and other stimulants, as well as γ-hydroxybutyrate (GHB). Fatal interactions between ecstasy and ritonavir have been reported.[130,147]

Considerations in Pharmacologic Treatment

Depression

For a variety of reasons, patients with HIV infection are very sensitive to small doses of medications, similar to what is seen in geriatric patients. Helping the patient tolerate medications is ultimately more important than is raising the dose quickly. The general principle is, start low and go slow. However, patients still need to receive an appropriately high dose of any psychotropic. Because of the

pill burden and complicated schedules patients with HIV infection must often endure, once-a-day antidepressant therapy is generally preferable. Anticholinergic medications should be avoided or minimized because of their deleterious effects on cognition and the possibility of delirium or even seizures. Decreased saliva can also predispose to the development of thrush.[46]

Selective Serotonin Reuptake Inhibitors

The SSRIs remain the drugs of choice for depressive disorders in HIV patients because of established efficacy[148] in this patient population and a favorable risk-to-benefit profile. Fluoxetine, with the longest half-life ($t_{1/2}$), is a good option for patients who have tumultuous lives and who might miss doses. Use of fluoxetine weekly is also an option. On the other hand, if there is a side effect or an unpleasant interaction, it will take 2 weeks or more for it to clear. Citalopram and its L-enantiomer escitalopram are the SSRIs that might have the fewest drug interactions. All SSRIs are associated with sexual side effects, akathisia-like activation (or the serotonin syndrome when toxic levels are present), and GI symptoms.

Tricyclic Antidepressants

The TCAs are often used in small doses for neuropathic pain, insomnia, or headaches. The side effect of constipation may be helpful in some HIV-infected patients with diarrhea. TCAs can be lethal with ingestion of a 2-week supply. The least anticholinergic ones, nortriptyline and desipramine, should be used with an awareness that anticholinergia can worsen cognition. TCAs should be monitored with ECGs and plasma levels.

Serotonin–Norepinephrine Reuptake Inhibitors

Venlafaxine, its metabolite desvenlafaxine, and duloxetine are serotonin and norepinephrine (hence, "dual") reuptake inhibitors. The extended-release form of venlafaxine is a reasonable first-line medication because of its once-a-day dosing and relative lack of drug interactions. SNRIs can be initially stimulating, and some patients have difficulty tolerating them. SNRIs can raise blood pressure unacceptably in hypertensive patients, and blood pressure monitoring is required. Milnacipran and sibutramine are SNRIs marketed in the United States for fibromyalgia and weight loss, respectively.

Bupropion

The antidepressant least likely to have sexual side effects, bupropion, does not treat anxiety. Bupropion's continued stimulant effect, if tolerable, can benefit patients with fatigue or apathy, although, unlike psychostimulants, bupropion tends not to improve HIV-related cognitive slowing.[46] Bupropion lowers the seizure threshold in a dose-dependent manner, which is a concern in patients who have a history of seizures, poorly controlled seizure disorders, head trauma, or other threshold-lowering pathology (e.g., space-occupying lesions, infections, or alcohol or psychoactive substance abuse). Patients with eating disorders or metabolic derangements from drug side effects (such as vomiting or diarrhea) may be at increased risk for seizures. The slow-release forms may be safer with regard to seizure risk.

Trazodone

Primarily used for its major side effect, trazodone makes people very sleepy within 20 to 30 minutes of ingestion, usually at a low dose of 25 or 50 mg. In low doses, it is minimally anticholinergic. Men of all ages must always be informed of its rare but serious side effect, priapism (prevalence is about 1/7000).

Mirtazapine

At low doses, mirtazapine is useful for patients who have difficulty eating and sleeping, even in the absence of clear depression. At higher doses, it is also an effective antidepressant, albeit with major long-term management issues related to histaminergic side effects (e.g., daytime drowsiness and significant weight gain). Patients who receive mirtazapine should be weighed at regular intervals.

Monoamine Oxidase Inhibitors (MAOIs)

Because of the myriad drugs patients with HIV infection might need over time, MAOIs are relatively contraindicated in these patients. They should specifically not be co-administered with zidovudine.

Psychostimulants

In low doses, psychostimulants can improve appetite, energy, and mood. They work quickly, often within hours, and have few side effects or interactions. Especially useful in patients who are unresponsive to or intolerant of other antidepressants, stimulants also effectively improve the early symptoms of cognitive decline; they help patients attend and stay more focused and organized. In late HAD, however, they can become toxic. Stimulants should also be avoided in the presence of psychotic symptoms or in those with a history of seizures. Abuse is rare in patients who have no history of a substance disorder. A history of a substance disorder is not a contraindication to the use of stimulants but it does require that the prescriber be more cautious. Modafinil is a wakefulness-promoting nonstimulant psychotropic drug that is sometimes used instead of a psychostimulant for HIV-related fatigue and depression.[149]

Anxiety

Anxiolytic Antidepressants

For prolonged use in anxiety disorders, the SSRIs as well as SNRIs and TCAs are beneficial, and they decrease the needed dose of benzodiazepines when these medications are co-administered.

Benzodiazepines

For more time-limited episodes of intolerable anxiety, short- to medium-acting benzodiazepines without active metabolites and the least drug–drug interactions (such as lorazepam or oxazepam) should be used. Alprazolam may be helpful for procedures in which a very quick onset and short duration are required. For more continuous use, however, the rapid offset of alprazolam predisposes to mild withdrawal or rebound anxiety. This rapid offset leads to extreme discomfort several times a day or to a gradually increased frequency of dosing and puts patients at risk for becoming addicted. Alprazolam and triazolam are contraindicated in patients who are being treated with a PI-based HAART regimen.

Buspirone

An option for patients on PIs, buspirone unfortunately takes several weeks to become effective. Concomitant use of benzodiazepines may be necessary to help the patient through the initiation and titration period. In advanced systemic illness, but not less-symptomatic disease, buspirone has worsened cognition and triggered mania.[46]

Antipsychotics

Although generally not recommended for anxiety because of potentially serious long-term toxicities, low doses of atypical antipsychotics may be effective if fear or pain are prominent. In addition, some of the second-generation antipsychotics are now indicated for use in depression. If antipsychotics are prescribed, medical monitoring, particularly to prevent tardive dyskinesia and the metabolic syndrome, is necessary, regardless of indication.[150]

Mania

Although lithium bypasses hepatic metabolism, it carries the risk of serious neurotoxicity and nephrotoxicity in patients prone to fluid loss from diarrhea, vomiting, inadequate intake, or HIV nephropathy. Valproic acid may be more effective for patients with secondary mania and brain abnormalities on MRI.[151] Carbamazepine is less useful because of its potent induction of the 3A4 isoenzyme (increased clearance of PIs) and possible blood dyscrasia. Although benzodiazepines have antimanic properties, they carry the risk of disinhibition, anterograde amnesia, and confusion; they are generally not considered to be primary pharmacologic treatment of mania. For medically complex patients with HIV disease, antipsychotics may be preferred over the standard mood stabilizers.

Psychosis

Antipsychotics are the treatment of choice for psychotic symptoms of almost any cause. Patients with HIV infection, however, are extremely sensitive to side effects of antipsychotics and are at risk for extrapyramidal symptoms (EPS) and neuroleptic malignant syndrome (NMS) with high-potency agents and confusion or seizures with low-potency agents.[20,98,152] The second-generation antipsychotics are often chosen because of better tolerability, particularly with regard to EPS. Very low starting doses and cautious titration are recommended. Risperidone and olanzapine have each been used effectively for HIV-related psychosis without causing undue sedation or cognitive impairment.[20,153] The deleterious effect of many second-generation antipsychotics on glucose metabolism, however, can limit their usefulness, especially in patients already at risk for diabetes, such as those taking PIs. Quetiapine is the least apt to induce parkinsonian symptoms, making it a reasonable first-line medication for advanced neuropsychiatric disease.

Substance Abuse

The treatment and management of hospitalized patients with HIV infection and substance abuse disorders has five main features, depending on the patient's level of addiction or recovery: prophylaxis against or treatment of withdrawal; encouragement to enter a recovery program, including referral to a comprehensive addictions program; maintenance of recovery during the stress of hospitalization; adequate pain control, including the use of narcotic medications, if appropriate; and careful monitoring for drug–drug interactions, especially for patients on methadone maintenance.

If the patient is on methadone maintenance and opiate analgesia is required, an agent other than methadone should be used to maintain clear boundaries for the patient and the methadone maintenance program. For patients with active addictions problems, HIV infection and AIDS community-based organizations might have addictions outreach programs that send a worker to the patient's bedside. Prescribed medications that are being abused might need to be discontinued. There are limitations to the model of harm reduction used in many addiction-treatment programs, and the psychiatrist should know that prescribing oral forms of abused injection drugs does not promote recovery from substance disorder. This practice might only introduce the problems of dependence on high doses of oral substances.[154] For patients on methadone maintenance with symptomatic HIV infection or with $CD4^+$ lymphocyte counts below 500/μL, the initiation of some antimicrobial agents can have pharmacologic consequences.[155] For example, methadone increases zidovudine serum levels, which can lead to increased toxicity. Treatment with rifampin can increase methadone metabolism and potentially precipitate acute opiate withdrawal. In this instance, the daily methadone dose needs to be increased. The discharge plan would need to include notifying the patient's methadone clinic of this dosage change.

Pain

The treatment of HIV-related neuropathy is similar to the approach used with a chronic pain syndrome. Low doses of TCAs can be effective, either alone or in combination with other analgesic therapies. No systematic studies have been conducted to compare the effectiveness of different TCAs, and no evidence exists for the superiority of amitriptyline for HIV-related neuropathy. Desipramine and nortriptyline are better tolerated and appear to be as effective.

Anticonvulsants in low doses can be effective for neuropathic pain, either alone or in combination with other analgesic therapies. Both carbamazepine and valproic acid have been effective, but hematopoietic and hepatic side effects and drug interactions must be monitored. Gabapentin may be effective for neuropathic pain; its use avoids hematopoietic and hepatic side effects. Low-dose clonazepam can be particularly effective for hyperpathic pain. Lamotrogine has support for its use for HIV-related sensory neuropathy from a controlled trial.[110]

Some antiarrhythmics also have local anesthetic properties and can be useful for some types of pain syndromes. Postherpetic neuralgia can be highly disabling in HIV-infected patients, particularly those who have had multidermatomal herpes zoster. IV lidocaine can offer relief, often with once- or twice-weekly infusions, and a significant dose reduction in narcotic analgesics.

Opiates are beneficial for short-term use or for periods of pain exacerbation, but they can induce tolerance and abuse or dependence. A history of a substance disorder does not preclude the use of opiates required for adequate analgesia, but it requires careful monitoring to prevent

unauthorized escalation of the dosage. In discharge planning for patients with advanced HIV disease, the psychiatrist should remember that cognitive impairment can make compliance with as-needed dosing schedules difficult, and patients can accidentally overuse analgesics. The use of a pill alarm or box can help. If long-term therapy with opiates is needed, the psychiatrist should consider long-acting oral or transdermal formulations. The latter are particularly helpful in the care of terminally ill patients, many of whom have odynophagia or dysphagia.

CONCLUSION

Neuropsychiatric symptoms are part of the HIV infection and AIDS and have multiple etiologies. HIV CNS infection and primary psychiatric disorders should always be considered. Other CNS infections or lesions, medications, drugs of abuse, drug–drug interactions, and metabolic derangements need to be explored. Whenever identified, underlying causes should be treated, but the psychiatric symptoms can require more immediate, symptomatic treatment.

Patients with HIV infection are often sensitive to small amounts of medication, and they should generally be given geriatric doses with careful monitoring and slow dosage titration; ultimately, however, an effective dose must be prescribed. The PIs, and to a lesser extent the NNRTIs, are responsible for the majority of the drug–drug interactions with psychotropic medications. These interactions occur largely because of interference with the hepatic CYP enzyme system. Having access to frequently updated and reliable resources assists with the choice of safe pharmacologic alternatives in this population. Optimal psychiatric care (e.g., effective remission of depression) can help patients achieve sufficient adherence to antiretroviral treatment and even improve their prognosis *quo ad vitam*.

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27 Patients with Cancer

Ilana M. Braun, M.D.
William F. Pirl, M.D., M.P.H.
Donna B. Greenberg, M.D.

The seriousness of the diagnosis of cancer challenges the capacity to survive, set a course in life, and fulfill hopes and dreams. Over the 20th century, even as cancer treatments improved and some patients were cured, psychiatrists in the tradition of humane psychiatry used their skills to stand by patients who were overwhelmed and help them make complex treatment choices by which they can shape the rest of their lives or their end-of-life care. Psychiatrists have offered expert diagnosis and management of co-morbid psychiatric syndromes and collaborated with oncologists so that treatable psychiatric illnesses have not stood in the way of technical oncologic care. In addition, specific cancer-related or cancer treatment–related neuropsychiatric syndromes (Table 27–1)[1–5] can, and should, be recognized and treated.

Since Weisman and co-workers explored how to help patients cope with cancer when they were demoralized,[6–8] psychiatrists have tried to understand who their patient was before the diagnosis and the nature of the patient's existential predicament. The psychiatric interview can assess the personal past, present plight, anticipated future, regrets, salient concerns, physical symptoms, disabilities, coping strategies, and psychiatric vulnerabilities (Table 27–2).[7]

Denial and "Middle Knowledge"

Patients often seem to know and want to know about the gravity of their illness, yet they often talk as if they do not know and do not want to be reminded about their cancer.[9] Weisman used the expression "middle knowledge" for the space between open acknowledgment of death and its utter repudiation. Patients may deny facets, implications, or mortal threat of an illness.[9] Middle knowledge is most apparent at transition points (e.g., when a cancer recurs). However, denial is an unstable state; it is almost impossible to maintain denial against even the most reluctant patient's inner perceptions. To preserve a relationship, patients often deny their knowledge of impending death to different people at different times.[10] Tactful discussions of mortality allow patients to be responsive to those closest to them for as long as possible.[9]

Hope and the Doctor–Patient Relationship

Physicians convey respect when they explore the patient's capacity to cope. That respect allows the patient to nurture courage and resiliency[11] and regain a sense of control while appraising and reappraising his or her choices. Presenting the facts to a patient about an illness does not break the trust established between a patient and a doctor. Furthermore, hope is not merely related to prognosis. The patient's capacity to hope is also related to an ego ideal and the conviction of one's influence on the world. As the physician bolsters the patient's self-esteem, a sense of purpose adds value to life regardless of the time frame. The psychiatrist's capacity to listen nonjudgmentally allows patients to express doubts and weaknesses and accept who they are and why they see things as they do. The physician's presence protects patients from abandonment and offers a place where they can explore what is meaningful to them.[11,12]

Medical Choices

The psychiatrist also clarifies with the patient which choices are feasible. Unfazed by personal shock, anxiety, and denial and armed with a medical education, the psychiatrist is in an excellent position to understand (better than the patient) the individualized medical plan, as set forth by medical experts. Diagnosis, treatment, and prognosis are complex. As the psychiatrist learns how the patient thinks and adds appropriate psychopharmacologic treatments for symptoms or Axis I diagnoses, as needed, the psychiatrist can focus on necessary anticancer treatments that are most likely to give the best outcome. Focusing on problems, setting priorities, making clear what the patient is doing and not doing about a problem, and exploring strategies are key elements of care. By doing so, patients can make the decisions that are most important for them. Meanwhile, the psychiatrist, in collaboration with oncology staff, sorts through differential diagnoses as psychological symptoms develop and the medical condition and treatment progress. The psychiatric assessment involves an evaluation of affective, behavioral, cognitive, and physical symptoms and the creation of a differential diagnosis. The work also includes education about how to support significant others and how to allow help or relinquish control to those who have shown themselves trustworthy. Honest communication allows for acceptance, a reduction of bitterness, and replacement of denial with the courage to confront what cannot be changed.[10]

Distress

In the study of newly diagnosed cancer patients, Weisman and Worden found that the peak period of distress ranged from 1 or 2 days to 3 months but that the intense distress lessened over time.[13] Those who were more depressed and anxious, who had less financial and social support, who abused alcohol, who had more troubled relationships, and

TABLE 27–1 Neuropsychiatric Side Effects of Cancer Drugs

Hormones[1]

Anti-estrogens

Tamoxifen, toremifene: hot flashes, insomnia, mood disturbance
Anastrazole (Arimidex), letrozole (Femara), exemestane (Aromacin): hot flashes, fatigue, mood swings, and irritability
Leuprolide (Lupron), goserelin (Zoladex): hot flashes, fatigue, and mood disturbance

Androgen Blockade

Leuprolide (Lupron), goserelin (Zoladex): hot flashes, fatigue, and mood disturbance
Flutamide (Eulexin), bicalutamide (Casodex), nilutamide (Nilandron): hot flashes, fatigue, and mood disturbance

Glucocorticoids

Insomnia, hyperactivity, hyperphagia, depression, hypomania, irritability, and psychosis

Biologicals

Interferon-alpha[2,3]

Depression, cognitive impairment, hypomania, psychosis, fatigue, and malaise

Interleukin-2

Delirium, flu-like syndrome, dose-dependent neurotoxicity, and hypothyroidism

Chemotherapy

Vincristine (Oncovin), vinblastine (Velban), vinorelbine (Navelbine)

Neurotoxicity is dose-related and usually reversible; fatigue, malaise, and rarely seizures are noted; postural hypotension related to autonomic neuropathy

Procarbazine (Matulane)

Mild reversible delirium, depression, and encephalopathy

Asparaginase (Elspar)

Depression, lethargy, and delirium with treatment

Cytarabine (ARA-cell, Alexin)

Confusion, obtundation, seizures, coma, cerebellar dysfunction, and leukoencephalopathy

Fludarabine (Fludara)

Rare somnolence, delirium, and rare progressive leukoencephalopathy

5-Fluorouracil (5-FU)

Fatigue, cerebellar disfunction, encephalopathy lethargy, headache, and seizures

Methotrexate

Delirium and with administration, intrathecal seizures, motor dysfunction, chemical arachnoiditis, and coma
Dose- and route-related risk of delirium

Pemetrexed (Alimta)

Depression and fatigue

Gemcitabine (Gemsar)

Fatigue, flu-like syndrome, and a rare autonomic neuropathy

Etoposide (Eposin)

Postural hypotension and rare disorientation

Carmustine (BCNU)

Delirium, only at high dose, and rare leukoencephalopathy

Thiotepa

Rare leukoencephalopathy

Ifosfamide (Ifex)

Transient delirium, lethargy, seizures, drunkenness, parkinsonism, and cerebellar signs that improve within days of treatment
Leukoencephalopathy

Cisplatin

Rare reversible posterior leukoencephalopathy with cortical blindness
Peripheral neuropathy
Sensorineural hearing loss

Carboplatin

Neurotoxicity only at high doses

Oxaliplatin (Eloxatin)

Acute dysesthesias of hands, feet, perioral region, jaw tightness, and pharyngo-laryngodysesthesias

Paclitaxel (Taxol)

Sensory peripheral neuropathy and rarely seizures, transient encephalopathy, and motor neuropathy

Docetaxel (Taxotere)

Like paclitaxel but less neurotoxicity

Continued

TABLE 27–1 Neuropsychiatric Side Effects of Cancer Drugs—*cont'd*

Inhibitors of Kinase Signaling Enzymes[4,5]

Imatinib (Gleevec)
Fatigue, confusion, and papilledema

Sunitinib (Sutent)
Hypothyroidism

Sorafenib (Nexavar)
Fatigue, asthenia, and rarely hypophosphatemia

Bevacizumab (Avastin)
Fatigue and rarely reversible posterior leukoencephalopathy

Thalidomide
Drowsiness and somnolence, improving over 2-3 weeks, dose-related, associated with dizziness, orthostatic hypotension, tremor, loss of libido, hypothyroidism, and rarely confusion

Bortezomib (Velcade)
Postural hypotension and asthenia; confusion, psychosis, and suicidal thoughts have been reported

Rituximab (Rituxan)
Headache and dizziness

Trastuzumab (Herceptin)
Headache, insomnia, and dizziness

IV, Intravenous; *MAO,* monoamine oxidase; *SIADH,* syndrome of inappropriate antidiuretic hormone; *TSH,* thyroid-stimulating hormone.

who were burdened by illness were more distressed. The researchers learned that certain patients were unable to generate alternative coping strategies.[7] Vulnerable patients tended to overuse strategies that were ineffective for finding relief and resolution. Weisman and co-workers defined a treatment to reduce distress, correct deficits in coping, reclaim personal control, and improve morale and self-esteem. They asked patients to examine their relationship to cancer (their current concerns), articulate their understanding of what might interfere with effective coping, and envision options that might lead to satisfactory solutions. Staff viewed that change as possible; patients could be helped to help themselves, as problems were broken down into manageable portions. Members of the treatment team focused on coping and adaptation rather than on psychopathology; they conveyed an expectation of positive change, a sense that options and alternatives are seldom exhausted, and an awareness that perceiving problems in a flexible fashion helps to generate support. They studied both brief psychodynamic and behavioral techniques; both were effective in reducing distress and denial.[7]

Screening

Weisman and Worden defined a screening instrument and a concise interview to identify patients who were vulnerable and had ineffective coping skills (because those individuals were most apt to benefit from psychosocial intervention). To make screening more efficient, Zabora and co-workers validated the Brief Symptom Inventory–18[14] and the Index of Current Concerns (now a Brief Symptom Inventory–11)[15] to identify those with more anxiety and depression, somatic symptoms, and distress. To call the attention of oncology staff to distressed cancer patients, Holland and colleagues operationalized a visual nomogram (a distress thermometer score ≥ 5) with a variety of needs assessed (in the National Comprehensive Cancer Network [NCCN] guidelines).[16]

Psychosocial Interventions

Weisman's work foreshadowed larger studies of preventive psychosocial interventions for cancer patients. Fawzy and colleagues[17–20] described a 6-week structured group intervention for patients with melanoma (stages I and II); the intervention included health education, stress management, instruction about coping skills, and supportive group psychotherapy. They also taught simple relaxation exercises (e.g., progressive muscle relaxation, guided imagery or self-hypnosis, as well as problem-solving and coping methods). The interaction of the patients in the group also provided emotional support.[17–20] The group that received 6 weeks of treatment demonstrated a survival benefit at 5 to 6 years (but it was not as evident in the 10th year).

Spiegel and others went on to develop a group therapy supportive–expressive intervention for women with metastatic breast cancer. Although in two randomized multisite studies, the benefit for survival was not found, the intervention reduced distress, offered patients social support and safe conduct, and increased their ability to confront difficult challenges.[21–24]

More recently, Chochinov[25] focused on conserving dignity at the end of life by asking patients what they felt was most important and what they wanted their loved ones to remember. Informed by the work of Frankl,[26] Greenstein and Breitbart[27] and Breitbart and colleagues[28] reported on a group intervention for advanced cancer patients that focused on faith and meaning.

Combinations of interventions augmented patients' coping skills.[29] Teaching about relaxation has benefited cancer patients,[29,30] and a variety of educational interventions (e.g., stress management, cognitive therapy, behavioral training) tailored to disease type and phase have improved coping and decreased distress in adult patients[31] and the children of cancer patients.[32]

TABLE 27–2 Concerns of Patients with Specific Cancer Types

CANCER TYPE	POSSIBLE CONCERNS
Prostate cancer	Significance of serum prostate-specific antigen (PSA) test results: anxiety
	Once diagnosed, the initial choices are watchful waiting, surgery, or radiation treatment
	Side effects of surgery or radiation, including incontinence or erectile dysfunction
	Sexual function and dysfunction
	Androgen blockade and its effects on fatigue, mood, and sexual interest
Breast cancer	Body image related to mastectomy or to reconstruction
	Adjuvant chemotherapy and its side effects, including alopecia, weight gain, fatigue, and impaired concentration
	As a result of adjuvant treatment, anti-estrogens, or aromatase inhibitors, menopausal symptoms, including insomnia, sexual dysfunction, and hot flashes
	The question of prophylactic mastectomy
	Sexuality and fertility
	In those with known genetic risk factors, health of loved ones
Colon cancer	Adjustment to surgery or an ostomy
	Body image and sexual function
	Bowel dysfunction
	In those with known genetic risk factors, health of loved ones
Lung cancer	Physical limitations of reduced lung capacity
	Post-thoracotomy neuralgia
	Cough
	Guilt about nicotine addiction (past and present)
Ovarian cancer	Anxiety about the tumor marker CA 125
	Sexual dysfunction and infertility
	Pain and recurrent bowel obstruction
Pancreatic cancer	Maintenance of adequate nutrition
	Poor appetite
	Bowel function (and the need for pancreatic enzymes and laxatives)
	Pain
	Diabetes
	Depressed mood
Head and neck cancer	Facial deformity
	Dry mouth
	Poor nutrition
	A weak voice and difficulty with communication
	Post-treatment hypothyroidism
	Guilt about alcohol and nicotine addiction (past and present)
Lymphoma	Corticosteroid-induced mood changes
	The need for recurrent chemotherapy and its effects
Hodgkin's disease	Post-treatment hypothyroidism
	Fatigue
Osteosarcoma	Amputation/prosthesis vs. bone graft
	Impaired mobility
	Post-thoracotomy neuralgia

ANXIETY SYNDROMES

Claustrophobia becomes clinically important when magnetic resonance imaging (MRI) is required for diagnostic purposes or when patients are trapped in bed by orthopedic care (e.g., after repair of a leg riddled with osteogenic sarcoma). Needle phobias also occur and can be problematic; they may be treated with rapid desensitization.[33]

Some patients live on tenterhooks awaiting the results of the 3-month scans to assess disease recurrence. They develop significant anxiety a week or so before each reassessment. The roller coaster ride of life-threatening experiences and uncertainty associated with cancer treatment parallels the unpredictable aversive stimuli that provoke conditioned helplessness and depression.[34] For some patients the challenge of cancer generates chronic anxiety, but many patients come to cancer treatment with a predisposition to generalized anxiety disorder, phobias, or panic disorder. Patients anticipate the results of cancer markers (e.g., women with ovarian cancer who await the report of the CA 125 test); their mood rises and falls with the results of tumor markers or progressive disease.[35] Most patients are alert to physical symptoms after treatment and worry that such symptoms signify disease recurrence. A visit to the doctor can be reassuring for most, but for some the alarm signifying danger does not turn off. These patients are preoccupied with fear, and every symptom signals cancer recurrence. Fortunately, antidepressant medications suppress such anxiety. Benzodiazepines are best used for specific anxiety-provoking procedures. Implementation of cognitive-behavioral therapy (CBT) also improves coping.

Posttraumatic stress disorder (PTSD) is uncommon (occurring in 3% to 10%) in patients treated for cancer[36]; however, Pitman and colleagues[37] have shown that women with breast cancer have a physiologic response 2 years after hearing a narrative of the two most stressful experiences during their cancer treatment. Leukemia survivors who developed anticipatory nausea with treatment were also more apt to become nauseated in response to reminders of their treatment.[38] The numbness and tingling of peripheral neuropathy can also serve as a reminder of treatment; they can trigger intrusive thoughts and avoidant behaviors of PTSD[39] and be associated with co-morbid depression.[37]

Panic disorder and other anxiety disorders occur among cancer patients with the same frequency as they do in the general population.[40] However, specific cancer-related symptoms (e.g., embarrassment related to unexpected diarrhea) can contribute to anticipatory anxiety and agoraphobia. Disability and poor quality of life have been associated with co-morbid anxiety disorders and physical conditions.[41]

In patients with cancer, the differential diagnosis of panic attacks includes temporal lobe seizures, acute hypoxia resulting from pulmonary emboli, and congestive heart failure.

Nausea and Vomiting

A host of chemotherapy agents and radiation treatments cause nausea and vomiting. Even in this era of advanced antiemetics, highly and moderately emetogenic chemotherapy is associated with nausea in 60% of patients, and vomiting occurs in 36% of patients. Delayed nausea, which comes after the first days of chemotherapy, significantly compromises quality of life even more than vomiting does.[42] As a result of vomiting during chemotherapy, patients can develop conditioned nausea and anxiety associated with the smells and sights linked with treatment. They may have nausea and vomiting even before arriving at the hospital for treatment.[43] Conditioned nausea morphs into anticipatory anxiety, insomnia, and aversion to treatment. Hypnosis, CBT techniques, and antianxiety agents (e.g., alprazolam, lorazepam) can reduce phobic responses as well as anticipatory nausea and vomiting (both during and after chemotherapy).[44]

The best antiemetic drugs make conditioned vomiting less likely, but patients may continue to vomit after administration of doxorubicin, cisplatin, or carboplatin (even when a 5-hydroxytryptamine-3 [5-HT_3] receptor antagonist and dexamethasone are employed).[45] Some patients who develop anticipatory anxiety avoid the hospital and its routine smells long after cancer treatment has ended. Anticipatory nausea and vomiting are more likely to occur in younger patients, those who have had more emetic treatments, and those who have trait anxiety.[43] Nausea may also be a symptom of anxiety that persists as part of major depressive disorder (MDD).

DEPRESSION

In people with cancer, MDD is associated with poor quality of life, worse adherence to treatment, longer hospital stays, greater desire for death, and an increased rate of suicide and mortality.[46–49] Reports of its prevalence (10% to 25%) in people with cancer have varied widely.[50] However, people with a history of MDD are more likely to develop MDD after the diagnosis of cancer, and about half of the cases of MDD occur in those without a history of MDD.[51]

The diagnosis of MDD in people with cancer relies on the same *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria as are used in those without cancer. However, the diagnosis can be complicated by symptoms that overlap with cancer and with cancer treatments. To address this issue, alternative criteria have been proposed, such as the Endicott criteria, which substitute psychological symptoms for physical symptoms in the DSM criteria. Although the inclusion of physical symptoms that could be related to cancer or cancer treatments in the diagnosis of MDD remains controversial, alternative criteria have not yielded markedly different results.[52]

As with the evaluation of other medically ill patients who appear depressed, the evaluator must consider possible medical contributions in the differential diagnosis. Untreated pain, hypothyroidism, and medications (e.g., corticosteroids, chemotherapies such as alpha interferon, pemetrexed, procarbazine) may contribute to MDD. Delirium, especially the hypoactive subtype, is often erroneously labeled as depression. Although mood symptoms may occur as part of delirium, key features of delirium include a generalized impairment of attention and cognition, symptoms that wax and wane in severity, and a disturbance of the sleep–wake cycle. Fatigue is a common cancer-related symptom that can be difficult to tease apart from MDD. Anhedonia may be one of the most surefire factors for MDD.[53] Apathy (e.g., that results from lesions in the frontal lobes) can also be reminiscent of MDD. With apathy there are delayed responses, cognitive impairment, and a loss of spontaneous action or speech.

The treatment (which consists primarily of antidepressant medications, psychotherapy, or both) of MDD in people with cancer is quite similar to the treatment of MDD in people without medical co-morbidities. Severe cases of MDD, especially those associated with wasting because of diminished appetite, may be treated with electroconvulsive therapy (ECT). Although complementary treatments (e.g., herbal preparations, acupuncture, massage) are available, little data exist supporting their efficacy in the treatment of MDD in cancer patients.

Although antidepressants are commonly used to treat MDD that is co-morbid with cancer, few placebo-controlled trials in cancer patients have been conducted, and there is some evidence to show that depression in patients with medical co-morbidities is more resistant to antidepressant therapy.[50,54,55] Potential side effects may affect the choice of an antidepressant medication in a person with cancer. Patients may already have constipation or nausea from their cancer medications, and an antidepressant should be chosen that does not exacerbate these symptoms. Frequently, antidepressants are selected for their side-effect profile (e.g., sedation, increased appetite), which in some cases may be desirable. Some of the selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine) and bupropion can interfere with the use of chemotherapeutic agents, including tamoxifen (because of their effects on cytochrome P450 2D6 system).[56] If an antidepressant is necessary in the setting of tamoxifen use, venlafaxine, escitalopram, or citalopram (which are less potent 2D6 inhibitors) should be selected.[57] Stimulants (e.g., methylphenidate, dextroamphetamine) may also be beneficial for MDD (i.e., insofar as they may lift mood, increase appetite, and improve cognitive difficulties and fatigue) in the medically ill, but there is little evidence to support this practice. When improvement follows use of stimulants, it is usually seen within the first week of treatment.

Although little research has been conducted on medications for MDD in people with cancer, several studies confirm the efficacy of psychosocial interventions.[50] Both the severity of cancer-related symptoms (e.g., fatigue, nausea) and the demanding schedules for anticancer treatments limit participation in traditional weekly 50-minute psychotherapy visits. Therefore psychotherapy visits should be flexible and involve shorter visits, meetings during chemotherapy treatments, and greater use of phone contacts.

FATIGUE

Fatigue is the most commonly reported symptom in people with cancer and the symptom that causes them the most functional impairment.[58] It is often confused with MDD.[59]

Although fatigue is not a psychiatric disorder, psychiatric conditions can cause fatigue; therefore fatigue could be considered a psychosomatic illness.

Prevalence

The prevalence (estimated at 60% to 90%)[60,61] of fatigue in people affected by cancer varies widely because of differing measures of fatigue and the heterogeneous populations studied.

Diagnosis

Fatigue may occur before the diagnosis of cancer, during active cancer treatment, and into the survivorship years. The diagnosis is made primarily by asking questions about the presence and severity of the symptoms. Although there are validated instruments for the measurement of fatigue[59] (e.g., the Functional Assessment of Chronic Illness Therapy–Fatigue scale [FACIT-F]), administration of these questionnaires may not be feasible in busy clinical settings. The National Comprehensive Cancer Network (NCCN) recommends screening for fatigue at visits with a one-item, 0-to-10 scale, similar to that used for the screening of pain, with 0 being "no fatigue" and 10 being "the most severe fatigue." Scores of 4 or greater should prompt further evaluation. (The full set of guidelines also includes a review of the literature and can be viewed at www.nccn.org.)

The NCCN recommends that the primary evaluation include exploration of the modifiable causes of fatigue (e.g., anemia, pain, sleep disturbance [insomnia, difficulty staying asleep, and sleep apnea], emotional distress [MDD and anxiety], poor nutrition, inactivity or deconditioning, use of medications and chemotherapies that cause fatigue [e.g., gemcitabine, corticosteroids, narcotics, antiemetics, and β-blockers], and other medical conditions [e.g., hypothyroidism, hypogonadism, adrenal insufficiency, hypercalcemia, hepatic failure, and cardiovascular or pulmonary compromise]). Fatigue may also be a side effect of radiation therapy.

Treatment

The primary treatment for fatigue is modification of its contributing factors; this should be done in conjunction with the patient's oncologist or primary care physician. Mental health clinicians can provide treatment for any underlying psychiatric disorder as well as offer fatigue-specific interventions (e.g., use of stimulants, exercise, behavioral interventions).

Stimulants

Stimulants (e.g., methylphenidate, dextroamphetamine, modafinil) are commonly used in the treatment of fatigue. However, there has been mixed support for this treatment in clinical trials. Open-label trials have suggested a benefit from their use, but response rates for placebos have also been remarkably high in the few randomized, placebo-controlled trials conducted.[62] In addition to reducing fatigue, stimulants also improve mood, concentration, and appetite. However, stimulants can raise blood pressure and heart rate and increase the risk of sudden death. For these reasons they should be used with caution in patients with cardiac disease. Common side effects include constipation, sleep disturbance, anxiety, and (at higher doses) anorexia.

Exercise

Abundant evidence supports exercise as a treatment of fatigue, with several studies demonstrating the benefit of exercise for fatigue in people with cancer.[63] Mental health clinicians can encourage exercise through motivational interviewing and through behavioral changes. Because patients can have serious physical morbidities, such as large bone metastases that could lead to fracture, consultation with the oncologist is recommended before initiating exercise. A physical therapist can assist in designing an exercise program that contains both strength and aerobic training and is appropriate for a person with physical limitations resulting from cancer or cancer treatments. For more medically complicated patients, exercise might best be done in a cardiovascular or pulmonary rehabilitation center.

Behavioral Interventions

Behavioral interventions (e.g., CBT, energy conservation) may be beneficial as both primary and adjunctive treatments for fatigue in cancer patients. CBT emphasizes managing fatigue rather than attempting to cure it.[64] Energy conservation is similar to CBT in some respects; it focuses on prioritizing activities and delegating, problem-solving difficulties caused by the fatigue, and improving organizational skills.[65]

CONFUSION AND COGNITIVE IMPAIRMENT

Whereas infections, metabolic abnormalities, and recent surgery account for an abnormal mental status in most hospitalized cancer patients, drugs (especially opiates and benzodiazepines) are the most common culprits causing delirium in cancer patients. Older patients, as well as patients with structural brain disease; vascular disease; or lung, kidney, or liver impairment, are predisposed to delirium.[66] Specific cancer-related syndromes involving cognitive impairment in cancer patients are listed in the subsequent paragraphs.

Hypercalcemia

Hypercalcemia (in patients with metastatic lesions to the bone or with tumor-related ectopic production of parathyroid hormone–related protein) secondary to cancer can cause cognitive impairment or delirium. Hypercalcemia is associated with both fatigue and thirst. A serum protein-bound calcium count below 11 mg/dL may initially appear normal when the free calcium is elevated or when serum albumin is low and not taken into consideration. Hypercalcemia can be treated with diphosphonates, hydration, and diuresis.

Hyponatremia

Hyponatremia, a common in-hospital metabolic abnormality, often results from the syndrome of inappropriate antidiuretic hormone (SIADH) (secondary to paraneoplastic syndrome, especially from small cell carcinoma, but also from non–small cell lung cancer, mesothelioma, pancreatic

cancer, duodenal cancer, lymphoma, endometrial cancer, leukemia, and other conditions). SIADH is associated with lung infections, cerebral tumors, brain injuries, and use of many psychotropic medications (e.g., phenothiazines, SSRIs, carbamazepine, and tricyclic antidepressants [TCAs]). If the sodium is less than 125 mmol/L or if it falls rapidly, it may cause agitation, confusion, and hallucinations; chronic hyponatremia is associated with falls and inattention in the elderly.[67]

Brain Tumors

Some patients with cancer become confused in association with brain metastases. The incidence of primary brain tumors is 6.6 per 1,000,000, but the rate of metastatic brain tumors is higher (ranging from 8 to 11 per 100,000). While the majority of brain metastases originate in the lung, melanoma is most likely to metastasize to the central nervous system. The incidence of brain metastases is 20% for lung cancer, 7% for melanoma, 6.5% for renal cancer, 5% for breast cancer, and 2% for colorectal cancer.[68] Brain metastases are less common but also occur with sarcoma and thyroid, pancreatic, ovarian, uterine, prostate, testicular, and bladder cancers. In patients with small cell lung cancer, brain metastases are anticipated, and prophylactic whole brain radiation is often recommended.[69] Isolated brain metastases caused by non–small cell lung cancer may be treated surgically, and modern radiation techniques target small areas of the brain.

Patients with primary brain tumors, particularly low-grade tumors, present problems for cancer diagnosis and chronic brain injury. Tumors (particularly of the frontal, temporal, and limbic lobes) that affect the hardwiring of motivation, attention, mood stability, and memory come to psychiatric attention. Temporal lobe epilepsy can be associated with neuropsychological symptoms (e.g., memory dysfunction, anxiety, hypergraphia, viscosity). For these patients neuropsychiatric consultation, testing, and cognitive rehabilitation may be of critical importance to define and treat the specific loss. Multimodal interventions for attention, memory, word-retrieval, and problem-solving abilities may be appropriate.[70] Loved ones can understand more clearly the basis of some limitations, and the patient can acknowledge his or her deficits and take whatever control is possible. Psychotropic medications, used appropriately, are adjuncts to anticonvulsants and anticancer treatment.

Leptomeningeal Disease

In the syndromes of carcinomatous meningitis, or leptomeningeal disease, cancer cells infiltrate the meninges or obstruct the flow of cerebrospinal fluid. If there are no focal signs or findings on neuroimaging, the associated malaise may be considered (erroneously) psychiatric. Cranial nerves (particularly III, IV, VI, and VII) may be affected. Mental changes, headache, difficulty with walking, limb weakness, and seizures are common. Dizziness and sensorineural deafness have also been noted. The tumors most often implicated are breast cancer, lung cancer, and melanoma; the histology usually involves adenocarcinoma. Leptomeningeal disease also occurs with non-Hodgkin's lymphoma, leukemia, and cancers of the head and neck, cervix, ovary, kidney, and bladder. Malignant cells in the cerebrospinal fluid confirm the diagnosis, but a sufficiently large fluid sample improves the chance for a positive diagnosis; 50% to 70% may be falsely negative. A magnetic resonance imaging (MRI) scan of the brain may be unremarkable in 20% but more likely will show hydrocephalus, brain metastases, or contrast enhancement of the sulci or cisterns.[71,72]

Delirium in Stem Cell Transplantation

In patients who receive a peripheral stem cell transplantation, delirium is common because of metabolic abnormalities, infection, and subdural or intraparenchymal brain hemorrhage. Wernicke's encephalopathy has occurred rarely. An engraftment syndrome may cause delirium with fever, headache, and rash. Usually this syndrome occurs when the neutrophil count is greater than 500/mm^3 and with a cytokine effect of the hematopoietic colony-stimulating factors.[73,74]

In the transplant setting, immunosuppressive drugs (e.g., cyclosporin, tacrolimus, the antifungal drug amphotericin B) can cause delirium. Hypertension, use of steroids, uremia, and previous radiation to the brain are risk factors.[75] Drug serum levels may facilitate diagnosis; tremor occurs in 40%, and paresthesias in 11%. Hypomagnesemia increases the risk of seizures. Immunosuppressants are rarely associated with a syndrome of reversible posterior leukoencephalopathy that causes headache, visual loss or blurring, visual hallucinations, and confusion.[76] Parkinsonism, ataxia, or dystonia may also occur. White matter edema is documented in the parieto-occipital area on fluid-attenuated inversion recovery (FLAIR) sequences. If this syndrome has occurred with one immunosuppressant, either tacrolimus or cyclosporin, the other may be used.[77]

Hyperviscosity Syndrome

Hyperviscosity syndrome in myeloma or lymphoma patients results from paraproteins that impair blood circulation in the brain. A serum viscosity level above 4.0 centipoise (1.56 to 1.68 cp) has been associated with symptoms.[78,79] The clinical signs are bleeding, visual signs and symptoms, and delirium.

Hyperammonemia

Idiopathic hyperammonemia may be associated with lethargy, confusion, ataxia, coma, and death in patients with cancer. Although extremely rare in this population, it occurs more often in those with hematologic malignancies who are neutropenic following bone marrow transplantation and in patients with solid tumors receiving 5-fluorouricil.[80] Management centers on limiting protein intake and on increasing ammonia excretion, both through use of ammonia-trapping agents and, if necessary, hemodialysis. Hyperammonemic encephalopathy is also an uncommon but severe complication of multiple myeloma and, in this instance, seems to improve with appropriate chemotherapy.[81]

Cushing's Syndrome

Cushing's syndrome may cause delirium, psychosis, and muscle weakness in adrenocortical carcinoma or tumors with paraneoplastic production of adrenocorticotropic

hormone (ACTH). Psychiatric disorders are a feature of the syndrome of ectopic ACTH production in 53% of patients. Specific treatments for this syndrome include steroidogenesis inhibitors or glucocorticoid receptor antagonists (e.g., ketoconazole, metyrapone, aminoglutethimide, opDDD, etomidate, or mifepristone).[82]

Paraneoplastic Neurologic Disorders

Paraneoplastic neurologic disorders include a myasthenic syndrome, cerebellar degeneration, or diffuse encephalomyelitis.[83] These syndromes may manifest before the cancer is diagnosed. An afflicted patient may develop an immune reaction against neural tissue when exposed to a tumor antigen that reacts against normal nervous system tissues in the setting of dying tumor cells. The exact mechanism of the immune reaction has not been established. Typically, there are more T and B cells and plasma cells in these tumors. Small cell lung cancer is the tumor most commonly associated with this syndrome, and anti-Hu antibody syndromes are often noted.[84]

Limbic Encephalitis

Limbic encephalitis is a specific autoimmune encephalopathy that causes memory difficulties, anxiety, depression, agitation, confusion, hallucinations, and complex partial seizures. This syndrome is most likely to occur in the context of small cell carcinoma of the lung and more likely related to anti-Hu antibody, but it also occurs with Hodgkin's lymphoma; thymoma; and cancers of the testes, breasts, ovaries, stomach, uterus, kidney, thyroid, and colon.[83,85] Changes in mood and personality occur over weeks. Recent memory is affected more than remote memory. In one third of patients the neurologic findings are limited to the limbic system. MRI findings, if present, include abnormal hyperintensity on the T_2-weighted image, sometimes with contrast. Anticonvulsants and empirical use of psychotropic medications may be the only aid as the tumor is diagnosed and treated. The prognosis is limited.

Toxic Leukoencephalopathy

White matter injury can be an early, a temporary, or a late consequence of cancer treatment. Whole brain radiation and certain anticancer drugs (including methotrexate, carmustine, cisplatin, levamisole, fludarabine, thiotepa, ifosfamide, cytarabine, and fluorouracil) can injure the projection fibers, association fibers, and commissural tracts that affect cognition and emotion. Acutely, confusion is related to patchy, reversible edema and later to widespread edema and demyelination. More severe delayed consequences result from loss of myelin and axons related to vascular necrosis and thrombosis. Risk of leukoencephalopathy is related to patient age, total dose of radiation, fraction size, and timing of chemotherapy. In most cancer protocols, the doses and timing have been adjusted to minimize these adverse effects. However, patients with vulnerable brains or delayed metabolism of the drug may be unexpectedly affected. Neurobehavioral sequelae occur acutely in 28% of patients and are a consideration in cancer survivors.[86]

The frontal lobes, the lobes with the most white matter tracts, are the ones most likely to be injured. Patients with mild leukoencephalopathy may complain of difficulty with concentration and vigilance as well as problems with attention. Apathy, anxiety, irritability, depression, or changes in personality may be seen with memory loss, slowed thinking, and failure of executive oversight. In more severe cases, dementia, abulia, stupor, and coma occur with necrotic areas and diffuse hyperintensity of white matter seen on the MRI scan. This injury, unlike that seen in Alzheimer's disease, spares language, praxis, perceptions, and procedural memory. The key bedside tests on mental status examination are the elements that test attention (e.g., digit span, serial sevens, three-word delayed recall, clock-drawing test for visual–spatial skills and alternating motor sequences for frontal function). The contribution of white matter injury should be documented on the T_2-weighted MRI.[87]

This toxicity is seen in patients who have received high-dose methotrexate and radiation treatment for childhood acute lymphoblastic leukemia (ALL) or primary central nervous system lymphoma. In the latter a rapidly progressive subcortical dementia with psychomotor slowing, executive and memory dysfunction, behavioral changes, ataxia, and incontinence can be seen. Diffuse white matter disease and cortical–subcortical atrophy are also noted.[88]

Toxic effects of drugs or radiation may add to white matter damage of hydrocephalus, trauma, alcoholism, and hypertension. Patients with a history of psychosis or affective disorder also tend to have more evidence of abnormal white matter on imaging.

Cognition and Sleep Changes Related to Chemotherapy or Hormonal Change

Patients receiving adjuvant chemotherapy for breast cancer complain about troubles with working memory and concentration. Despite the reputation of "chemo brain," subjective complaints often do not match the deficits seen on neuropsychiatric testing. At the very least, fatigue, catabolic treatment effects, and hormonal changes combine to cause impairment that seems to improve gradually. In half of the published studies that test breast cancer survivors in the neuropsychological domain, memory has been affected.[89] Patients in greater distress report more cognitive failures but not specific neuropsychiatric deficits.[90]

Women who receive adjuvant treatment for breast cancer often develop menopausal symptoms because of a direct effect on the ovary that decreases hormone levels and hastens menopause. Menopause is a goal of treatment for those with estrogen receptor–positive tumors.[91] Estrogen therapy, however, may selectively improve executive function during verbal-recall tasks, and women may notice the loss of estrogen.[92] Estrogen treatment during perimenopause has been associated with regional benefits, for instance in the posterior cingulum.[93] Raloxifene, a selective estrogen-receptor modulator (at 20 mg per day), tended to slow cognitive decline over 3 years in postmenopausal women (regarding verbal memory and attention).[94]

Tamoxifen is a mixed agonist–antagonist of estrogen that is associated with hot flashes and insomnia. Aromatase

inhibitors reduce estradiol to barely detectable concentrations. There seem to be no distinctions in quality of life measures in women taking tamoxifen or an aromatase inhibitor (e.g., anastrozole), and vasomotor symptoms are frequent with both drugs. Endocrine-related vaginal symptoms are worse at 3 months but improve slightly or stabilize thereafter. About 10% report mood swings and irritability.[95,96]

In menopausal women and women who undergo estrogen deprivation therapy for breast cancer, SSRIs reduce the frequency and severity of hot flashes and improve mood, sleep, anxiety, and quality of life. The reduction in hot flashes may be related to the affinity of the norepinephrine transporter because the benefit is not consistently seen with citalopram or fluoxetine.[97–100] Venlafaxine (extended release 75 mg per day) and paroxetine (20 mg per day) have shown benefit. Gabapentin (300 mg tid) has also been beneficial.[101] A pilot study suggested that bupropion did not have a similar benefit.[102] Hot flashes are also a problem for men with prostate cancer treated with pituitary antagonists (e.g., leuprolide).[103]

Treatment of Cognitive Deficits

Some causes of impaired cognition associated with cancer are treatable. Sobriety can lead to reversal of atrophy and to improved cognitive function in alcoholic dementia, a condition with disproportionate white matter damage, particularly in the frontal lobes. Oxygen treatment, at night or all day, may improve the cognition of lung cancer survivors who are chronically hypoxic. Stimulants may improve attentional deficits. Erythropoietin and an intervention with four visits and three phone calls, education about possible problems, stress management, arousal management, and compensatory strategies for memory and attention improve cognitive function and energy in patients with hemoglobin levels below 12.[104]

Diagnosis and treatment of delayed hypothyroidism may improve thinking in cancer survivors. Radiation over the neck, for instance, for Hodgkin's disease, can injure the thyroid, and radiation to the head may affect the pituitary. Thyroid-stimulating hormone is high if the thyroid itself is injured, but recognition of secondary hypothyroidism because of a pituitary injury would require measurement of free thyroxine.

Survivors of Childhood Cancer

The most common diagnoses for children with cancer are leukemia, lymphoma, brain tumors, osteogenic sarcoma, Ewing's sarcoma, and Wilms' tumor. Childhood cancer is now more commonly considered a serious chronic illness rather than a uniformly terminal illness. Child psychiatrists work side by side in the outpatient setting with the pediatric hematology–oncology teams to treat the emotional needs of the child in age-appropriate ways during active treatment and thereafter. With consideration of the child's stage of development, psychiatrists can judge what the child will understand and what the child will want and need to know.

The most common consultation questions include evaluation of the child with anticipatory anxiety, sleep disturbances, behavioral problems, or mood changes. Anticipatory anxiety still affects many children despite advances in antiemetic medication. The child may feel nauseated or vomit on approaching the hospital, clinic, or phlebotomist. Behavioral modification, visualization and relaxation, and medication are helpful. Sleep disturbances may be related to the child's worries about the illness or to medications such as steroids. Child psychiatrists are also consulted for behavior problems in younger children who become more aggressive or difficult to manage. The emphasis in treatment of depression or withdrawn states is on the child's ability to enjoy life. Overall, children tend to be quite resilient. Although children and parents are very distressed at the time of diagnosis, the prevalence of psychological problems among survivors of childhood cancer is similar to that in the community.[105]

Children treated for ALL or a brain tumor with cranial irradiation are at risk for cognitive decline,[106] which is progressive over at least 10 years (possibly related to a radiation-induced microvasculopathy). Children are particularly prone to radiotoxicity in the first 2 years of life because of the rapid growth of the brain and white matter development in those years. Cognitive defects have been seen in verbal comprehension, perceptual organization, distractibility, and memory in survivors of ALL, and visual–motor integration, sequential memory, fine motor coordination, processing speed, and math abilities may also be affected. Risk factors include young age, female gender, and time since radiation; the volume and dose of radiation are also thought to be factors. The combination of radiation treatment and intrathecal methotrexate increases the risk of cognitive impairment. Children exposed to cranial irradiation may also suffer from hypothyroidism and growth hormone deficiency. Children who have been treated for leukemia or brain tumors should be monitored for cognitive and endocrine dysfunction.

CONCLUSION

Psychiatrists can help patients cope with affective, behavioral, cognitive, and physical symptoms associated with cancer and its treatment as well as with developmental losses, changes in relationships, and the effects of cancer on families.[107]

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28

Burn Patients

Megan Moore Brennan, M.D.
Atilla T. Ceranoglu, M.D.
Gregory L. Fricchione, M.D.
Frederick J. Stoddard, Jr., M.D.

Burn injuries are as ancient as fire. All afflicted individuals need help and many require psychiatric consultation; their psychiatric care is as challenging as their surgical care.[1] Physicians and nurses new to a burn unit often experience trepidation and fear, but these feelings moderate as they relieve pain, help patients survive, and see the repair of disfiguring scars. Nevertheless, the burn unit is stressful for all—viewing an acutely burned infant, child, or adult can satisfy the stressor criteria for posttraumatic stress disorder (PTSD) and evoke nightmares in staff and patients.

Burn units bring together specialists from several disciplines. The Massachusetts General Hospital (MGH) Level 1 Trauma Center treats burned adults at the MGH and children at the affiliated Shriners Burns Hospital; together they treat about 400 acute burn patients per year. Since 9/11, all burn centers in the United States have enhanced their disaster preparedness; psychiatric education regarding disasters is important for staff on burn units in order to enhance resilience and increase preparedness.[2]

HISTORY

The current era of burn treatment and research began more than 60 years ago at the MGH after the Cocoanut Grove fire on November 28, 1942. Cobb and Lindemann,[3] eminent early MGH psychiatrists, collaborated with other physicians and surgeons and chronicled the deliria and posttraumatic reactions of the survivors of that terrible tragedy in which 491 people died. Lindemann,[4] in a classic paper (based in part on his work with 13 bereaved disaster victims of the Cocoanut Grove fire and their close relatives and with relatives of members of the armed forces), reported for the first time the symptoms and psychotherapeutic management of acute grief. Their studies involved psychiatric treatment and subsequent research on grief that would be applied to soldiers, civilians, and the bereaved.

Burn injuries challenge hospital staff and hospital systems. In 2003, as in the Cocoanut Grove fire, The Station nightclub fire in Rhode Island wreaked havoc. It resulted in 100 deaths and tested emergency and burn trauma disaster plans at the MGH, the Shriners Burns Hospital, and the entire region; the triage system worked superbly. Unlike the September 11, 2001 terrorist attacks when staff readied for transfers to their burn units but were disappointed with how few survived to be treated, scores survived (despite severe burns to the lungs, face, hands and upper body) this nightclub fire because of the advances in modern burn care. As described earlier by Cobb and Lindemann,[3] some of these survivors, their children, and other relatives developed and were treated for survivor guilt, traumatic grief, and what is now recognized as PTSD.

In the last 35 years, strong leadership and new research have led to improved methods of resuscitation and transportation, excision and grafting,[5] anesthesia,[6] pain control,[7,8] anxiety management,[9] pulmonary care,[10] cardiovascular and infection control, application of artificial skin and skin substitutes,[11] psychiatric assessment and treatment (Table 28–1), plastic surgery techniques,[12] and rehabilitative efforts that include interventions for those with disfiguring facial and body burns. Taken together, these innovations have dramatically improved both mortality rates and the morbidity associated with burn injuries in the United States.

Just as Cobb and Lindemann did for adults, Bernstein,[13] Galdston,[14] and others pioneered the psychiatric care of burned children and their families; moreover, they conceptualized consultations to the burn team. Childhood injuries, including burns, are now, after years of neglect, a priority for medical research and treatment.[15] A key resource regarding education about, and research for, burn care is the American Burn Association,[16] which is linked to federal agencies, a variety of foundations, and the International Society for Burn Injuries. Many patients also benefit from self-help groups, like the Phoenix Society, which is an international organization for children and adults with burns (and their families).[17] Its mission is to increase our understanding of burned individuals and to support their care.

EPIDEMIOLOGY

Because of improved fire and burn prevention, and the expansion of burn centers in the United States, acute hospitalizations for burn injuries were cut in half between 1971 and 1991.[18] Between 2001 and 2002, the majority of acute burns admitted to burn centers shifted from referrals from outside hospitals to direct admissions from pre-hospital settings, likely a result of efforts to streamline triage to regional burn care centers.[19] Roughly 1.25 to 2.5 million burns occur annually in the United States; these account for about 5500 deaths,[15] of which about one third occur in children.

TABLE 28–1 Ten-Point Plan for Consulting to Burned Patients

1. Speak with the patient at the bedside, and ensure the patient's safety.
2. Consult directly to the burn or trauma team, the surgeons and other physicians, nurses, social worker, and others, about the patient, clarifying your time availability and role. Within psychiatry, arrange for supervision, peer consultation, and departmental support.
3. Obtain the history of the burn circumstances, psychopathology, or substance abuse, and social and family function.
4. Diagnose the patient: Assess the developmental stage, burn severity, other stressors, mental status (including pain, stress, memory), psychiatric risk (delirium, suicide, child abuse), prognosis, medical and surgical issues including medications and their interactions, alcohol or drug withdrawal, current risk factors, language/cultural factors, legal status, and staff or family concerns. Recommend special studies or consultations as indicated.
5. Monitor, explain, and treat pain, delirium, stress, insomnia, and depression. Provide staff support and, for complex cases, plan a team conference.
6. Assess, treat, and support the dying child or adult and the family, and assist the clarification and the resolution of ethical dilemmas.
7. When the patient has survived the acute phase, progress to treating residual mental disorders, substance abuse, and other problems.
8. Facilitate grieving and adaptation of the patient and family to cosmetic or functional losses.
9. Collaborate in planning plastic and reconstructive surgical follow-up if possible and communicate psychiatric findings and recommendations to the primary care physician. Support re-entry to school or work, including special education and rehabilitation services.
10. Remain available for follow-up consultation to the patient and caregivers, clarifying the psychiatric issues, and assist the patient and family in obtaining psychiatric services if needed.

According to the National Burn Repository 2007 report,[20] which compiled acute burn admission data between 1998 and 2005 at 73 hospitals in 33 states, nearly 70% of cases were men and the mean age was 35 years (children under the age of 5 years accounted for 12% of the cases, whereas those over the age of 60 years represented 14% of cases). Most (69%) individuals had less than 10% total body surface area (TBSA) burns. The two most common types of burns were from fire and scalds, the latter being most prevalent in children under the age of 5 years and in the elderly. Other mechanisms that led to burn care, in decreasing order of prevalence, included contact with hot objects, electrical burns, chemical burns, skin disease, and radiation exposure. The vast majority of burns are non–work accident related (63.9%); next are work-related accidents (15.4%), other (7.1%), recreational accidents (4.6%), and cases of suspected assault/abuse (1.6%), suspected child abuse (1.2%), suspected self-inflicted (1.2%), and suspected arson (0.1%).

The most common complications of burn treatment are pneumonia, respiratory failure, cellulitis, septicemia, and wound infection; these clinical complications are in large part a function of the number of days spent on the ventilator (with the risk increasing dramatically after four or more days). The average length of hospital stay for survivors is best approximated by figuring on one day per percent TBSA burns.

TYPES OF BURNS

Burns are classified by the depth of the injury (from first- through fourth-degree burns).[21] First-degree burns are characterized by intact epithelium (that is pink, dry, and painful); these burns require no specific care. Second-degree burns are wet, pink to red, and edematous; these changes signify that the dermis is damaged. These burns are further categorized into superficial and deep and they must be monitored closely. Third-degree, or full thickness (of dermis), burns are leathery, dry, and lack sensation; these burns require surgical treatment. The most severe burns are fourth degree; these extend through the subcutaneous tissue to the tendons, muscles, and bones and they require complex surgical reconstruction.

The operative treatment of burns includes wound débridement, escharotomy and fasciotomy (release of burned skin and muscle, respectively), and grafting. The nonoperative treatment involves daily wound care (performed multiple times each day) and systemic care and management of associated medical and surgical problems.[21]

RISK FACTORS

Risk factors for burn injuries are different for children, adults, and elderly. A combination of developmental and familial factors contribute to the risk of burns in children. Increased exploration by young children, access to scalding or flammable liquids or flames, childhood depression, behavioral disturbances, and parental psychopathology each predispose children to burns. Burns to children should not be indiscriminately labeled as due to neglect or to abuse because, on careful assessment, they may be the result of a combination of developmental, environmental, and family variables. However, child neglect or abuse accounts for between 6% and 20% of pediatric burns; the age of maximum risk of abuse is 13 to 24 months, and scalds are the most common type of inflicted burn.[22] Factors suggestive of abuse include a caretaker's changing the story of what occurred (from one interview to the next), prior injuries or accidents, a parent who neither visits nor is attentive, a consistently awake but withdrawn child who appears immune to pain, a burn distribution inconsistent with the history, and other signs of abuse (e.g., fractures).[23] Suspected abuse must be reported to the appropriate state agency in most states.

Among adults, risk factors for burns include drug and alcohol intoxication and dependence,[24] major mental illness, an antisocial personality disorder, and exposure to occupational hazards (Tables 28–2 and 28–3).[24–32] Certain populations, such as the homeless and the elderly, have an

TABLE 28–2 Risk Factors for Burns in Adults

Alcoholism
Drug abuse
Depression
Suicide attempts
Antisocial personality disorder
Schizophrenia
Bipolar disorder
Chronic medical illness
Dementia
Abuse/homicide
Occupational hazards

TABLE 28–3 Risk Factors for Burns in Child and Adolescents

Neglect
Abuse
Poverty
Unsafe housing
Family discord
Risk-taking behaviors
Learning disabilities
Depression
Fire-setting

increased risk of burns. Homeless patients are more likely to be assaulted by burning and to have higher rates of substance abuse and psychiatric illness as compared with domiciled burn patients.[33] Demented elders are also at risk for burns; scalds are more common than flame burns and typically occur during routine activities of daily living.[25]

PREBURN PSYCHOPATHOLOGY

Psychiatric illness is overrepresented in individuals with burn injuries. Dyster-Aas and associates,[34] in a prospective case series of 73 patients with burns, used structured clinical interviews and found that two thirds of patients had at least one lifetime psychiatric diagnosis (i.e., major depression [41%], alcohol abuse or dependence [32%], simple phobia [16%], and panic disorder [16%] were most common). Wisely and co-workers[35] looked at 72 patients admitted to a burn unit over a 5-month period and found that 35% had a psychiatric diagnosis before the burn; depression, drug and alcohol abuse, personality disorders, and psychotic disorders were most often detected.

Individuals with self-inflicted burns often have a high prevalence of severe mental illness (e.g., schizophrenia or major depression).[36–38] One review of 582 patients with self-inflicted burns found that 78% had a psychiatric history,[37] an increased likelihood of psychotic symptoms, of being prescribed psychotropic medication at the time of the burn, and of being a psychiatric inpatient.[39] Our experience also shows that patients with bipolar disorder (while manic), schizophrenia, a conduct-disorder, and alcoholism are at risk for self-immolation. Sometimes it is difficult to discern whether a burn was accidental, a parasuicidal gesture, or a *bona fide* suicide attempt. Attempts at suicide via self-immolation occur worldwide and often result in massive, disfiguring burns.[40]

A study of adolescent self-immolators revealed serious untreated or partially treated psychopathology (including drug abuse, psychosis, intense conflict with parents, and physical or sexual abuse). Studies of adults have similarly found elevated rates of alcoholism, depression, psychosis, and personality disorder as preexisting factors.[41–43] These patients tend to arouse intense feelings in caregivers and are among the most difficult surgical and psychiatric patients. Despite their burns and severe psychopathology, most patients cope well with psychiatric treatment that is initiated on the burn unit.

Finally, in some parts of the world, suicide attempts may turn out to be homicide attempts as part of the "honor killing" of victims accused of incest or of seducing a rapist.[44] The psychiatrist, consulting to units where patients may be admitted from around the world, must be aware of patients' cultural and ethnic background in order to understand the circumstances surrounding the burn injury. Unfortunately, because of barriers in reporting, an exact estimate of prevalence of these injuries is not known.

ASSESSMENT AND MANAGEMENT OF PATIENTS WITH BURNS

Psychiatrists who work in the general hospital are frequently called to assess burned patients. The role of the psychiatrist changes in parallel with the patient's recovery; in general, it begins with a brief assessment in the acute phase that focuses on management of delirium and pain, then it morphs to the evaluation and treatment of symptoms of PTSD in the months after the burn, and then it targets psychosocial adjustment to disfiguring burns in the years after the burn. These phases can be divided into acute, intermediate, and long-term recovery.

Diagnosis and Developmental Assessment

Setting the stage for a discussion of the acute, intermediate, and long-term management of burn patients, we will review a diagnostic approach that incorporates a developmental model; this aids in the formulation and treatment of all medical and psychological problems experienced by the burned patient. This is particularly important for assessing children; consideration of the developmental stage provides the necessary context for understanding children's responses to trauma.[45] A developmental model for the assessment of burned children follows[46]; it has been supplemented by a developmental model that is useful throughout the life cycle.[47] For infants through adolescents, additional discussion relating to developmental stage is provided before the case example.

Developmental Stage and Burns: Case Examples

Infancy (Birth to 2.5 Years Old)

Infancy is the period from birth to emergence of language (typically until 2 to 2.5 years old). Infants experience the world in the moment and require immediate gratification of needs, whether related to pain, hunger, or absence of nurturance. For infants there is little separation between them and their primary nurturer; burn injuries, with the

necessary procedures and monitoring involved, inevitably disrupt this primary attachment. As much as possible, pediatric burn care minimizes the disruption by providing surrogates to mitigate the depressive reactions to absent parents and by providing as soothing and nurturing an environment as possible. Because of infants' cognitive immaturity and inability to make sense of what is happening to them, they take their cues largely from parents and caregivers, who (witnessing their infant in pain, and having fears of death and disfigurement) typically experience significant guilt and distress over the burn circumstances. Care of the burned infant is inevitably intertwined with care of the parents; the more stable the parents, the better the infants' recovery.

Case 1: A 4-month-old girl was admitted with 20% TBSA scald injuries to the face, neck, and chest. Her parents felt intense self-reproach and feared future scars; intermittently they had difficulty soothing her because of their own distress. Psychiatric consultation was requested to deal with her refusal to eat, her crying in anticipation of painful dressing changes, and her anxiety that was aroused by her mother's departure for home to be with her older children. With support of nursing staff, social work, and child psychiatric staff, the mother roomed with the infant, pain was reduced by use of opiates, and the infant healed with skin grafting (over a 2-week period) and appeared to resume her normal developmental course. This case illustrated typical signs of distress in a burned infant, manifestations of parental stress, and an approach (involving the parents and the child) to intervention.

Preschool Age (2.5 to 6 Years Old)

Egocentricism (belief that world revolves around them and that others see the world from their perspective alone), magical thinking (interweaving of reality and fantasy such that medical events have magical causes), and preoccupations with body integrity are the hallmarks of preschool children. Children in this age group may develop notions of guilt and punishment during the hospitalization and see injuries and painful treatments as punishment for bad deeds or thoughts. Some may regress, withdraw, and stop speaking. The child psychiatrist provides understanding and reassurance to relieve guilt-ridden parents. Similar to infants, preschool children are generally interviewed with the parent present. As the children get older, therapeutic play with drawings, puppets, and games is often used as both a diagnostic and therapeutic tool. Through play they can safely show their cognitive skills, express their feelings and traumatic memories, and resume normal development.

Case 2: A 3-year-old boy with smoke inhalation and 30% TBSA burns, mostly partial thickness, became increasingly withdrawn, except when in his brother's company; when with his brother, he would play with toys and be more outgoing. He was interpersonally inhibited and afraid of wound dressing changes. His pain was only partially relieved by oral morphine and lorazepam; he clung to nursing staff, and he appeared to regress. His speech was indistinct; what he did say was repeated over and over. Consistently somber, he stared silently at staff and did not speak or interact in a meaningful way. Psychiatric assessment determined that he suffered from a combination of an acute stress disorder and a mild anoxic brain injury. These conditions,[48,49] and possibly depression, were the consequences of his burn.

School-Age (7 to 12 Years Old)

Ability to understand their bodies, curiosity, a rule-bound cognitive style, and continuous efforts to gain control are the hallmarks of school-age children. With respect to burn injuries, they will want to understand the injury and its treatment and seek to gain control over it. They benefit from having a schedule of the treatments and other activities.

Case 3: A 10-year-old boy sustained 40% TBSA electrical burns when his kite got entangled on high-voltage electrical wires. His treatment involved frequent wound dressing changes, which he tolerated well initially. However, he refused to start physical therapy and this reluctance spread to his participation in wound care; he would yell and cry upon seeing medical supplies. On interview, he told the psychiatrist that he never signed up for physical therapy and that the exercises were very painful; he felt the assignments were unfair. With the surgeon and nurse taking time to explain the need for, and the prospected course of, these treatments (providing the duration of each session and their frequency) and eliciting his questions, he became visibly relaxed and ready to work out a schedule that allowed him to watch his favorite cartoons before and after his wound dressing changes and physical therapy sessions.

Adolescence

Although adolescents have the capacity to understand the injury, its treatment, and ramifications on their lives, they remain quite vulnerable. This stage of development is marked by striving for independence while managing ongoing dependency on their parents. Additionally, fitting in with peers and maintaining one's body image are of paramount importance to teenagers; therefore the potential disfigurement related to burn injuries can be particularly devastating to them.

Case 4: A 15-year-old boy sustained 85% TBSA flame and inhalation injuries in a grease fire from a cookstove; a friend perished in the fire. Trouble sleeping, bad dreams, and flashbacks of the fire plagued him. Nightmares persisted for 6 weeks. He tried to think about "positive things during the day" so that his dreams would be positive. One month later, he described a different type of dream. He described romantic fantasies about a female staff member who was caring for him. He was relieved to hear from the psychiatrist that such dreams were not unusual when a close relationship develops between a patient and a caregiver. He became able to acknowledge age-appropriate emotions. Near discharge, his nightmares of the fire recurred, as did positive dreams related to returning home and resuming his life. This case illustrates how dreams of burned patients can evolve and how they can be used to adapt to severe injury.

Young Adulthood

Case 5: A 23-year-old father of two was admitted with 40% TBSA burns to his face, neck, upper torso, and arms following a house fire. He received morphine for pain and diazepam for anxiety. He became acutely delirious (with agitation, disorientation, and combativeness), which required physical restraints and 10 to 20 mg of IV haloperidol per day for the first few days of the admission. The delirium seemed secondary to smoke inhalation and cerebral anoxia. He healed well over a 2-week period, and all medications (except for morphine that was used for dressing changes) were tapered. He was observed to be inappropriate, "strange," and to be "more like a kid." Psychiatric reassessment also revealed terror and posttraumatic intrusive thoughts and nightmares of the fire. He faced several stressors (e.g., severe burns suffered by his wife, two young sons, and younger brother) and his grief was intense. He recalled, but was unable to cope with, images of the fire and the injuries to himself and his loved ones; they were all nearby, in various stages of recovery. He responded well to emotional support, to clarification, and to reassurance, as well as to tranquilizers that restored adequate sleep and reduced the intensity of his terror. This case illustrates the combined effects of anoxic brain injury, delirium, acute stress, and acute grief in a young adult.

Elderly

Case 6: A 77-year-old woman caught her housecoat on a gas stove and sustained 15% TBSA first-degree and second-degree burns to her left side. Care providers called her "lovely" but cognitively impaired. She had a history of valvular disease with congestive heart failure (CHF), metastatic breast carcinoma (requiring bilateral mastectomies), and deep venous thrombosis (DVT). Confusion decreased when doses of diazepam and morphine were reduced. This case involved an ill, elderly woman who responded slowly, but well, to acute care.

Acute Phase: Assessment and Treatment

From the day of admission, assessment and treatment proceed hand in hand. Initial assessment is often difficult and history must often be obtained from others,[46] because the patient may be unable to communicate.[50] When reviewing the record, the consulting psychiatrist pays particular attention to all aspects of the initial presentation (e.g., police and emergency medical service records [that describe the circumstances in which the patient was found], toxicology screens [that yield important information about drugs and alcohol and risk for withdrawal], and chemistries and tests of kidney and liver function [that reveal current contributions to delirium]). Special studies, including brain imaging (when there is concern for head injury, stroke, severe hypoxic insult, or worsening mental status not explained by available data) and electroencephalography (EEG) (when there is concern for seizure or to verify presence of delirium) are often indicated.

Explanations about the burn and its treatment are followed by an assessment of the efficacy of these interventions. Communication should involve a vocabulary that the patient can understand and should be appropriate to the patient's cognitive and emotional ability. Because a burned patient may be confused, afraid of death or dismemberment, and anxious about pain, the initial history may need to be obtained from other individuals. Explanation, reassurance, and relief of pain help to reduce fear and confusion. A formal mental status evaluation is necessary to diagnose subtle changes in mental function. The patient's initial emotional reactions (e.g., denial, fear, guilt, grief, anger, or emotional withdrawal) should be noted. A history of developmental, mental, or substance abuse disorders; medical illness; and psychiatric treatment should be obtained; the social context should also be established. When family members understand, feel supported, and are reassured, they are better able to calm their loved one; however, when this support is absent the opposite is often true. As an alliance with the patient and family develops, additional history typically clarifies the circumstances of the injury.

In the acute assessment of children, the psychiatrist routinely assesses for abuse and neglect. Clinginess to nursing staff, exacerbation of fear response in the presence of parents or caregivers, and co-existing injuries not explained by the burn (e.g., fractures, bruises, soft tissue contusion, cigarette burns), should raise concerns of child abuse or neglect. Protective measures should be taken and mandatory reporting to social services completed.

Burn-Induced Delirium

Burn-induced delirium usually occurs soon after the injury and it portends an increased risk of death. The confused, agitated, or aggressive patients can hit staff, attempt to leave the hospital, fall, self-extubate, and dislodge intravascular lines and skin grafts. Delirium occurs in approximately 10% to 30% of burn patients and signals the patient's unstable condition; the more severe the burn the more likely it is that delirium will develop. With severe burns, patients are often kept anesthetized and intubated until grafting is completed; thus, acute delirium is often masked. Delirium has multiple causes; a more complete discussion of this subject can be found in Chapter 10. Prompt evaluation, the maintenance of safety (which may necessitate the use of restraints), treatment of the causative factors, and institution of environmental changes and supportive personal contact with staff and family are indicated.[51,52]

Acute Stress Disorder

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)[53] criteria for acute stress disorder (ASD) include symptoms of dissociation, re-experience of the trauma, avoidance, and anxiety or arousal. The symptoms must last for at least 2 days and occur within 4 weeks of the trauma; the condition is not due to drugs or medications or to the patient's medical condition. Some studies have found symptoms of acute stress occur in 11% to 32% of burn patients; the rates vary in part by virtue of the measurement methods used.[31,54,55] Risk factors for developing ASD include the scope of the burn, poor premorbid mental health, and the tendency to blame others for the burn.[56] Awareness and recall of the injury may be delayed until

opiates and benzodiazepines are tapered, at which time the intrusive recollections, nightmares or night terrors, and associated arousal states may begin. In children, emotional withdrawal or overreactivity may occur in association with re-experiencing or with hyperarousal. They may become agitated or combative during wound dressing changes or other painful procedures; having parents leave the room during these treatments may exacerbate the child's reaction. Later in the recovery period depression may develop, with interpersonal withdrawal and a decreased appetite. In children, anhedonia, sleep and appetite disturbances, emotional withdrawal, and irritability are the most common accompaniments of depressed mood. Brief supportive psychotherapy, alliance building, treatment of pain and anxiety, and provision of appropriate reassurance are of benefit.

PAIN ASSESSMENT

Pain is ubiquitous in burn patients; partial thickness burns (with intact nerve endings) are more painful than are full-thickness burns (where nerve endings are largely destroyed). Although the burn itself is painful, a significant amount of the pain is associated with daily débridement and wound care. Pain is often underestimated and undertreated, because staff fear that respiratory depression or death will result from treatment[57]; organizational approaches (implementation of pain management guidelines and educational programs) have reduced this problem. In responding to this, Szyfelbein and associates[58] and others have used self-rating scales and measured serum endorphin levels; they proved that high-dose IV opiates were needed to provide relief from pain for those with severe burns. Improving pain relief[59,60] and sharpening the focus on psychological as well as pharmacological interventions is important to improve outcomes; unfortunately, pain in many burn patients remains undertreated.[61]

The addition of short-acting IV and oral agents (especially opiates, midazolam, and propofol) to target acute pain and anxiety has dramatically lessened the suffering secondary to acute burns. Initially the location(s), source, quality, intensity, course, and duration of pain are identified; then, with nursing staff, self-reported ratings of pain (from 0 to 10 with 10 equaling the most pain) are monitored in response to treatment. Burn pain correlates with endorphin levels and with the extent and depth of the burn.[62] Because infants cannot provide self-reports, behavioral measures (e.g., facial expressions, body movements, and crying) and physiological parameters (e.g., heart rate, blood pressure, respiratory rate, oxygen saturation), and if available, levels of epinephrine, norepinephrine, growth hormone, and cortisol are useful in monitoring pain responses.[63] For children who are unable to verbally communicate, self-reported measures (such as the Faces Scale, the Visual Analogue Scale, and the Oucher Scale) are useful; among staff-rated scales the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) has utility.[64] The most easily used self-rating scales for burn patients are 0 to 10 visual analogue scales[65]; these rate pain from 0 to 10, with 0 as no pain and 10 being the most severe pain experienced. In general, for patients unable to communicate (e.g., owing to use of paralytic agents or to intubation), much information about pain, anxiety, and fear may be gathered by noticing facial expressions (e.g., grimacing or wincing), body language (e.g., withdrawing, pushing away, or startle reactions), and autonomic signs (e.g., changes in heart rate and breathing rates with disturbing or soothing stimuli). When a patient is in a medically induced coma with no objective or subjective means to measure pain, estimates of maximum analgesic requirements for body weight are recommended.

Psychological Treatment of Pain

It is widely accepted that emotional and cognitive states modulate the experience of pain, and vice versa. Psychological techniques to ease burn pain include education, hypnosis, relaxation, patient participation in dressing changes, and biofeedback; these techniques do not predispose to side effects or toxic effects as do medications. Patients can be trained to use these methods,[61] and they can discover that they are capable of achieving self-control over pain.

Developmentally targeted psychological approaches to pain management are effective for both children and adults. Hypnosis for burn pain is effective and practical,[66–68] but it requires more staff time than when relying solely on the use of analgesics. Hypnosis[69] and simple and complex relaxation techniques (such as focused imagery) are in wide use and are practical for children (who are the most hypnotizable subjects) and for adults. Spiegel and Spiegel[70] described a method that is generally applicable for burn patients. Intriguingly, Ewin[71] has reported that hypnosis can acutely prevent the postburn inflammatory response, thereby lessening burn severity. Patient-mediated methods involve the patient's active participation and are designed to shift the locus of control in burned children to themselves.[59,72] This involves preparation for painful procedures and increases the patient's ability to choose when, for how long, and who will perform invasive procedures by encouraging their participation at each step. This structured method can lead to fewer maladaptive behaviors, improved outcomes, and use of lower dosages of narcotics.

Children may develop conditioned fear responses to recurrent painful procedures, such as dressing changes. These responses may escalate to the point that the child is terrified at the mere sight of someone in scrubs or white coats, or worse, the child is continuously afraid that someone may arrive to "hurt" them. Interventions depend on the developmental stage of the child; however, preprocedure treatment of anxiety often reduces the intensity of the experience and the expressed fear, and changing the location of the treatment helps children compartmentalize the reaction. For older children, explaining the procedures and providing schedules enhances their sense of control and improves their understanding and reactions.

Pharmacologic Treatment of Acute Burn Patients

Opiates

The vast majority of burn injuries require narcotic analgesia for adequate pain relief of baseline pain and procedure-related acute pain. This is true for patients in all age groups; a recent prospective descriptive study of

burn victim children under the age of 4 years revealed that 96% of children received at least one dose of morphine.[73] Initially, continuous infusions of morphine or fentanyl, or patient controlled analgesia (PCA) are used. When transitioning from continuous or high-dose IV opiates, background pain can be effectively managed with long-acting opiates (either long-acting preparations of morphine or oxycodone, or methadone). Procedure-induced pain is often treated with a short-acting opiate (such as fentanyl, morphine, or hydromorphone).[74,75] For the acutely burned child, morphine sulfate is often started as a continuous infusion (starting at 0.05 mg/kg per hour with intermittent IV boluses of 0.05 to 0.1 mg/kg every 2 hours); the guideline for midazolam (if anxiety is otherwise unrelieved) is to start at 0.01 to 0.02 mg/kg per hour and then administer an intermittent IV slow push every 4 to 6 hours (0.04 mg/kg per hour). Respiratory depression may require use of opiate or benzodiazepine antagonists. Reversible neurological abnormalities have been reported in children following long-term midazolam use.[76]

Pain reduction is effective whether the cause is biological or psychological, because pain "disrupts metabolic, autonomic, and thermoregulatory" as well as immune functions.[77] Studies have clarified the efficacy of high-dose morphine for relief of burn pain, using either IV or oral administration. PCA with burned adults has been universally useful, but PCA is still useful in selected patients, usually after the first few days of treatment. Adjuvants (e.g., methylphenidate, tricyclic antidepressants, and neuroleptics) can enhance the efficacy of opiates.

Benzodiazepines

Benzodiazepines are often used in hospitalized burn patients to induce sedation, reduce agitation, and decrease anxiety. Given that alcohol dependence and intoxication are risk factors for burn injuries, alcohol withdrawal is commonly encountered and benzodiazepines are used in the treatment of withdrawal. A host of benzodiazepines are available for use, including short-acting agents (e.g., midazolam [which has rapidly assumed a significant place for brief procedures],[78] lorazepam,[79,80] oxazepam, and triazolam) and long-acting agents (e.g., chlordiazepoxide, diazepam, clonazepam, flurazepam). There are few indications for use of psychotropics in recently burned children other than for the management of pain, anxiety, or delirium. As is true for pain, anxiety is often undertreated.

Neuroleptics

Neuroleptics or antipsychotics are frequently used to control delirium-related[81] agitation or severe insomnia in older adolescents and adults. IV haloperidol (although not approved by the Food and Drug Administration [FDA] for IV use) is the most widely studied and accepted neuroleptic for the management of delirium in critical care settings.[82] Before using any neuroleptics, a baseline electrocardiogram (ECG) is obtained to measure the QTc (ideally less than 450 msec); serum potassium and magnesium levels should be within normal range. For acute agitation in patients are who are smaller, younger, elderly, neuroleptic-naïve, or who have mild agitation, one should begin with small doses of IV haloperidol (0.5-2 mg) and titrate to an effective dose depending on the clinical response. A general rule of thumb when titrating IV haloperidol is to wait 20 to 30 minutes after giving the first dose; if it was ineffective, double the dose and repeat this until a dose is reached that calms the agitated patient. If a patient requires escalating doses of haloperidol, an ECG should be repeated to monitor the QTc, and one should also continuously re-evaluate whether other immediately reversible causes may be contributing to agitation (e.g., hypoxia or pain). Once an effective dose has been reached, that dose can be repeated every few hours as necessary to control agitation. Patients who are larger, have been on antipsychotics regularly, or have moderate to severe agitation, may need larger doses (5 to 10 mg) at the outset, after which a similar titration to an effective dose can be pursued. Very high doses have been used safely and with good results.[83] Extrapyramidal side effects (e.g., dystonia) may occur, but their incidence is exceedingly low,[84] and dystonia can be largely prevented by use of antiparkinsonian agents. Occasionally, when severe agitation occurs and when the goal is to enhance deep sedation, a propofol drip and/or IV haloperidol, lorazepam, and a narcotic may be necessary.[85] This state reduces the metabolic demand imposed by agitation, minimizes pain, and produces amnesia that may decrease the vulnerability to PTSD. Haloperidol is not indicated for use in young children with burns because of the risk of hypotension, which is common. Such children usually respond to benzodiazepines.

Newer oral, atypical antipsychotics (e.g., risperidone, quetiapine, ziprasidone, olanzapine, paliperidone, and clozapine) are increasingly used for adult burn patients, adolescents, and (primarily risperidone) with some children, though they have not been systematically studied in burn patients. Olanzapine (IM and oral forms), risperidone (oral forms), and quetiapine (oral forms) are more commonly used for management of agitation secondary to delirium, intense fear, and severe insomnia. See Chapter 10 for more information on management of delirium in the medically ill.

Drug Side Effects, Toxicity, and Adverse Interactions

Side effects, toxicity, and adverse interactions can occur with just about any agent used in burn care. Given that the consultation psychiatrist most frequently employs opiates, benzodiazepines, ketamine (in children), and antipsychotics in the acute management of burn patients, we will review those medications.

With antipsychotics, side effects and adverse reactions can be grouped by the following receptors or channel interactions: potassium-delayed rectifier channel (QT prolongation), anticholinergic side effects (e.g., tachycardia and constipation), antihistaminergic effects (e.g., sedation and weight gain), alpha antagonism (orthostatic hypotension), and dopamine antagonism (e.g., akathisia, dystonia, tardive dyskinesia, and neuroleptic malignant syndrome [NMS]). Of these, the gravest and least common are NMS and torsades de pointes (associated with QT prolongation). These syndromes are described in other chapters.

Opiates have an array of side effects (including exacerbation of delirium, respiratory depression, and development of physiologic and psychological dependence and

withdrawal) with which the consulting psychiatrist should be familiar. Burn patients who require high amounts of opiates over a matter of weeks will become physiologically dependent; tapering is recommended to prevent an uncomfortable withdrawal syndrome. Minor withdrawal symptoms may be managed with clonidine and dicyclomine (to reduce stomach cramps). The interaction of opiates and benzodiazepines may cause delirium, excess sedation, and respiratory depression.[86] Opiate toxicity can be reversed by naloxone.

Side effects and adverse reactions of benzodiazepines include paradoxical worsening of agitation, respiratory depression (which can be additive with other medications), and similarly to opiates, development of tolerance and therefore withdrawal. In children, midazolam infusions are not associated with lactic acidosis believed to result from the accumulation of propylene glycol, a problem seen occasionally with lorazepam infusions.[87] Benzodiazepine toxicity can be reversed by use of flumazenil; however, seizures may be induced if this medication is administered to benzodiazepine-dependent individuals. Signs and symptoms of benzodiazepine withdrawal include anxiety, dysphoria, insomnia, abdominal cramps, nausea, vomiting, sweating, tremors, and seizures. Benzodiazepines must be tapered because the withdrawal syndrome can be complicated by seizures.

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is one of the most well known psychotomimetic drugs[88] frequently used for rapid sedation in children; the long-term neurodevelopmental effects of it are unknown. Though clinicians seek to balance the risks and benefits of aggressive pain management with ketamine, for years it has been in wide use in pediatrics because of its ability to manage procedure-related pain, without major adverse short-term or long-term effects.[89]

Pharmacologic treatment of patients with burns is often complicated by prior substance use and abuse, the possibility that use of pharmacologically-active agents will adversely alter mental state, the critical condition of the patient (especially with respiratory failure or renal insufficiency), drug interactions, altered pharmacodynamics, and the need to balance the benefits of the medication against the risks of unwanted side effects or toxicity.[90] When this is the case, reducing the dosage of medications or stopping medications in favor of psychotherapeutic interventions may be safest.

Of note, although patients with burns may develop a physical dependence to analgesics and anxiolytics, addiction is rarely caused by use of these agents in the context of burns. Additionally, substance abusers may at first require higher doses of opiates or benzodiazepines to effectively treat symptoms than do others without similar histories.

Intermediate Phase

The intermediate phase, during which the patient is healing, is less stressful. Lengthy hospitalizations, however, are the period for which the term *continuous traumatic stress* may be most fitting.[91] During this time, the psychiatrist may be called to see a burn patient with a premorbid psychiatric condition who is depressed, displaying symptoms of PTSD, or who is having special difficulty adapting to the frequent stresses of burn care. Even the most resilient of patients may have difficulty with body image disruption or a re-experience of trauma symptoms upon rehospitalization for ongoing burn treatment. These patients benefit from individualized psychological and psychopharmacologic treatment.

Psychological Interventions

A shift from the acute to the intermediate phase occurs when survival is assured, when most burn wounds are grafted, and when the patient approaches ambulatory status. At this time, it is possible to assess more fully the mental status and to begin differentiating issues of mourning the prior body image, grieving the loss of loved ones, depression, and PTSD. In addition, assessment and diagnosis of neurological or preexisting psychiatric impairment becomes feasible. The patient's awareness of functional losses and disfigurement is eased by responsive staff and by supportive, informed family members. Psychotherapeutic interventions also focus on phase-related issues (e.g., forthcoming surgery, return to home and school, and rehabilitation).

Adaptation of the family usually follows the course of the patient's recovery. Remarkably similar feelings and defensive responses are observed in the patient and his or her family. Psychotherapeutic support (often several sessions per week) during this phase, especially regarding guilt feelings and grief, assists the family and enables them to support the patient's coping through this phase.

Some hospitals provide groups that offer brief psychotherapy, education, and rehabilitation. Several types of group interventions have been used: a children's group structured to encourage expressive drawing and puppet play, an adolescent or adult group for hospitalized patients, and family groups for parents or families of acutely ill patients. These group interventions focus on education about treatment, grief, and one's response to hospitalization, surgery, stigmatization, discharge, and re-entry into society. In England, Rivlin and associates[92] conducted parent groups using a multidisciplinary approach, which the parents rated as helpful.

Body Image and Plastic and Reconstructive Surgery

After the acute treatment of burns, the intermediate phase often involves ongoing care with plastic and reconstructive surgeons. Although the surgeries they perform may begin early in treatment, they may continue for years after the initial burn. Many burn survivors with changed appearance have ongoing difficulties with psychological and social adaptation.[93] One longitudinal study of body image of survivors of severe burn injury found that one year after injury, body image satisfaction and distress was the most significant predictor of overall psychosocial function. [93] The more one defines one's self by physical appearance, the greater the self-consciousness about appearance.[94] Certain problems or mental disorders should prompt psychiatric consultation in those returning for postburn plastic and reconstructive surgery. For children, lack of age-appropriate preparation, preoperative panic, PTSD, parent–child disturbances, attention deficit hyperactivity disorder (ADHD), depression, and enuresis or encopresis are not unusual. For adults, PTSD, psychosis, substance abuse, malingering, or factitious disorder may occur. Certain burns that require

cosmetic surgery (e.g., of the face and head, breasts, or genitalia) and are associated with functional deficits (e.g., burns to the mouth, hands, arms, and lower extremities), including amputations and revisions, require special consideration and, at times, special expertise in preoperative psychological assessment and postoperative management.

Plastic surgeons develop psychological skills for the evaluation of burned patients and may seek psychiatric consultation for their patients.[95] Because much of acute treatment, even with recent improvements in care, is outside the control of the patient and the family, a central psychological goal at this point is to increase the patient's and the family's role in the treatment, its timing, and the long-term plans. Although staff assist the patient to see himself or herself anew,[96] the consultant, in turn, becomes aware of the experience of being burned through the eyes of the patient. By age 2 to 3 years, body image is a relatively stable part of the self-concept, although it is subsequently modified by growth, puberty, trauma, and aging. Interviewing a burned patient provides a window to the development of body image and, usually, on the adaptation and recovery that follow. Attitudes of family and staff toward the patient's physical defects help to shape body image. Burns in children and adults may profoundly alter the subsequent body image, level of self-esteem, interpersonal relations, and ego function,[97,98] but body image disturbances are not inevitable. Body image revision occurs through plastic surgery, allowing another stage of reintegration of body image and healing of the damage to appearance and to self-image. Focused, short-term supportive and educational psychotherapy is helpful, and protocols for these treatments have been developed.[99]

The capacity to tolerate fear and anxiety associated with rehospitalization should be assessed before embarking upon plastic and reconstructive surgery. If there is significant psychopathology, review of records and a preoperative assessment are indicated to reduce postoperative complications. Preoperative problems include phobic reactions to surgery, unrealistic expectations of "perfect" surgical results, embarrassment or shame related to severe disfigurement, and resurgence of PTSD symptoms (e.g., flashbacks or nightmares). Reality-oriented preoperative psychotherapeutic interventions support the patient's coping and facilitate a positive attitude following surgery.

Occasionally, evaluation of emotional readiness for elective surgery results in a recommendation to postpone the surgery. Though such readiness should be part of preadmission assessment, such reactions may not be apparent until the patient arrives for surgery and is immersed in the hospital environment. A patient who presents with panic upon admission and re-experiences prior burn-related trauma may require postponement of elective surgery until outpatient desensitization treatment for the phobia, treatment of panic disorder, or both can be started (before undergoing surgery).

Massively Burned Persons

Today, children and adults usually survive once they reach an acute burn unit, even with massive burns. Despite suffering severe burns to the bronchial tree, face, torso, or extremities (which may require deep, disfiguring excisions of fat and muscle, or amputations), people survive. In fact, in 1984 the percent of burns associated with a 50% mortality was 65% and by the early 1990s it increased to 81%.[100] Many of these survivors drew on personal strengths and family supports and were incredibly resilient.

Psychiatric treatment of those with massive burns initially focuses on the management of pain, stress, or delirium, then deals with grief and injury to body image. Next, treatment focuses on support, restoration of mobility, self-esteem, and hope. Finally, treatment helps the burn survivor resume educational, occupational, and social function. Encouragement, education, and advocacy for the massively burned patient is crucial to mobilize resources so that life, school, and work outside the hospital can be resumed and that the social stigma of disfigurement can be endured.

LONG-TERM PHASE AND OUTCOMES IN BURNS

In many ways, the long-term phase of postburn treatment is a continuation of the intermediate phase, with ongoing assessment and treatment of recurrent or emerging psychiatric illness and reintegration of a patient's sense of self, having been forced to grieve various aspects of their body, function, and even life roles. The general hospital psychiatrist should be aware of this dynamic phase of recovery.

General Outcomes

Many small studies of varying quality and a few larger ones relate to outcomes after burns.[101–103] Clearly, the quality of burn and reconstructive treatment has improved; this makes conclusions based on earlier studies unreliable when attempting to predict current outcomes. Tarnowski and Rasnake,[101] in a review of child outcome studies, believed that "collectively, findings indicate that little empirical data exists to support the contention that the majority of pediatric burn victims exhibit severe poor postburn adjustment." Patterson and colleagues[102] essentially agreed with these conclusions for adults from a rehabilitation psychology perspective. They suggested that poor outcomes were mainly a result of severe preburn psychopathology, which is significant. In another study, Park and co-workers [104] conducted a cross-sectional survey of 686 patients with burns; they found that lack of family support and living expense burden were the two most significant risk factors for patients with acute burns; and those factors, in addition to medical expenses burden, were the risk factors associated with psychosocial problems in chronic burn patients.

Although there is much preburn psychopathology in adults and some in children, this theory underemphasizes the severity and chronicity of posttraumatic reactions. Issues of vulnerability, resilience, and the effects of traumatic stress on emerging personality development[105] have been thoroughly summarized. Although pessimistic conclusions about outcomes are unwarranted, serious psychiatric and psychological morbidity after severe, disfiguring burns merit attention, especially for adolescents who are more vulnerable to depression. For instance, Stoddard and associates,[106] in a cross-sectional follow-up study of children aged 7 to 19 years with severe burns (mean injury, 38% TBSA) readmitted for plastic surgery, found that a majority had mental disorders (including PTSD, depression, and

enuresis) at some time following the burn, whereas 20% developed no disorders. Blakeney and colleagues,[103] while following a sample of 72 children with over 80% TBSA burns, found that 47 achieved "positive psychosocial adaptation," while moderate to severe difficulties in 24% to 30% of cases, a comparable level to those seen with lesser burn injuries.

Posttraumatic Stress Disorder (PTSD)

In child and adult studies, the prevalence of PTSD after burns ranges from 20% to 45%,[107–109] but partial PTSD is more frequent. In a longitudinal study of burn victims, van Loey and colleagues[110] showed that severe stress reactions immediately after injury are common and generally decrease over time; pain-related anxiety predicts posttraumatic stress symptoms 1 year after the burn; consecutive painful wound treatments related to burn severity have a cumulative effect and predisposes towards posttraumatic symptoms in the long term; however, the absence of early posttraumatic stress symptoms did not necessarily prevent development of chronic posttraumatic stress symptoms. Several studies have identified predictors of PTSD, including the presence of ASD,[31] premorbid personality,[32] and premorbid affective and substance abuse disorder.[108] For children, DSM-IV PTSD criteria include "disorganized or agitated behavior" in response to trauma and posttraumatic play, "frightening dreams without recognizable content," and "trauma-specific reenactment" as symptoms of re-experiencing. In a study of PTSD of 60 burned children readmitted for plastic surgery, Stoddard and associates[106] found that about one third had full-syndrome DSM III-R–defined PTSD, and more than half had posttraumatic symptoms. Similarly, Kravitz and co-workers[111] found both a high incidence of sleep disorders in 82 children and, like Stoddard and associates,[106] enuresis in 24%. In adult burn survivors, PTSD occurred among 20% to 45% of subjects, often with associated sleep disorders. Roca and colleagues[112] followed 43 patients (from discharge to follow-up 314 months later): 7% initially fulfilled criteria for PTSD; this increased to 22% at 4 months. Perry and co-workers[113] also found an increase from 35% at 2 months to 45% at 12 months. Powers and colleagues[114] found similar findings a year following discharge from the burn unit, with 38% fulfilling DSM-III-R criteria and 43% using the DSM-IV criteria. Most studies and clinical observation indicated a gradual attenuation of PTSD symptoms, but these studies suggested that it might not be so. Behavioral, cognitive, and pharmacologic therapies all have a place in treatment of PTSD; new short-term treatments are being tested.[115]

Additionally, early and aggressive treatment of pain may have an effect on the incidence of PTSD in burn victims. One study by Saxe and associates[116] demonstrated that early postburn administration of IV morphine reduced the emergence of posttraumatic stress symptomatology in older children, and probably in 1- to 4-year-old children.[117] Lastly, perioperative administration of ketamine was associated with reduced rate of PTSD in adult burn victims[118]; however, administration during the first 3 days was associated with an increased rate of ASD symptoms.[119]

Depression

Depression is also found to occur at higher rates in post-burn patients compared to those in the general population. Several studies have sought to evaluate the prevalence of depression among burn patients. Similar to PTSD, patients with premorbid mood disorders and particular coping styles are more likely to develop depression. One study found that patients with premorbid affective disorder were five times more likely to develop a mood disorder in the first year following a burn.[108] A review by Thombs and associates[120] found that major depression was identified (using structured interviews) in 4% to 10% of adult patients 1 year after a burn. The prevalence of depressive symptoms varied depending on the scale used; the Hospital Anxiety and Depression Scale yielded rates of 4% to 13%, whereas the Beck Depression Inventory yielded rates of 13% to 26% for moderate to severe symptoms and 22% to 54% for mild symptoms.

Surgical reconstruction improves appearance and strikingly enhances social and emotional adjustment. One study demonstrated a prevalence of at least mild to moderate symptoms of depression in 46% of patients undergoing burn reconstruction[121]; depressive symptoms were largely predicted by body image dissatisfaction and by physical function. Outcome studies in adults suggest that a majority adjusted well to their burns over the long term, but that those with facial burns are more likely to experience social rejection, impaired self-esteem, and withdrawal. These results do not resolve the likelihood of severe burn-related emotional disability in burned adults. As with children, improved treatment methods appear to improve outcomes, but definitive studies are lacking.

Chronic Pain

Although pain subsides once the burns heal, ongoing pain has been documented years following burns[122,123]; two studies found that about one third of burn patients 1 to 9 years out from a burn continue to have significant pain, and the majority of these patients had sleep, work, or social disruption related to the pain. In addition to pain, itching, particularly in deep thermal burns with hypertrophic scars, is one of the more disturbing physical complaints endorsed by patients with burns, and it can become chronic in some patients.[124] A study by Van Loey in 2008[124] prospectively followed burn patients for 2 years and found that at 3 months 87% of patients complained of mild to severe itching, and this decreased steadily over the next 21 months (such that at 2 years, 21% of burn patients had moderate to severe itching). The study showed that at 2 years, posttraumatic stress symptoms and the number of surgical procedures predicted itching. Although itching has a fairly well understood biological basis, psychological factors may also contribute to the chronicity of itching. Psychoactive medications, including naltrexone,[125] gabapentin, and doxepin[126] have been tried with some success. More research is needed in this area.

Lastly, observations of patients who do well following burn injuries has led to insights about resiliency factors and a growing body of literature regarding predictors of success in recovery. Positive emotions, self-efficacy, resilience, ability to sleep during recovery, and baseline resilience at the time of injury have all been identified as protective factors.[127–130]

END-OF-LIFE CARE

The mortality rate on adult units is much higher than on pediatric burn units because of more extensive burns, severe medical and psychiatric risk factors, an increased mortality risk associated with being older, and the limits of what medical care can achieve. Elderly patients with burns are more likely to require ventilatory support, more intensive care, and have higher mortality rates.[25] Most burn-related deaths occur during the initial phases, but some patients survive for months before death arrives, and some patients survive within the acute burn care setting and then fail in less intensive rehabilitation settings.

The psychiatrist is often consulted to assist in the care of dying patients and their families to minimize pain and suffering and to assist in the process of decision-making at the end of life.[131–133] With massive burns, decisions whether to continue treatment may arise. This is challenging emotionally and spiritually to all involved; patients may benefit from pastoral care; burn teams may benefit from optimal care or ethics committee consultations. Some patients and families, in collaboration with the burn team, choose palliative care (or "comfort care") rather than enduring the pain and suffering of treatment and the cosmetic, functional, and psychological sequelae of burns.

Although it is often traumatic when an adult dies, it is always emotionally traumatic when a child dies from burns.[131–134] It is essential to provide accurate explanations about the risk of death to families and to patients when possible, as well as emotional preparation for this possibility. Support in their grieving is helpful to relatives of burn patients who die, especially from members of the burn team who worked closely with them. Many grieving family members are very grateful for the care their loved ones have received.

STAFF SUPPORT, STAFF STRESS, AND BURNOUT PREVENTION

Psychiatric skills are especially valuable and valued by burn patients; stressed staff also know their benefits. It is useful to understand organizations in which one works, the rapid changes that affect hospitals and health care, and the virtues of developing a relationship with a multidisciplinary team to care for severely traumatized patients. One's introduction to the unit may be followed by shock, dismay, fear, frustration, and sadness as the full meaning of burn care takes hold.[13,133] Respect for the coping styles of the staff is crucial, since it may at times appear that individuals are harsh, regressed, or overinvolved. The psychiatrist on the team, simply by his or her presence, encourages communication; a reflective attitude about staff members' feelings as well as those of their patients is helpful. Encouraging staff to ask questions, the psychiatrist can enable them to think diagnostically and therapeutically about their patients' and their future and provide them with a sense of satisfaction and hope. Gratitude for sharing the burden of tragic or irreversible situations and for lending an ear may be forthcoming. The psychiatrist is often able to place trauma in a positive perspective and to broaden and deepen the psychiatric knowledge of the entire burn team.

ETHICAL CONSIDERATIONS

Ethical issues stimulated by burn care may be a source of difficulty for staff and the family; these issues may be magnified by costs, which may exceed $1 million for a single patient. Ethical issues[50] include consent to treatment, quality of life, prevention of intolerable pain, organ donation, decisions about resuscitation or withdrawal of life support, cost of care versus potential benefit, responsibility for long-term care of most severely burned, right to treatment, and determination of disability. Consultation by the ethics committee to the burn team in difficult cases is often helpful to provide optimal care to the patient and family.

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Chronic Medical Illness and Rehabilitation

29

Guy Maytal, M.D.
Terry Rabinowitz, M.D., D.D.S.
Thomas D. Stewart, M.D.
Gregory L. Fricchione, M.D.

Most of us take for granted our ability to function well physically: to open a tube of toothpaste, answer the telephone, tie our shoelaces, use the toilet, or comb our hair. We forget that each task took considerable time and effort to master. The same is true for our good physical health. When we are still quite young, we can depend on our bodies to get us from place to place, to keep us out of danger, and to adjust to changing environmental demands seamlessly and without much mindful input. However, the development of these capabilities is dramatically altered by the onset of a persistent medical illness in childhood (e.g., the effect of rheumatic fever on the heart, the impact of polio on the musculoskeletal system, or the effect of cystic fibrosis on the lungs). Likewise, the sudden loss of physical function (e.g., from traumatic amputation, or hemiparesis after a stroke) dramatically alters one's relationship to physical function.

For individuals with chronic medical illnesses or for those who need rehabilitation, the behaviors, functions, and outcomes that most of us expect in response to our brain's request that our body perform may never again be available in the same manner. This chapter addresses the unique problems and challenges faced by patients with chronic medical illnesses and by the psychiatrists who treat them.

PSYCHIATRIC COMPLICATIONS IN CHRONIC MEDICAL ILLNESS AND REHABILITATION

In the United States, discharging patients from acute care facilities as quickly as possible is common practice. Moreover, there is an increasing tendency to divert patients from acute care hospitals to other (lower-cost) facilities to keep costs in check.[1] Thus, there is a growing need for appropriate aftercare after acute treatment. Many larger hospitals have rehabilitation hospitals attached to them (or close by); smaller hospitals may have to rely on distant rehabilitation centers to provide the specialized, long-term care that they cannot offer.

Unfortunately, many who require rehabilitation and have a chronic illness are at substantial risk for developing one or more psychiatric complications. Rates of depression, for example, among amputees range from 35% to 58%; for those with multiple sclerosis, from 6% to 27%; and for those with cancer, 6% to 25%.[2]

Prevalence rates of suicide and of suicidal intent[3] are also substantially higher among those with chronic illnesses than among those without. For example, compared with the general population, individuals with cancer have suicide rates that are 15 to 20 times greater, those with spinal cord injuries have a rate 15 times greater, and those with multiple sclerosis have a rate 14 times greater.[2,4]

The consulting psychiatrist is often asked to evaluate and to help care for patients with affective, behavioral, and cognitive difficulties, and with a variety of diagnoses, while they are receiving rehabilitative care. The most challenging of these patients are those with traumatic brain injuries, spinal cord injuries, and prolonged and catastrophic medical illnesses. Patients with preexisting psychiatric conditions (including personality disorders) may decompensate under the stress of prolonged hospitalization, adding further complexity to their care.[5–7]

Problems That Occur during Rehabilitation

Patients receiving rehabilitative treatments tend to spend a large portion of their time worrying about the future. They anticipate (correctly or not) difficulties that they will face while adjusting to their new (more medically compromised) lives. A patient may worry about returning home, obtaining financial independence, driving, returning to work, adjusting to changes in appearance, socializing, dealing with stigmatization, engaging in sexual activities, and managing decreased functional capacity.[8–11]

Rehabilitative services may be obtained in a rehabilitation hospital or on an outpatient basis. This component of the treatment may continue for months or years—much longer than the acute treatment—causing serious disturbances in patients' usual schedules. During this phase of treatment, patients meet new caregivers, including physiatrists, nurses, occupational therapists, physical therapists, social workers, vocational therapists, recreational therapists, psychologists, clergy, and psychiatrists. Interactions with this many personnel may be stressful and may affect the quality of therapeutic relationships. Likewise, patients receiving rehabilitative treatments may be exposed to many new, uncomfortable, or painful procedures.

At times, the challenges that arise for clinicians and patients affect empathic connectedness. Cultural differences may play a role in this regard, and it takes time to

TABLE 29–1 Differences between Psychiatrist and Patient That May Affect the Quality of Their Interaction

Gender
Race
Sexual orientation
Age
Religion
Education
Appearance
Financial status
Health
Personality
Profession
Partner or marital status
Living situation

Adapted from Rabinowitz T, Stern TA: The patient requiring rehabilitation. In Stern TA, Herman JB, Slavin PL, editors: *The MGH guide to primary care psychiatry*, ed 2, New York, 2004, McGraw-Hill.

learn to trust a new consultant. Table 29–1 lists some characteristics of patients and caregivers that should be considered when a clinician, especially a psychiatrist, tries to make an empathic connection with a patient undergoing rehabilitation.

The Rehabilitation Environment

Patients must adapt to a large number of rehabilitation personnel and to the rehabilitation setting, which is often dramatically different from the acute hospital setting. Perhaps one of the most important issues for the rehabilitation patient is the possibility of lengthy physical displacement. The patient receiving treatment far from home and for an extended period, who is therefore separated from loved ones and familiar objects and surroundings, may be at increased risk for developing depressed mood, apathy, or hopelessness.

Other problems common to prolonged rehabilitation (e.g., disruptions in school or work attendance, stresses on a marriage or partnership and parent–child relationships) may hinder timely and successful recovery and may produce long-term negative effects for a recovering patient. Patients may also believe that they and their illnesses are a financial and emotional burden for loved ones, and they may feel guilty about the amount of time spent on them and on their care. This may lead to withdrawal from caregivers and loved ones in a paradoxical attempt to lessen their burden.

Psychiatric Problems Common in Patients Undergoing Rehabilitation

The consulting psychiatrist should expect to encounter the full spectrum of psychiatric conditions in patients with chronic illness who require rehabilitation. However, certain psychiatric diagnoses and conditions are more common in this population: depression, cognitive impairment, adjustment disorders, and behavioral difficulties.[1,2]

Many patients receiving rehabilitative care and coping with chronic medical illnesses appear depressed, confused, or anxious. However, when standard clinical criteria are employed, a large proportion of these patients do not meet diagnostic criteria for these conditions as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV).[12] The somatic symptoms used in standard assessments of depression (e.g., low energy, difficulty concentrating, sleep disturbance) are not useful. Other means of assessing and conceptualizing the patient's psychological reactions to medical illness (i.e., psychological instruments that do not use somatic indicators of depression, such as the Hospital Anxiety and Depression Scale) can give a more accurate assessment of depression and anxiety in the medically ill.[13]

These patients, nevertheless, may be demoralized by their circumstances. As characterized by Jerome Frank,[14] demoralization represents a persistent failure to cope with a chronic stressor. It is characterized by patients' having the experience of failing to live up to their own or others' expectations. It is accompanied by feelings of hopelessness, helplessness, confusion, and subjective incompetence. However, there is a lack of consensus on the definition of demoralization and on its differentiation from major depressive disorder (MDD), and it is difficult to distinguish between these two conditions. To address this issue, Clarke and colleagues[15,16] performed a factor analysis of the psychiatric symptoms of 312 medical patients selected at random, and they analyzed 108 different symptoms. They noticed that the symptoms could be divided into three clusters—anhedonic depression, demoralization, and grief—suggesting that these are three distinct syndromes experienced by patients with persistent medical illness, each of which requires a distinct diagnostic and therapeutic approach. Further research is required on demoralization to better characterize its contribution to depressed mood in patients with medical illness.[15,16]

Regardless of the syndrome underlying the depressed mood or anhedonia in these circumstances, it is most appropriate to treat symptoms rather than diagnoses. Moreover, the symptoms should be treated early and aggressively, as more (and more severe) symptoms often appear quickly and are more difficult to manage once they have developed fully.

The inability to reach a diagnostic threshold may result in part from difficulties in communication between the clinician and the patient. Many conditions that afflict rehabilitating patients impair their ability to communicate their most basic feelings and emotions. Likewise, clinicians may be fooled because the usual affective "music" associated with various mood states in the healthy population may not be present in the chronically ill. In these circumstances, it is far better to err on the side of too much treatment than too little.

Delirium is of particular importance in rehabilitation patients. A patient may have an acute confusional state during hospitalization, and it may continue at the rehabilitation center without having been detected or treated. This may adversely affect prognosis and lead to an increased length of stay or the need for a nursing home placement.[17] However, delirium may develop during rehabilitation when, for example, a new medication is administered or an infection develops.[18] Of 2158 subjects newly admitted to a rehabilitation facility after being in an acute care facility, 16% had delirium, and over two thirds had at least one

symptom of delirium.[19] Furthermore, in a study of 551 patients similarly transferred from an acute care to a rehabilitation facility, Marcantonio and colleagues found that 23% had symptoms of delirium on admission, and 1 week later, 12% had more symptoms of delirium.[20] Patients who have chronic illness and are undergoing rehabilitation often present with risk factors that predispose for, or precipitate the development of, delirium (e.g., a visual or hearing impairment, a cognitive impairment, a history of stroke, an intracranial lesion, an ongoing infection, the use of psychotropic drugs or polypharmacy, and medical complexity).[19]

The Potential Impact of Disabling Neurologic Conditions on Psychiatric Diagnosis and Treatment

Disabling conditions can limit the ability of patients to express their thoughts and feelings, confounding both psychiatric diagnosis and treatment. For example, depending on the location of a stroke, its clinical manifestations can interfere with the expression of cognition or affect, which are necessary for making the psychiatric diagnosis.[21] Furthermore, psychiatric treatment can be affected—for example, when acute cervical spinal cord injury is accompanied by psychosis and delirium.

The clinical manifestations of stroke depend on the location of the ischemic injury. Strokes can generate disorders of communication that can mislead treating physicians. The most common barrier to communication faced by stroke patients occurs in dominant-hemisphere injuries. The most prominent communication difficulties caused by dominant-hemisphere strokes are the aphasias. Fluent aphasia, such as Wernicke's aphasia, is a well-articulated incoherence and failure to comprehend without a motor–sensory deficit. This disordered, fluent speech can be confused with the loose thinking found in schizophrenia. History is the key for differentiating fluent aphasia with sudden onset in a previously well-functioning patient from schizophrenia, where an insidious onset along with emotional and social impoverishment is evident.

Nonfluent aphasia (e.g., Broca's aphasia) features slow and telegraphic, but coherent, speech with impaired word-finding ability. Through yes-or-no questions, such patients can be helped to express their feelings. Facial expressions associated with depression remain intact.

Lesions in the nondominant hemisphere can also cause disorders of communication and make the accurate diagnosis and treatment of psychiatric illness more challenging. Aprosodia is an example of dysfunctional communication after a stroke. It involves an impaired ability to receive or to convey affect (through inflection, gesture, and facial expression).[22] The damage is in the nondominant frontotemporal region, and it is an analogue of aphasia, which is associated with the frontotemporal region of the dominant hemisphere. Expressive aprosody disrupts the emotional undertone (i.e., the "music") of communication.

Aprosodic patients sometimes have depressive cognitions, but they cannot easily convey their depressive mood; this leads to underdiagnosis of depression. On the other hand, a patient with expressive aprosody is sometimes misdiagnosed as having depression when the unemotional speech is taken as a sign of a mood disorder. Several approaches can detect defects in prosody. First, confirm that the nondominant hemisphere is damaged (e.g., by physical findings, such as hemiplegia, or by brain imaging). Then ask the patient to repeat a neutral sentence, such as, "I am going to the store," with several different emotional tones (e.g., happiness, sadness, anger). Failure to do these well suggests expressive aprosody. On the other hand, if the patient cannot detect changes in tonality when the *examiner* recites the phrase (when the patient cannot see the examiner's face), a receptive aprosody is suggested. In aprosodic patients, careful observation of somatic signs and symptoms of depression (e.g., changes in appetite or sleep) takes on a greater significance, as does a personal and family history of depression.

Furthermore, strokes in the nondominant parietal lobe can produce anosognosia. This condition involves denial of deficits on the left side of the body; however, it can also involve irritability, crying, and denial of depression, which are all too evident to family and staff. The patient's failure to report depressive experience in anosognosia can also lead to underdiagnosis.[23]

On the other hand, strokes (as well as other neurologic illnesses, such as multiple sclerosis and Parkinson's disease [PD]) can lead to the overdiagnosis of MDD. For example, lesions of the frontal lobe can produce abulia, a syndrome featuring apathy, loss of motivation, and loss of goal-directed behavior. Abulia can lead to the misdiagnosis of depression as the cause for the observed amotivational state.

A few observations can reduce the likelihood of diagnostic error in patients with abulia. Sudden onset is characteristic of abulia related to a cerebrovascular accident, but not of MDD. Abulic, but not depressed, patients may display a wide affective range despite lacking motivation. They are also less apt to be preoccupied with suicide. As is true for patients with aprosodias, careful observation of vegetative symptoms along with knowledge of the patient's history can help in differentiating neurologic conditions from psychiatric ones.

Pathologic crying and pseudobulbar affect can mislead clinicians and patients about the presence of MDD. This type of crying, or sometimes laughing, is spontaneous and incongruent with the thought content. Neurovegetative symptoms of depression are minimal or absent between affective displays. Selective serotonin reuptake inhibitors (SSRIs) are recommended as first-line pharmacotherapy for this disorder. When they fail or are not tolerated, a variety of second-line treatments may be useful (including tricyclic antidepressants [TCAs], noradrenergic reuptake inhibitors, dopaminergic agents, and uncompetitive *N*-methyl-D-aspartate receptor antagonists).[24]

Other brain-related disabilities (e.g., PD, Alzheimer's dementia [AD], and temporal lobe epilepsy [TLE]) also create perplexing problems for the clinician diagnosing and treating depression in the rehabilitative setting. Apathy, masked facies, cognitive slowing, sleep disturbance, and fatigue are features of both PD and MDD, complicating the diagnosis. The symptoms that correlate most significantly with depression in patients with PD, as measured by the Hamilton Depression Scale, are suicidal thoughts and feelings of guilt.[25] The highest correlations using the Montgomery-Asberg Depression Rating Scale were

observed for depression (0.75) and anhedonia (0.74).[26] Moreover, although several studies have shown that, in general, neurovegetative symptoms do not help separate depression from underlying PD, appetite disturbance and early morning awakening do have discriminative power to help diagnose depression.[27]

Further complicating the clinical picture, the pathophysiology of PD overlaps with that of MDD. Reduced catecholamine neurotransmitter release in the midbrain is implicated in both, thus explaining the high incidence of depression in PD patients and raising interesting possibilities for treating both conditions with the same medication.[28] Unfortunately, convincing evidence is lacking that improvement in dyskinetic movements with dopaminergic treatment lessens depression. SSRIs, on the other hand, can lessen depression in this population; unfortunately, they may worsen dyskinesia through the reductions in dopamine release that accompany increased serotonin receptor activity. Conclusive evidence that dyskinesia worsens in patients with PD when SSRIs are used is lacking.[29] In a recent randomized, controlled trial of 52 patients with PD and depression, nortriptyline was found to be more effective than paroxetine controlled-release.[30] Electroconvulsive therapy is effective in both MDD and PD, relieving depression and reducing parkinsonian symptoms for up to several weeks.

AD shares several features with both PD and MDD.[31] All three have depleted brainstem aminergic nerve cell function. This common pathology contributes to the apathy, impaired concentration, and reduced short-term memory seen in all three. The high co-morbidity of MDD in patients with AD and PD is understandable. MDD may be the initial presentation in late-life AD, and it is prominent in the differential diagnosis for reversible dementias.[32] In addition, depression occurring at any time appears to increase the risk for AD.[33]

Several factors distinguish the presentation of late-life depression from the depression associated with AD. Depressed individuals with AD are less apt to experience excessive guilt, disturbed sleep, and feelings of worthlessness; however, they are more apt to describe indecisiveness and an inability to concentrate, which is consistent with cognitive decline. It is noteworthy that there is no change in the frequency of the features of MDD with the severity of AD, except for psychosis, which increases with the severity of AD.

When it is co-morbid with AD, depression is associated with poorer quality of life, greater disability in activities of daily living, a faster cognitive decline, a high rate of nursing home placement, higher mortality, and a higher frequency of depression and burden in caregivers.[34] Therefore, successful treatment of MDD in patients with AD can reduce the risk for all of these outcomes. Antidepressants with significant anticholinergic properties (e.g., TCAs or paroxetine) should not be used, because they undermine the already depleted cholinergic reserves seen in those with AD. In apathetic AD patients, it is reasonable to use antidepressants that increase synaptic catecholamines, such as bupropion and venlafaxine (with a dosage greater than 200 mg/day). For those who are anxious and agitated, an SSRI or mirtazapine is appropriate.[34]

Temporal lobe epilepsy, including complex partial seizures, is the type of seizure disorder most associated with psychiatric findings (roughly 20%); 14% of these patients exhibit psychosis during postictal and interictal states.[35,36] Psychiatric diagnoses associated with TLE should be made while patients have a clear sensorium, not when they are ictal or when they are in a postictal state.

There is psychopathology during interictal periods in people with TLE. The interictal syndrome (also known as Geschwind syndrome) features hypergraphia, seriousness, humorlessness, and an intense interest in philosophic, moral, or religious issues. In addition, afflicted patients are often experienced as viscous by others; that is, they have a tendency to talk at length and circumstantially about a restricted range of topics.[37] Two clinical clues should raise suspicion that TLE, and not primary psychiatric illness, is the driving force behind persistent psychiatric symptoms. The first is the presence of treatment-resistant psychosis. Neuroleptics can reduce the seizure threshold and can thus lead to unintentional worsening of the psychosis related to TLE.[38] The second is incongruity between the severity of the psychotic symptoms and the patient's level of function when psychotic symptoms are quiescent. Making the diagnosis of TLE leads to treatment of the underlying seizure disorder and to the amelioration of the psychosis. Nevertheless, there is a risk for interictal psychosis in these patients, which increases with the frequency of the seizure episodes.

However, TLE is often difficult to diagnose because the behavior associated with ictal periods can be highly complex (and sometimes not readily identifiable as seizure activity), and because the electrical activity of TLE may be deeply imbedded in the limbic system. Deep electric signals are not easily accessible to surface electrodes, and at times not even to sphenoidal electrodes used during sleep.[39] The failure to find those signals can lead to an incorrect diagnosis of conversion disorder or of malingering. Therefore, it is important to include TLE on the differential diagnosis when a case defies easy diagnosis. Ultimately, the diagnosis of seizures and epilepsy, particularly TLE, is based largely on the clinical state and not solely on the electroencephalogram.

Spinal cord injury can also confound psychiatric diagnosis and treatment. Acute high cervical injury can lead to sensory deprivation (because of the sudden loss of sensory input from the neck down, coupled with head restraint by tongs). The apathy and withdrawal under these conditions can be misread as MDD. However, patients with spinal cord injury have an increased risk of developing MDD in rehabilitative settings (about 30%) as well as when they return to the community (about 25%).[40] Treatment of depression should start after the first month of quadriplegia to allow increased sensory input as more stimulation becomes possible and depression-inducing steroids are no longer used to treat spinal cord edema. When symptoms of MDD persist 1 month after the injury, it is reasonable to begin treatment.[41]

Another potential psychiatric issue after spinal cord injury is the persistence of body perception (i.e., being in the same position as one was in at the time of the injury, such as riding on a motorcycle). The patient knows this compelling perception is untrue and may feel as if he or she

is becoming mentally ill. Asking "Do you have any strange sensations?" can unearth this problem and permit a reassuring explanation.

Psychiatric treatment considerations are particularly important for patients receiving rehabilitation because some may cause conditions that may adversely affect a patient's recovery. For example, oculogyric crisis after neuroleptic use for acute cervical injury can be minimized with the use of atypical neuroleptics. Should an injectable neuroleptic be required for severe agitation in the setting of acute cervical injury, IM ziprasidone or olanzapine is preferable to IM haloperidol because of a lower incidence of extrapyramidal symptoms, or one can use IV haloperidol.

Orthostasis is a problem for patients with quadriplegia because of disruption of central nervous system controls (both excitatory and inhibitory) over the paraspinal sympathetic ganglia. This autonomic vulnerability requires that psychotropic medication with potent α-blocking properties (e.g., TCAs and low-potency neuroleptics) be avoided immediately after the injury.

Managing sexual dysfunction is important for a patient's emotional and psychological well-being after a spinal cord injury. Complete spinal cord lesions can cause genital anesthesia, but some patients retain some genital sensation, genital response, and even orgasmic capability (if the lesion is partial). Some men can ejaculate without pharmacologic assistance, but most cannot. Many women and men report the development of new areas of arousal above the level of the lesion, sometimes leading to satisfying "phantom orgasms" with caressing or other tactile stimulation.[42,43]

Men may be able to achieve reflex erections sufficient for intercourse, or they may respond to treatment with prostaglandin E_2 agents (with variable results). Patients treated with sildenafil have improved erection response rates, and a substantial number of individuals with complete lesions, regardless of level or lower motor neuron lesions, also benefit from it.[42,44] Women are similarly affected but can use supplemental lubricants if vaginal lubrication is insufficient and intercourse is desired. Difficulties with positioning, bowel and bladder incontinence, autonomic dysreflexia, and spasticity during sexual activity can be a problem for both women and men. Some patients find that their sexual preferences evolve in a manner that supports their remaining physical capabilities (e.g., increased interest in providing the partner with oral–genital stimulation).[45]

After a spinal cord injury, many patients despair over the loss of present and future sexual intimacy. The treating psychiatrist can assist these patients in developing hope for continued psychological intimacy and sexual activity. Patients (and their sexual partners) find it beneficial to learn that many women and men who experience spinal cord injury–related losses regain active sexual lives. Sex therapists and physicians with expertise in assistive reproductive technologies can be consulted as a part of this process.

Depression, Cardiovascular Disease, and Cardiac Rehabilitation

Over the past 2 decades, research has established a bidirectional link between depression and cardiac disease: patients with depression are more likely to develop cardiac disease, and patients with cardiac disease are more likely to suffer from depression. In fact, MDD is recognized as an independent risk factor in the development of cardiovascular illness[46] (see Chapter 23). We will briefly discuss the interplay between cardiovascular disease and depression in the rehabilitation setting. Depression after a myocardial infarction (MI) has been found to have significant deleterious effects on recovery. A meta-analysis[47] found that depression after an MI was associated with an increased risk of recurrent cardiac events and death. It has been suggested that depression after an MI can be divided into clinical subtypes that are probably not prognostically equal. Compared with patients who have a prior history of MDD, patients with incident (new) depression after an MI experience a heightened risk of recurrent cardiac events and mortality during the subsequent 5-year period.[48]

Addressing depression after an MI is important in the rehabilitation setting. Some evidence suggests that patient participation in cardiac rehabilitation programs greatly improves the depressive symptoms. For example, Milani and colleagues[49] studied the effect of cardiac rehabilitation and exercise training on depression after a major cardiac event. They studied 338 consecutive patients who had experienced a major cardiac event 4 to 6 weeks previously and who were participating in cardiac rehabilitation (36 sessions over a 3-month period). Depression was prevalent in 20% of these patients. The researchers found that the symptoms of two thirds of the patients who were initially depressed resolved by study completion.[49] In a similar study, Milani and Lavie[50] evaluated the impact of cardiac rehabilitation on depression and its associated mortality in coronary patients. They followed 522 consecutive coronary patients in cardiac rehabilitation and compared them with a control group of 179 patients not completing rehabilitation. Depressive symptoms decreased 63% after rehabilitation, and depressed patients who completed rehabilitation had a 73% lower mortality rate than controls. This reduction in mortality was related to improvements in fitness, but only mild improvements in fitness level were required to produce these effects. Every effort should be made to enroll post-MI patients in cardiac rehabilitation programs.

However, for patients whose depression remains despite cardiac rehabilitation and for those who are unable or unwilling to attend such programs, medical treatment for depression may be indicated during the post-MI period. In large, randomized trials, sertraline, citalopram, and mirtazapine have been shown to be safe and effective for treating depression in cardiac patients. The other SSRIs may also be safe, but they have not been studied as extensively.[51–53] Thus far, there is no convincing evidence for using manualized psychotherapy techniques (e.g., cognitive-behavioral or interpersonal therapy) in cardiac patients (see Chapter 23).

DIAGNOSTIC DILEMMAS

Psychiatrists are sometimes asked to assess physically disabled patients when there is no established diagnosis for their pathophysiology. The question asked is, "Does this patient have conversion disorder?" As many as 50% of those diagnosed as having conversion disorder subsequently develop a medical diagnosis consistent with a disability. Often, multiple sclerosis is involved.[54,55] A more

recent study, possibly reflecting improved diagnostic techniques, has shown that only 4.3% of those with conversion disorder developed a subsequent medical illness that could have explained the prior findings.[56] The same study, however, revealed substantial psychiatric co-morbidity in this population, with 50% meeting the *International Statistical Classification of Diseases and Related Health Problems*, revision 10 (ICD-10) criteria for mental illness, especially personality disorder.

Although undetected medical illnesses in patients with conversion disorder now appear to be common, paraneoplastic disorders are an infrequent, but important, exception. Paraneoplastic neurologic disorders are characterized by the presence of neurologic dysfunction in the setting of a remote cancer, most commonly small cell lung cancer or gynecologic tumors.[57] Paresthesias and memory loss are two findings that can appear without a supporting medical diagnosis until it is discovered as a *forme fruste* of cancer.[58] These symptoms appear to be mediated by the immunologic response to the tumor that attacks neural tissue.[59] Thus, an oncologic evaluation and work-up for otherwise unexplained memory loss or paresthesia is warranted.

Conversion disorders can produce medical complications. For example, conversion-based lower extremity paralysis can lead to Achilles tendon contracture, decubitus ulcers, and pulmonary emboli. Psychiatric consultation for these patients should draw attention to the prevention of such complications. In addition, aggressive treatment of co-morbid psychiatric conditions (including depression and psychosis) can reduce emotional suffering. However, addressing psychiatric co-morbidity does not usually ameliorate the conversion-based physical findings.

Nonpsychiatric medical disabilities influence psychiatric diagnosis and treatment in ways that are specific for each condition. Although assessment currently relies as much on art as on science, psychiatric diagnosis and treatment can enhance quality of life among persons suffering from disabling conditions.

DIAGNOSIS AND TREATMENT

Psychiatric treatment in the context of rehabilitative medicine or chronic illness sometimes bears little resemblance to routine psychiatric care. Patients from these groups may be engaged in so many activities during the day that it is impossible to sit with them for long. They may require intensive physical and occupational therapy, time-consuming diagnostic studies, and longer and more frequent rest periods. In addition, visits from family and loved ones tend to take precedence over the treatments and interviews needed to treat their psychiatric conditions.

Psychiatrists unfamiliar with this milieu may become frustrated by their inability to capture enough quality time with a patient. However, this challenging group provides an opportunity for development of broader clinical skills and effective assessment, and treatment can take place over time. The initial step for a successful psychiatric consultation in a rehabilitation hospital is for the consultant to clarify the question embedded in the request for consultation. In addition, the psychiatrist should assess the personality and coping styles of the patient who faces the challenges of chronic medical illness. Often, it is maladaptive coping that delays or prevents improvement in the patient's condition. Supporting adaptive strategies is important in the psychiatric care of these patients. Table 29–2 presents domains that should be explored *before* a consultation is begun. Table 29–3 provides questions to be answered for all patients with chronic illness in a rehabilitation facility, and Table 29–4 offers more specific questions.

In the rehabilitative setting, psychiatrists have access to the same treatment modalities as in other settings (e.g., pharmacology, psychotherapy, somatic treatments). However, the way these treatments are delivered to these patients is often unique. Treatment guidelines for specific psychiatric diagnoses are covered elsewhere in this text.

The psychotherapeutic modality chosen should be appropriate to the particular patient,[2] many of whom have not experienced psychotherapy and may doubt its efficacy. Furthermore, most patients in rehabilitative settings are struggling with some basic physical and psychological problems (e.g., learning to walk with a prosthesis, adjusting to the need for continuous oxygen, adapting to loss of cognitive function). A psychotherapeutic approach that focuses on the chief complaint and on supporting enhancement of resilience is often most effective. The psychiatrist should expect to take an active role in the psychotherapy of these individuals (e.g., giving advice and guidance where appropriate). It may also be useful to include limbic probes. For instance, commenting on a patient's affect by saying, "You seem so down today. Are you feeling blue?" may give a patient who is emotionally guarded the opportunity to express emotions that are difficult to bear. Likewise, a nonoffensive joke or silly gesture may slide past cortical sentinels to the limbic system, evoking an expansive smile or a hearty laugh in someone who is despondent but who wants to feel better.

TABLE 29–2 Questions To Be Addressed Before Consultation

Who is requesting the consultation?
What is the problem? (or what are the problems?)
This is best determined through personal contact with the physician requesting the consultation, rather than from information obtained by secretaries or others.
Who will implement the recommendations?
Many recommendations are never implemented because of miscommunication between the consultant and the person requesting the consultation.
Orders should be written by the patient's attending physician (or designated house officer), except when waiting would significantly compromise patient care.
Does the patient know that a consultation has been requested?
If not, why not?
Is there a concern about capacity or competence?
If there is no concern about competence or capacity, the patient should be informed of the request for consultation and should consent to its performance.
When is the best time to see the patient?
Can time be reserved for an interview?
If not, what are potentially available times?
Can family/friends and important others (e.g., RN, LPN, and MD) be available if necessary?

TABLE 29–3 Questions for All Patients Receiving Rehabilitation or with Chronic Illness

Has the patient ever been under the care of the psychiatrist or received psychiatric treatment?
Does he or she take medications for a psychiatric condition?
Has he or she ever been suicidal or made a suicidal "gesture"?
Is there any history of violence or a threat of violence?
Has he or she ever received inpatient or outpatient treatment for substance abuse or dependence?
Has he or she ever been in trouble with the law?
  Any jail or prison time?
Has he or she ever received rehabilitative treatment before?
What was the outcome?
  Were they cooperative, disruptive, threatening, or violent?
Is there any history of delirium?
Is there any history of head trauma or brain injury?
Are there current concerns regarding intellectual or cognitive function?
  Has there been a change from baseline?
What are the patient's main social supports?
  Are they reliable, that is, providing consistent emotional support and logistical help?
  Have they been consistently helpful in the past?
Has the patient had contact with anyone who has a similar illness or injury?
  Is that person reasonably emotionally intact and functioning well?
Before the need for rehabilitation, how well did the patient function:
  In school?
  At work?
  With their partner or spouse and family?
  In the military?
  In new situations?

Adapted from Rabinowitz T, Stern TA: The patient requiring rehabilitation. In Stern TA, Herman JB, Slavin PL, editors: *The MGH guide to primary care psychiatry,* ed 2, New York, 2004, McGraw-Hill.

TABLE 29–4 Focused Questions for All Patients in Rehabilitation or Chronic Illness Settings

What is the meaning of the illness or injury to the patient?
Is the condition hereditary?
  Are there affected relatives?
  If yes, how are they doing?
  If the condition is hereditary, are there markers that can be searched for in others?
  How does the patient feel about such searches?
How has the condition or situation affected his or her self-esteem?
  Do not ask *if* self-esteem has been affected—this will give the patient the opportunity to say No and avoid further discussion of the topic.
How have relationships with friends and family been affected?
How is he or she adjusting to change or loss of function in the following areas:
  Academic
  Athletic
  Creative
  Intellectual
  Occupational
  Sexual
  Other
Is he or she taking medication for psychiatric symptoms, such as anxiety, fear, or depression?
  Is it helping?
  Are there side effects?
  What are they?

Adapted from Rabinowitz T, Stern TA: The patient requiring rehabilitation. In Stern TA, Herman JB, Slavin PL, editors: *The MGH guide to primary care psychiatry,* ed 2, New York, 2004, McGraw-Hill.

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Intensive Care Unit Patients

John Querques, M.D.
Theodore A. Stern, M.D.

Including a chapter on the psychiatric care of patients in an intensive care unit (ICU) runs the risk of suggesting that the evaluation of patients is somehow different depending on their location in the general hospital and that provision of their psychiatric care likewise differs because of that locale. Such a risk evokes the unfortunate appellation "ICU psychosis," with its erroneous suggestion that a psychotic condition could be induced by a patient's mere residence in an ICU and the absurd conclusion that transfer out of that environment is curative. We maintain that patients and their needs transcend geography; however, we also recognize that the critical nature of illnesses treated in ICUs creates a unique environment for patients, staff, and consultation psychiatrists alike. In this chapter, the serial presentation of a typical ICU psychiatric consultation highlights the distinguishing characteristics of this distinctive setting, the common reasons for consultation requests in the ICU, and the clinical approach to consultative practice in the ICU.

THE INTENSIVE CARE UNIT SETTING

The chief difference between the ICU and other hospital units is the severity of the morbidity treated there. Patients are admitted to ICUs when they require life support for organ system failure, close monitoring or treatment for potentially life-threatening complications, or careful observation and treatment that cannot be safely provided elsewhere in the hospital.[1,2] Some of the conditions commonly treated in the ICU include stroke, myocardial infarction (MI), arrhythmias, severe pneumonia, sepsis, multisystem organ failure, trauma, and burns.

Commensurate with this degree of morbidity, the intensity of the treatment arrayed against these life-imperiling conditions contributes significantly to the ICU ambiance. The numerous lines—wires, catheters, and tubes—wending their way to and from critically ill patients attest to the high-technology care rendered in the modern ICU. Patients routinely require mechanical ventilation, which entails endotracheal intubation and sedation and sometimes pharmacologic paralysis; use of vasopressors, cardiac monitors, pacemakers, parenteral nutrition, and several intravenous (IV) antibiotics is common. In more severe situations, renal replacement therapies, intraaortic balloon pumps, left ventricular assist devices, and heart–lung machines become necessary. In the center of, and almost eclipsed by, this mechanical mélange lies the patient, usually sedated and still, seemingly lifeless.

The flashing lights, sounding alarms, and constant whirrings of machines in action create an almost surreal, dehumanized atmosphere that is difficult for patients, families, and staff to tolerate. It seems odd that human lives hang in the balance in such a mechanized setting, the nature and purpose of which has been indicted for engendering delirium, anxiety, and depression in patients; tension and stress that can progress to fatigue and burnout in ICU staff; and feelings of hopelessness, helplessness, frustration, despair, and anger in family members, as well as patients and staff. The acuity of illness and potential for rapid changes in clinical status create a tremendous pressure for the staff to stay ahead of the curve and a powerful stimulus for families to remain on high alert. When a patient succumbs to an illness that ultimately proves a foe mightier than the awesome therapeutic forces arrayed against it, the staff confronts death and their own personal feelings of weakness, imperfection, insecurity, and impotence that may be stimulated by the loss of a patient. Amid their own struggles, they must somehow comfort bereaved family and friends.

THE PSYCHIATRIST IN THE INTENSIVE CARE UNIT

The psychiatrist called to assess a patient in the ICU approaches the task with all of the preceding in mind. The consultant must brace himself or herself for the experience of intense pressure that surrounds the care of critically ill patients, lest he or she be disarmed by it. The consultant is aware of the strain borne by the physicians and nurses who toil in this environment daily and respects that they might be preoccupied or busy with a clinical matter more pressing than the consultant's own. In dealing with families, the consultant is cognizant that their extreme apprehension might color their account of the patient's history and their appraisal of the current situation. Family members may be unimpressed by the need for a psychiatrist when their loved one is seen as barely clinging to life; they may think of such a consultation as superfluous and they might even be insulted, annoyed, or angered by what feels like an intrusion. Even staff might not be immune to this reaction to the psychiatrist, feeling that the brain—let alone the psyche—is less important than the "real" problem.

The consulting psychiatrist anticipates the likely moribund state of acutely ill patients, their consequent inability to participate in the usual psychiatric examination, and the need to modify the examination accordingly. Even more than usual, the history from the patient may be vague and spotty, if not entirely nonexistent. The consultant appreciates that the rapidity of clinical change in patients in the

ICU necessitates frequent (probably daily, if not twice-daily) visits; careful review of clinical developments as discussed with the team, culled from the chart, and gleaned from laboratory results; and a degree of accessibility greater than that required on general medical–surgical floors.

In the account of a psychiatric consultation in the ICU that follows, we highlight each of these characteristics of the ICU setting and review three common reasons for psychiatric consultation requests in the ICU: depression, altered mental status, and decision-making capacity. The fictitious, but typical, case also demonstrates that the consultee's question often shifts as the patient's clinical status changes and that a single consultation in the ICU often is actually several consultations in one. The case is presented in segments, much as a real case typically unfolds.

CASE 1

Mr. A, a 70-year-old man with a history of diabetes mellitus, hypertension, a stroke, and an MI was admitted to the ICU with severe pneumonia. He was febrile, tachypneic, and hypotensive, and the team was concerned about the possibility of sepsis. IV antibiotics were started, and by the next morning, the chest film and Mr. A's clinical status had improved, although blood cultures were still pending and the possibility of sepsis still loomed.

Because Mr. A looked depressed, a psychiatrist was called to evaluate depression. When the psychiatrist arrived at the bedside, Mr. A was diaphoretic and taking 30 breaths per minute. In place were two IV catheters, a cardiac monitor, and a Foley catheter. Because his breathing was so labored, Mr. A initiated no speech and he kept his answers short; they were almost inaudible. At times, he appeared to drift off even though he remained awake, and the psychiatrist had to regain Mr. A's attention periodically. Though he was not feeling particularly "joyous," as he said with as much of a laugh as his shallow breath allowed, he denied feeling depressed, sad, or "down in the dumps." Given Mr. A's discomfort, the psychiatrist terminated the interview early; his family was too overwhelmed to talk to the psychiatrist.

The psychiatrist's impression was that Mr. A was delirious due to infection and hypotension. He also suspected an underlying dementia but could not be sure given the paucity of information in the history. In the face of Mr. A's denial of depressed mood, a demonstrable (albeit small) affective display, and inattention, a diagnosis of major depression could not be made. Because the delirium was mild and was not associated with agitation, the psychiatrist recommended checking and monitoring "the usual suspects" but not instituting a psychopharmacologic intervention. Some clinicians would have opted to suggest treatment with a dopamine-blocking agent even in the absence of agitation.[3–5]

Consultation requests to "rule out depression" are common in the ICU. One reason for this is the notion held by some physicians and nurses that a patient in extreme clinical circumstances *must* be depressed. In this belief, such clinicians consider psychiatric diagnosis to be merely a matter of intuitive common sense rather than of expert clinical judgment.[6] One expects a patient with a serious illness to have certain feelings about his or her plight (e.g., sadness, worry, anxiety, dread, or anger). However, intuition alone is insufficient to make a diagnosis; careful clinical assessment is required. In this case, the observation that Mr. A looked depressed tipped the scale and prompted the consultation request for a more comprehensive examination and for an expert opinion.

Another reason consultations to assess depression are common in the ICU is mistaking *biography* for *history*,[6] as may have occurred if Mr. A had been asked if he was depressed and he answered affirmatively. The syndrome of depression is not just feeling depressed, sad, or blue, however, but rather is a constellation of specific affective, behavioral, and cognitive symptoms and signs. *It is only after a patient's current affective state is embedded in the context of an historical perspective that a diagnosis of major depression can be made*. Under extreme pressure of time and stress, ICU teams often defer to a psychiatrist to elicit the requisite history and to rule depression in or out.

Mr. A's clinical state precluded a thorough elicitation of historical evidence for depression; it highlighted the need for flexibility in modifying the usual clinical examination according to the patient's needs. Faced with a paucity of historical detail, the consultant placed a high premium on the mental status examination; most importantly, he noted inattention, which a diagnosis of depression does not readily explain. Some might argue that the consultant should not have ruled out depression because he did not collect the data required by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[7] and depression might underlie the delirium. Others, as do we, contend that a diagnosis of depression in the face of delirium is difficult if not impossible to make and that even if it were feasible, the presence of delirium trumps it. If depression is still suspected after the sensorium clears, the consultant can reinterview the patient and also elicit history from family and friends.

The consultant noted the possibility of dementia underlying the delirium. This suspicion was based on a knowledge of Mr. A's history of diabetes and hypertension (both of which can cause microvascular changes in the cerebral circulation), as well as prior stroke and MI (evidence of disease in two separate vascular territories) and knowledge that a "bad brain" or an "insulted brain" (a brain affected by age, trauma, structural lesions, extensive substance use, human immunodeficiency virus, or dementia) predisposes to delirium. Given the discomfort of Mr. A and the emotional state of the family at this point, the consultant did not yet have enough data to make this diagnosis definitively. It must await a change in the clinical circumstances.

A discussion of the "usual suspects" invoked by the consultant and the decision to forego pharmacologic treatment is beyond the scope of this chapter; the interested reader is referred to Chapters 10 and 11.

CASE 1, *continued*

When the consultant returned the following morning, he found that Mr. A had become agitated overnight and had removed both of his IV catheters, thus missing a scheduled dose of antibiotics. Whereas the day before the consultant believed that Mr. A had a quiet delirium, today he believed that the delirium was an agitated one. After ensuring that serum potassium, calcium, magnesium, and albumin levels, as well as the QT interval corrected for heart rate, were normal, he recommended haloperidol 1 mg orally twice daily.

This turn of events highlights the importance of frequent visits to the patient in the ICU. Given the development of agitation, the diagnosis shifted slightly from a quiet to an agitated delirium, which warranted a change in management (i.e., empirical treatment of the agitation with an antipsychotic). Moreover, the agitation in this case had already jeopardized Mr. A's treatment and would very likely continue to do so if not treated. While the team addressed the underlying causes of the delirium (infection and hypotension), empirical treatment with an antipsychotic was essential to quell the agitation.

Low serum levels of potassium, calcium, and magnesium and the administration of certain medications (including haloperidol and atypical antipsychotics) can prolong the QT interval, which itself heightens the risk of torsades de pointes, a potentially fatal polymorphic ventricular tachyarrhythmia. The QT interval varies with heart rate, age, gender, time of day, and a host of other factors. The proper measurement of the QT interval; the most accurate method for its correction for heart rate; and the relationship among QT prolongation, torsades de pointes, and antipsychotics are the subjects of considerable uncertainty and disagreement, even among experts. Several reviews of this complicated topic are available.[8–15] In short, the administration of haloperidol (or another neuroleptic medication) to an agitated or delirious patient often allows necessary medical treatment to proceed uneventfully. This benefit generally outweighs the risk of a cardiac dysrhythmia.

CASE 1, *continued*

When the psychiatrist returned later that day, Mr. A's respiratory status had worsened and the team was concerned about needing to intubate him. They had solicited his informed consent, but he had refused to give it. Given his altered mental status, they asked the consultant if Mr. A was competent to refuse intubation and mechanical ventilation.

Again illustrated is the propensity for clinical change in ICU patients, the consequent importance of frequent visits, and the broadening of the consultation question. In this way, the psychiatrist often becomes an integral member of the extended team, much as an infectious-disease or endocrine consultant would in this case.

The team mistook *competency* for *capacity*, the former being a legal notion that can be determined only by a judge. *Capacity*, on the other hand, is a clinical term that refers to a patient's mental capability to understand his or her situation (e.g., the illness, the recommended treatment, alternative treatments, and the risks and benefits of those interventions) and to accept or to refuse a treatment recommendation consistent with his or her own personal ideals and values.[16] Whereas any physician, regardless of training, is able to assess a patient's capacity (and, in fact, does so routinely any time he or she does even simple procedures like phlebotomy and IV insertion on a patient), given their special training in examination of affect, behavior, and thinking, psychiatrists are often called on to render these opinions.

These consultations often arise only when a patient *refuses* a recommended course of therapy. Paternalistic physicians tend to think that the patient's thinking process *must* be impaired if he or she disagrees with the treatment plan; if the patient accepts, his or her capacity is presumed intact. However, this common occurrence belies a fundamental misconception about decision-making capacity; that is, it hinges not on *what* the patient decides but on *how* the patient decides it. Whether the patient opts for the course of treatment recommended by the physician, or the therapy that the doctor would choose for himself or herself if the doctor were in the patient's shoes, is irrelevant. Rather, the patient must make a stable choice based on a full understanding of the facts and an appreciation of those facts as they pertain to him or her specifically, and that is consistent with his or her own goals and values.[16]

A layperson's understanding of the medical facts is sufficient. In this case, the consultant wants to assure himself that Mr. A knows and understands the following:

- He might stop breathing because of the pneumonia, an infection of the lungs.
- Should this happen, a machine can breathe for him by means of a tube inserted into his windpipe; without the tube and the machine, he will die.
- Generally, as pneumonia resolves, patients who require a breathing machine eventually resume breathing on their own.
- The risks of the tube include intubation of the food pipe, bleeding, infection, and hoarseness when the tube is removed.
- No alternative treatments exist.

In addition, the consultant must be sure that Mr. A appreciates what these facts mean for him specifically. The following are examples:

- His previous MI renders his heart more vulnerable to the stress of labored breathing and inadequate oxygenation.
- Although small, the risk of infection from the endotracheal tube is greater because he has diabetes.
- Although diabetes compromises his ability to fight the pneumonia, Mr. A does not have a terminal illness and his doctors expect him to recover, even if he requires mechanical ventilation.

Finally, the consultant looks for evidence that Mr. A's choice coincides with his values and goals. For example, if Mr. A repeatedly indicated that he wanted to live while steadfastly rejecting intubation (without which, as he has been told, he would most assuredly die if he stopped breathing on his own), the consultant would rightly detect an inconsistency between the patient's decision and his desire to live.

Because capacity is not global, a patient may have capacity to make some decisions but not others. The reason for this discrepancy lies in the risk-to-benefit ratio of the proposed diagnostic or therapeutic intervention.[17] When the benefit of a treatment far outweighs its risk, the standard for capacity to accept is low, but the standard for capacity to refuse is quite high. In Mr. A's case, the relatively small risk of bleeding, infection, and so on, compared with the overwhelming benefit of mechanical ventilation sets a high standard for capacity to refuse this treatment.

CASE 1, *continued*

The psychiatrist offered his opinion that Mr. A did not have the capacity to refuse intubation and mechanical ventilation. When his respirations became even more labored, he was sedated and intubated; mechanical ventilation commenced. He then could not speak and he had no enteral route. The consultant recommended administration of IV haloperidol.

Psychiatric examination and treatment of Mr. A became exceedingly difficult, but not impossible. The psychiatric consultant in the ICU must be creative, resourceful, and ready to accommodate to the changing clinical status of the patient. Lack of an oral route is easily circumvented, because medications can be crushed and delivered through a nasogastric tube or delivered parenterally. Although haloperidol is not approved by the Food and Drug Administration for IV use, widespread experience with this agent attests to its safe and effective use by this method in delirious, medically ill patients, with the same caveats that apply to oral use.

Intubated patients can communicate in several ways: by writing; by mouthing answers; by pointing to letters on a letter board; or by responding to yes–no questions with head nods, eye blinks, or squeezes of the examiner's hand. Requiring practice for both the patient and the physician, these maneuvers can be quite time-consuming and frustrating, especially when the patient is sedated (which is the rule in intubated patients).

A psychiatric consultant can feel stymied by an obtunded patient's inability to engage in a verbal dialogue. However, a host of physical findings can be made by simple observation (e.g., diaphoresis, dry skin, flushing, mydriasis, miosis, tremor, myoclonus, and facial asymmetry). Muscle tone, reflexes (primitive and deep tendon), and pupillary reaction to light are also assessable in a somnolent patient, as are the vital signs. Scoring of verbal, motor, and eye-opening responses according to the Glasgow Coma Scale[18] rounds out the examination of the lethargic patient.

CASE 1, *continued*

Over the next several days, the pneumonia and the delirium steadily improved. Mr. A was successfully extubated, and haloperidol was discontinued. Now able to speak in full sentences, albeit hoarsely, he provided the consultant with additional history. This information, added to collateral data obtained from the family, allowed the consultant to confirm his preliminary impression of the absence of major depression but the presence of an underlying dementia.

CONCLUSION

The successful denouement of this case showcases again the critical importance of flexibility, responsiveness, and resolve on the part of the ICU psychiatric consultant. First a competent physician, the psychiatric consultant must accept responsibility for the patient's care, see it through from initiation of the consultation to its end, and approach the patient and the family fully aware that the arc of each consultation is unique and unpredictable. Patients' beclouded sensoria and family members' taxed emotional states yield information in piecemeal fashion; history emerges only when the bits and pieces are stitched together. Attention to linguistic nuance and limbic music take a backseat to keenness of observation and physical and neurologic examinations. No place for premature diagnostic closure, the ICU adheres to an unfixed timetable and the clinical state of affairs largely resembles a moving target. In the ICU, one minute's certainty becomes the next minute's wild speculation, and the consultation psychiatrist assigned there must always be in "Condition Red."

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31 Genetics and Psychiatry

Daniel H. Ebert, M.D., Ph.D.
Christine T. Finn, M.D.
Joan M. Stoler, M.D.
Jordan W. Smoller, M.D., Sc.D.

Genetics strongly influences the incidence, clinical course, and treatment of psychiatric disorders. An assessment of the role of genetics in a patient who presents with psychiatric signs and symptoms in the general hospital setting enriches the formulation of a case. Unfortunately, the genetic basis of psychiatric disorders, and the role of genes in modifying treatment outcomes, is still largely unknown. Genes are beginning to be rigorously linked to neuropsychiatric disorders, allowing for opportunities to improve our understanding of the mechanism of disease for these disorders and to develop treatments specifically targeted to these mechanisms. We anticipate that over the next decade genetics will be increasingly important in the diagnosis and treatment of patients with psychiatric issues in the general hospital setting. For instance, psychiatric treatments may be tailored to specific genetic contexts.

In addition to primary psychiatric disorders, many genetic syndromes and metabolic diseases have psychiatric symptoms as part of their observed presentation. In fact, behavioral manifestations may be as important as other clinical features for the identification of underlying genetic illnesses. Whereas some patients may meet full *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for psychiatric disorders, others may have more general symptoms (e.g., hyperactivity, anxiety, aggression, cognitive deficits).

This chapter provides a brief overview of the genetics of major psychiatric disorders and a subset of genetic syndromes and inborn errors of metabolism that the general psychiatrist may encounter in the hospital or clinic setting. This chapter emphasizes several characteristics about the genetics of major psychiatric disorders. First, psychiatric disorders have a substantial genetic component. Second, the environment plays a substantial role in the expression of these disorders, and there are significant interactions between the genetic background and the environment that lead to disease expression. Finally, this chapter highlights several current approaches used to identify the genetic basis of psychiatric disorders and offers recent insights about psychiatric genetics derived from these approaches.

Although the genetic syndromes with psychiatric features presented in this chapter are relatively rare, knowing when to suspect that a genetic or metabolic issue may be contributing to the presenting condition of a patient is important in formulating a differential diagnosis. Proper identification of genetic and metabolic illness may allow for new opportunities for treatment or intervention directed at the primary process (e.g., correction of hyperammonemia in urea cycle disorders) rather than management of its downstream effects (e.g., delirium). For the most part, the disorders reviewed here may present in late childhood to adulthood; this chapter specifically excludes those disorders that are lethal in infancy or early childhood. Although it is not considered the role of the psychiatrist to diagnose specific genetic and metabolic illnesses, knowledge of these disorders aids clinical decision-making for all specialties. When an underlying genetic syndrome or metabolic disease is suspected, a consultation by a geneticist may greatly benefit the patient and help direct clinical management.

GENETICS OF PSYCHIATRIC DISORDERS

Epidemiology of Psychiatric Disorders

Epidemiologic studies have demonstrated that psychiatric disorders have a significant genetic basis. Twin, family, and adoption studies can assess the magnitude of genetic and environmental factors that lead to a phenotype.[1] Comparing concordance rates in monozygotic and dizygotic twins for various phenotypes can provide an estimation of the heritability of a disorder. A twin pair is concordant if both co-twins have the same phenotype or disorder. *Heritability* refers to the proportion of the phenotypic differences among individuals in a population that can be attributed to genetic factors. Heritability can be estimated by a formula comparing the co-twin phenotypic correlation for monozygotic twins and dizygotic twins. A disorder with a significant genetic etiology would be expected to be more concordant in monozygotic twins, who are genetically identical, than in dizygotic twins, who share, on average, 50% of their alleles. Heritability estimates the magnitude of genetic influences in a population and not in a particular individual. In addition, *heritability* refers to the additive sum of all the genetic influences on a trait in the population. Heritability does not provide information about the number of genes that are involved or the effect size of a given gene. For example, the heritability of breast cancer has been estimated at 27%, yet dominantly inherited single major genes, such as *BRCA1*, have been identified.[2]

Family studies usually measure the lifetime prevalence of a disorder among first-degree relatives of the index case. Adoption studies can help further disentangle genetic and environmental influences by comparing rates of a disorder in biological family members with those in adoptive

family members. In addition, comparing rates of a disorder in twins that were raised in the same household with twins reared in separate households and environments can provide further evidence about the genetic and environmental influences that lead to expression of the disorder.

Many epidemiologic studies have demonstrated that schizophrenia has a substantial genetic component. The concordance rate for monozygotic twins is approximately 50%, and for dizygotic twins it is 15%. The heritability of schizophrenia has been estimated at 70% to 89%. Family studies have shown that first-degree relatives of patients with schizophrenia have approximately a 10% risk of developing schizophrenia, compared with the population lifetime risk of approximately 1%. The risk drops to 4% for second-degree relatives and to 2% for third-degree relatives. Adoption studies have demonstrated that the prevalence of schizophrenia is approximately fourfold higher in biological relatives than in adoptive relatives.[3,4]

Bipolar disorder is also highly genetic. Concordance rates in monozygotic twins are approximately 40% to 45%, and in dizygotic twins the rate is 5%. The heritability of bipolar disorder has been estimated to be between 60% to 85%. Twin studies also suggest that genetic influences on bipolar disorder overlap with those contributing to major depressive disorder (MDD), schizophrenia, and schizoaffective disorder. From a host of family studies, the risk of bipolar disorder in first-degree relatives of patients with bipolar disorder is approximately tenfold higher than those in the general population. In addition, first-degree relatives have a twofold to threefold increased risk of developing MDD.[5]

MDD also has a significant genetic etiology, though less so than bipolar disorder and schizophrenia. Concordance rates between monozygotic twins range from 23% to 49% and for dizygotic twins between 16% and 42%. Heritability is estimated at 40%.[6] The largest twin study was of 15,000 Swedish twin pairs, and the heritability of MDD was estimated at 42% for women and 29% for men.[7] A meta-analysis of family studies found that the prevalence of MDD was threefold higher in relatives of patients with MDD than in relatives of unaffected controls.[6] Several clinical features—early onset, recurrent episodes, chronicity, suicidality, and greater levels of impairment—have been associated with increased familial risk.[8]

Anxiety disorders also are influenced by genetics. Concordance rates of panic disorder in monozygotic twins are approximately 24%, and in dizygotic twins they are 11%. The estimated heritability of panic disorder is 45%. First-degree relatives have an approximately fivefold increased risk of panic disorder compared with those in the general population.[9,10] Early-onset panic disorder confers an increased risk of the disorder for relatives.[11] Twin and family studies also suggest that the genes influencing panic disorder overlap with those influencing generalized anxiety disorder, phobic disorder, posttraumatic stress disorder, and depression. Heritability for phobic disorders has been estimated to range between 10% and 39%. First-degree relatives have a fourfold increased risk of phobic disorders compared with those in the general population.[9,10]

Substance use disorders, including those involving alcohol and drugs, have been shown to have a significant genetic component. For example, the heritability of alcohol dependence, a disorder commonly seen in the general hospital setting, has been estimated to be 35% to 60%.[12–14] Family studies demonstrate that first-degree relatives of individuals with alcohol dependence have a twofold to fourfold higher risk of developing alcohol dependence than those in the general population.[15] Adoption studies have indicated that there is an increased risk of alcohol dependence in adopted individuals who have a biological parent with alcohol dependence.[16]

Several disorders of childhood and adolescence have been demonstrated to have substantial genetic etiologies. For attention-deficit/hyperactivity disorder (ADHD), a bevy of twin studies have demonstrated a higher concordance rate in monozygotic twins than in dizygotic twins. The estimated heritability of ADHD is 75%. Family studies indicate that first-degree relatives of individuals with ADHD have a twofold to eightfold higher risk of developing ADHD than the relatives of controls.[17]

Autism is highly genetic. Concordance rates for monozygotic twins, 70% to 90%, are markedly higher than those for dizygotic twins (5% to 10%). The heritability of autism has been estimated to exceed 90%. The risk of autism in siblings of affected children is approximately 2% to 7%, which is 50 to 100 times higher than the prevalence in the general population. For first-degree relatives of individuals with autism, the risk for a broader autism phenotype, including autism spectrum disorders and milder abnormalities of social and language function, may be as high as 10% to 45%.[18–20]

These epidemiologic studies demonstrate that genetics substantially influences the expression of many psychiatric disorders (including psychotic, mood, anxiety, and substance use disorders; ADHD; and autism). Schizophrenia, bipolar disorder, ADHD, and autism have a particularly significant genetic basis. In addition, these epidemiologic studies suggest that the environment also contributes substantially to the expression of these psychiatric disorders, more so for MDD than for schizophrenia or autism. Environmental factors that contribute to the expression of these disorders include early life events, stressful life events, difficult family environments, lack of social supports, exposure to toxins and infectious agents, and a dysregulated immune system.[1]

Gene-by-Environment Interactions

Interestingly, genes and the environment can interact in individuals and contribute to expression of disorders. This gene-by-environment interaction was demonstrated in an often-quoted 2003 study of the interaction of the serotonin transporter gene and stressful life events in the onset of episodes of MDD.[21] The serotonin transporter is the target of selective serotonin reuptake inhibitor (SSRI) antidepressants. There is a common polymorphism in the promoter of the serotonin transporter gene that leads to a "long" allele or a "short" allele lacking a 44 base-pair sequence. The short allele is associated with a reduced expression of the serotonin transporter. The 2003 study by Caspi and colleagues examined a birth cohort of 1037 children followed to age 26 years for evidence of a linkage between the short or long allele of the serotonin transporter gene, stressful life events, and MDD.[21] Stressful life events included employment, financial, housing, health, and relationship problems. In the absence of stressful life events, the presence of either the short or long allele of the serotonin transporter gene was not associated with major depressive episodes or depressive symptoms

in these individuals. However, with an increasing number of stressful life events, individuals with the short allele of the serotonin transporter gene, compared with those with the long allele, have an increasingly greater number of major depressive episodes, depression symptoms, suicidal thoughts, and suicide attempts. The percentage of individuals with the short allele that had signs and symptoms of MDD increased as the number of stressful life events increased. In addition, individuals with the short allele had an increased probability of adult major depressive episodes with increasing childhood maltreatment, whereas individuals with the long allele did not have more adult depression with childhood maltreatment. In both of these examples, individuals heterozygous for the short and long alleles had an intermediate phenotype compared with individuals homozygous for the short or long allele.[21] These experiments show how an environmental factor, stressful life events, and childhood maltreatment interact with the genetic background of an individual, in this case a functional polymorphism in the serotonin transporter gene, to lead to psychiatric symptoms and disorders, MDD in this example. For a subset of patients in the general hospital, psychiatric signs and symptoms may be due to an interaction between genes and environmental factors, and such an interaction can be considered in the formulation of the case and creation of a treatment plan.

Identification of Genes and Genomic Regions Linked to Psychiatric Disorders

A major current undertaking in psychiatric neurosciences is to identify genes and genomic regions that influence the expression of psychiatric disorders. Identifying genes that lead to psychiatric disorders will provide opportunities to further understand the mechanism of disease and to develop new treatments. Like diabetes and many other medical disorders, the genetics of psychiatric disorders is complex. For many individuals with psychiatric disorders, a leading hypothesis is that many risk genes of small effect size interact with one another, and at times with environmental factors, to lead to the disease phenotype. However, there are examples of individual dominant genes that lead to a psychiatric disorder. For instance, more than 95% of Rett syndrome cases, an autism spectrum disorder discussed in the following section, are caused by mutations in *methyl-CpG-binding protein 2 (MeCP2).* Mouse models with alterations in expression of *MeCP2* led to autism-like phenotypes, providing further evidence that *MeCP2* dysfunction is the cause of an autism spectrum disorder.

Several approaches have been used to identify genes linked to psychiatric disorders. To find where in the genome a disease mutation or susceptibility locus may reside, linkage analysis measures the co-inheritance of alleles and phenotypes within families in which individuals have the disorder. In association analysis, the co-inheritance of alleles and phenotypes is assessed across families. One approach has been to pick candidate genes to examine in association studies. Candidate genes have included those involved in the monoaminergic neurotransmission (e.g., transporters, receptors, and enzymes involved in the metabolism of serotonin, dopamine, and norepinephrine). The serotonin transporter gene, discussed previously, is an example of a candidate gene that has been studied.

An exciting new approach is genome-wide association studies that test for associations of genomic regions with psychiatric disorders in a large sample of patients. In genome-wide association studies, new high-throughput genotyping technologies are used to measure single nucleotide polymorphisms (SNPs) throughout the genome and look for associations of particular SNPs with a disease phenotype. SNPs, in which one of the four nucleotide bases is substituted for another, are common forms of genetic variation. With the International HapMap project, SNPs throughout the genome were extensively cataloged, allowing for an assessment of an individual's SNPs throughout the genome. By associating particular SNPs with a phenotype, these genome-wide association studies determine which gene, or genomic region, variants occur more frequently with a particular psychiatric disorder. A critical parameter for these genome-wide association studies in psychiatric disorders is collection of sufficiently large samples of patients with the disorder so that the study has sufficient statistical power to detect an association between SNPs and phenotypes. Genome-wide association studies have been successful for other complex disorders (e.g., diabetes), providing hope for the study of psychiatric disorders.

An alternative approach to determine the genetics of psychiatric disorders is to identify, and find the genetic linkage to, intermediate phenotypes and endophenotypes. The hypothesis for this approach is that the clinical signs and symptoms that underlie diagnoses described in the DSM-IV may be far downstream of the more proximal effects of these genes on the brain. The effect of genes on intermediate phenotypes may be greater and more direct than the effect on the phenotype of a psychiatric disorder. Neuroimaging phenotypes are an example of an intermediate phenotype or endophenotype. For instance, the polymorphism in the serotonin transporter gene discussed previously has been associated with increased amygdala reactivity and reduced coupling of corticolimbic circuits.[22] Another intermediate phenotype that is studied is the inhibition of P50-evoked responses to repeated auditory stimuli, a phenotype that may underlie the abnormalities in sensory gating observed in schizophrenia.[23]

In molecular cytogenetic approaches, researchers study chromosomal abnormalities (e.g., balanced translocations, deletions, or duplications that correlate with psychiatric disorders). A compelling example of this approach was the discovery of the gene called *Disrupted-in-Schizophrenia-1 (DISC-1)* in a large Scottish family with a high incidence of schizophrenia. This family had a balanced translocation between chromosomes 1 and 11, and *DISC-1* was discovered at the breakpoint of this translocation.[24,25] Studies of *DISC-1* function are an active area of current neuroscience research. *DISC-1* is involved in regulating brain development, neuronal migration, and a signaling pathway important for learning, memory, and mood.[26–29] The translocation in this large extended Scottish family is associated with not only schizophrenia but also other major psychiatric disorders, such as bipolar disorder and MDD.[24,25] These findings highlight the concept that genes causing psychiatric illness may not fit neatly into DSM-IV diagnostic categories. Genes, such as *DISC-1*, that influence how the brain develops and function may impart a risk for multiple disorders and not be specific to a single disorder. In the future diagnostic categories for psychiatric disorders may be refined on the basis of findings about the genes involved in psychiatric disease.

An interesting new finding from psychiatric genetics is that patients with schizophrenia and autism have an increase in copy number variants (CNVs) compared with those in control populations.[30–35] CNVs are duplications or deletions of genomic segments ranging from 1 kilobase to several million bases. Through the use of high-throughput genomic technology and microarrays, CNVs and structural variants in the genome can be determined genome-wide in different patient populations. A 2008 study showed that novel deletions and duplications of genes were present in 15% of 150 individuals with schizophrenia and in 5% of controls, a difference that was highly statistically significant.[34] Most of the structural variants identified were different and rare, and these variants disrupted genes important for brain development. A larger study of 3391 patients with schizophrenia found a 1.15-fold increased burden of CNVs in patients with schizophrenia than in controls.[30] Rarer, single-occurrence CNVs were more strongly associated with schizophrenia. Several large deletions, including a deletion found in velocardiofacial syndrome (VCFS) discussed later, were found to be significantly associated with schizophrenia.[30] In addition, children with autism spectrum disorders were found to have a significantly increased burden of *de novo* deletions and duplications.[32,36–38] These studies indicate that schizophrenia and autism can be caused by specific genomic variations, including genomic deletions. These studies also suggest that a subset of schizophrenia and autism may be caused by mutations that have a large effect size on the disease phenotype and that these mutations may be rare and arise *de novo*, or of recent origin, in individuals and families.

SELECTED GENETIC SYNDROMES WITH PSYCHIATRIC FEATURES

The normal number of human chromosomes is 46, organized into 23 pairs. Chromosomes numbered 1 to 22 are autosomes; sex chromosomes make up the remaining pair. The sex chromosomes are made up of two X chromosomes in females (46, XX), and one X and one Y chromosome in males (46, XY). Abnormalities of chromosomes may include whole chromosomes (aneuploidy), chromosomal rearrangements (translocations or inversions), small deletions or duplications, or mutations in single genes. Visualization of chromosome number and gross structure is accomplished by karyotype analysis. More recently, other cytogenetic and molecular techniques have allowed for focused study of smaller regions of chromosomes or individual genes. Fluorescent in situ hybridization (FISH) is a cytogenetic technique that uses fluorescent probes to investigate the presence of small, submicroscopic chromosomal changes that are beyond the resolution of karyotype analysis.

Genetic syndromes are disorders with a characteristic set of features that are due to an underlying common mechanism. Features may include congenital anomalies, specific physical features, associated medical disorders, cognitive deficits, and psychiatric or behavioral symptoms. When considering a diagnosis of a genetic syndrome, clinicians may be guided by several Web-based resources (OMIM, Geneclinics) and software packages (POSSUM) that allow the option of searching for disorders on the basis of observed findings and historical information.

Currently, there are no available treatments that can cure genetic syndromes or replace missing genetic material. For this reason treatment is directed at symptomatic management of physical malformations, surveillance for associated medical conditions, and early developmental interventions. Special education or additional academic supports may be needed. Management of psychiatric and behavioral symptoms is accomplished by a combination of pharmacologic treatment and other therapies, including behavioral techniques.

Assessment of the Patient for Genetic Syndromes

Certain features of the medical history, family history, and physical examination may indicate the possibility of a genetic syndrome that underlies observed psychiatric and behavioral symptoms. In addition to the comprehensive review of systems and medical history completed during the initial assessment of patients, inclusion of questions about pregnancy and the perinatal period, birth defects, and surgeries in infancy or early childhood that may have been performed to correct congenital anomalies may provide valuable clues to an underlying genetic syndrome. In addition, careful review of the developmental history (with special attention paid to early developmental milestones) may reveal the presence of specific developmental delays, mental retardation, or learning disabilities. When inquiring about family history, the clinician should ask specific questions about recurrent miscarriages; stillborn children; early infant deaths; and a family history of mental retardation, seizures, or congenital illness, which may help in uncovering an underlying genetic disease, especially when the pattern of illness appears to be mendelian (e.g., dominant, recessive, or X-linked inheritance). Physical examination may reveal abnormalities of growth, dysmorphic features, or involvement of various organ systems. Results of imaging studies may aid in the assessment of underlying malformations suggested by physical examination (e.g., echocardiogram to rule out structural heart defects when a murmur is appreciated).

Selected Genetic Disorders

CASE 1

Ms. A, an 18-year-old woman, presented to the psychiatric emergency room with auditory hallucinations and paranoid ideation. She had a history of ADHD and oppositional behavior. Her full scale IQ was 78, and her verbal IQ was 15 points greater than her performance IQ, characteristic of a nonverbal learning disorder. Review of systems revealed surgery in infancy for correction of a congenital heart defect and frequent episodes of sinusitis, otitis media, and pneumonia. On physical examination she was short with a flat facial expression. Facial features included a high-arched palate; a small chin; and a nose with a broad, square nasal root. Ms. A was admitted to the inpatient psychiatric service and treated with atypical neuroleptics with a good result. Consultation with the Genetics service for her dysmorphic facial features and congenital heart defect, along with her cognitive and psychiatric symptoms, resulted in a diagnosis of VCFS.

Disorders Due to Chromosomal Abnormalities and Microdeletions

Velocardiofacial syndrome/DiGeorge syndrome: The cohort of patients diagnosed with VCFS, which also includes most patients previously diagnosed with DiGeorge syndrome, is due to a microdeletion on chromosome 22q11.2, which results in the loss of up to 60 known and predicted contiguous genes.[39] VCFS has been called a "genetic subtype of schizophrenia," and it is estimated that as many as 2% of patients with schizophrenia may have this disorder and be undiagnosed.[40,41] This rate may be even higher among patients with childhood-onset schizophrenia.[42] Psychiatric symptoms in those with VCFS and schizophrenia do not appear to differ from those without VCFS and schizophrenia based on factors such as description of psychosis or co-morbid illnesses. Overall, between 60% and 75% of patients with VCFS have significant psychiatric morbidity, including mood disorders, ADHD, autism, substance abuse, anxiety disorders, and oppositional defiant disorder.[41,43–50] The physical features of people with VCFS include a characteristic facial appearance (broad and squared nasal root, midface hypoplasia, short palpebral fissures, retruded chin), cleft palate, and velopharyngeal insufficiency (which may manifest as hypernasal speech, nasal regurgitation in infancy, or frequent ear infections), congenital heart defects, aplasia of the thymus (leading to immune problems), problems with calcium homeostasis, low muscle tone, and scoliosis. Facial hypotonia may result in a somewhat flat, expressionless appearance. Learning disabilities, especially nonverbal learning disorder, are common. However, patients can exhibit only some of these features, and the spectrum of findings may vary even within families. Diagnostic testing is available on a clinical basis and involves testing for the microdeletion with FISH techniques.

Smith–Magenis syndrome: Smith–Magenis syndrome is due to a microdeletion of chromosome 17p11.2, resulting in the loss of several contiguous genes at that location. In infancy these patients may exhibit failure to thrive and hypotonia. Physical findings, which may change over time, include short stature, scoliosis, eye abnormalities, renal problems, heart defects, peripheral neuropathy, and hearing loss (both conductive and sensorineural). Characteristic facial features include a square face with prominent forehead, deep-set and upslanting eyes, a broad nasal bridge with a short nose and fleshy nasal tip, full cheeks, and a "cupid's bow" tented upper lip. The jaw becomes more prominent with age. Although they may have hypersomnolence in infancy, a striking feature of this syndrome is marked sleep disturbance, with absence of rapid eye movement (REM) sleep in some patients. In addition, abnormalities of circadian rhythms and melatonin secretion have been documented.[51–53] Most patients have developmental delay, and their intelligence quotients (IQs) may range from borderline intelligence to moderate mental retardation. Patients are described with symptoms of ADHD, tantrums, impulsivity, and a variety of self-injurious behaviors, including onychotillomania (pulling out finger and toe nails) and polyembolokoilamania (insertion of foreign bodies), headbanging, face-slapping, and skin-picking.[52,54,55] In addition, they may show stereotypies, most commonly a "self-hug" when happy.[56] Abnormalities of lipid profiles have been seen in these patients, with elevations of cholesterol, triglycerides, and low-density lipoprotein.[57] Diagnostic testing involves testing for the microdeletion with FISH or quantitative polymerase chain reaction (PCR) techniques.[52,57]

Williams syndrome: A microdeletion on chromosome 7q11.23 results in Williams syndrome. Loss of the gene for elastin *(ELN)* is hypothesized to contribute to at least some of the observed phenotypic features, including short stature and microcephaly, cardiac defects (most often supravalvular aortic or supravalvular pulmonic stenosis), and connective tissue disease (joint laxity, hernias, soft skin). Patients with Williams syndrome are described as having an elfin facial appearance with a broad forehead that narrows at the temples, a short nose with a fleshy nasal tip, large and prominent ear lobes, a wide mouth with full lips, and a small jaw. The iris of the eye has a stellate or lacy appearance. Other characteristics include a hoarse voice and hyperacusis (hypersensitivity to sounds). Mental retardation in the mild to severe range is usually present, with an average IQ of 56. Specific learning deficits in visual–spatial skills are in marked contrast to strengths in verbal and language domains and are important for the identification and care of these patients. Psychiatric symptoms and conditions include autism, ADHD, depression, and anxiety. Patients with this syndrome may show circumscribed interests or obsessions and may be somatically focused. Despite being socially disinhibited and overly friendly, they tend to have difficulty with peer relationships and may become socially isolated. Affected individuals are described as overly talkative, a feature that may be, in part, reflective of generalized anxiety. Diagnostic testing involves the detection of the microdeletion with FISH techniques.[58–61]

Prader–Willi syndrome: Although several genetic mechanisms may result in Prader–Willi syndrome, the absence of a critical region of the paternally inherited chromosome 15q11-q13 is central to the disorder. This region of chromosome 15 undergoes the process of imprinting, by which genes are switched on or off depending on whether they are of maternal or paternal origin. In contrast to Prader–Willi syndrome, the absence of the maternally derived region results in Angelman syndrome (severe mental retardation, seizures, ataxia, and characteristic behaviors). Prader–Willi patients may be hypotonic and show failure to thrive in infancy. Most have short stature and small hands, feet, and external genitalia; some have fair skin and hair coloring. A characteristic facial appearance with upslanting almond-shaped eyes and a thin upper lip is seen. The hallmark behavior of this disorder is hyperphagia, with resultant morbid obesity, which develops early in childhood. Behavioral interventions have been effective in controlling this behavior if started at an early age. Psychiatric symptoms and conditions include obsessional thoughts, compulsions, repetitive behaviors, mood disorders, anxiety, psychosis, ADHD, autism, skin-picking, and temper tantrums. Afflicted individuals may have a high pain threshold, and they rarely vomit. These patients may show decreased IQ and learning problems, although they also show areas of relative strength in visual–spatial skills (e.g., as with jigsaw puzzles). Diagnostic testing for Prader–Willi syndrome involves analysis of the critical region for methylation status (the process that determines whether genes are turned on or off) or the detection of the deletion by FISH techniques.[62–65]

Down syndrome: The majority of individuals with Down syndrome are diagnosed soon after birth. This disorder is included in this chapter because of its known association with Alzheimer's dementia, in which cognitive decline or changes in behavior in adults with Down syndrome may prompt psychiatric consultation. In 95% of cases, Down syndrome is due to an extra free copy of chromosome 21; the remainder of cases are due to unbalanced translocations or duplications involving the Down syndrome critical region on chromosome 21. Down syndrome is the most common genetic cause of mental retardation; an increased incidence is observed with older maternal age. Most clinicians recognize the characteristic Down syndrome face, which consists of eyes with upslanting palpebral fissures, epicanthal folds, and Brushfield's spots (white spots in the iris), a flat nasal bridge, low-set ears, and a protruding tongue. In addition, they have a short neck, short stature, and single transverse palmar crease. These patients may also have a variety of congenital malformations, including heart defects and duodenal atresia, and they have high rates of hypothyroidism. Mental retardation is seen in the majority of patients, with an average IQ of 24. Social skills are usually more advanced than would be expected given the level of mental retardation. Decline in cognition or changes in behavior in middle-aged adults with Down syndrome may indicate Alzheimer's disease. The presence of an extra copy of the amyloid precursor protein *(APP)* gene (one of the causative genes in early onset Alzheimer's disease) on chromosome 21 is thought to contribute to increased rates of dementia in these patients. Nonspecific behavioral symptoms, depression, and anxiety may also be seen. Diagnostic testing for Down syndrome involves karyotype analysis of chromosomes.[66–69]

Turner's syndrome: The majority of cases of Turner's syndrome are due to the loss of an entire X chromosome, which is designated as 45, X. These patients are female, with physical characteristics of short stature; a webbed neck; and a flat, broad chest. Diagnosis may be delayed until adolescence, when these girls fail to develop secondary sexual characteristics (as a result of gonadal dysgenesis). Use of hormonal therapy can help afflicted girls achieve pubertal changes but will not result in fertility. These patients may also have involvement of other organ systems, including congenital heart or kidney disease. Psychiatric symptoms and conditions include ADHD, depression, anxiety, and problems with social skills. Specific learning disabilities (especially visual–spatial deficits) have been reported. Diagnostic testing for Turner's syndrome involves karyotype analysis of chromosomes.[70–72]

Klinefelter's syndrome: Klinefelter's syndrome is due to the addition of an extra X chromosome, resulting in 47, XXY. These patients are male and usually described as tall, and they may be somewhat hypotonic and clumsy. They typically have a small penis and testes. Contrary to earlier descriptions, they have a male distribution of body fat and hair, although gynecomastia may be seen. Again, these patients may be first diagnosed in adolescence, after they fail to enter puberty, or as part of an infertility workup. Use of testosterone can help with the development of secondary sexual characteristics. An increased incidence of ADHD, immaturity, and depression has been reported in these patients. Cognitively, specific learning disabilities are seen. Diagnostic testing for Klinefelter's syndrome involves karyotype analysis of chromosomes.[73]

47, XYY: Males with an extra copy of the Y chromosome have been of interest to the psychiatric profession for many years because of reported increased criminality and antisocial behaviors in these patients. Although early studies conducted on criminal populations were limited by ascertainment bias, more recent studies have continued to show small increases in these behaviors in 47, XYY males compared with controls. However, increased rates of antisocial or criminal behavior appear to be related to the cognitive deficits seen in some of these patients.[74] Physical findings may include accelerated linear growth in childhood and tall stature as adults. They may have a lower than average IQ or specific learning disabilities, especially in reading and language domains. Psychiatric conditions include ADHD and conduct disorders.[75] Overall, the majority of these patients may never receive medical attention because they may lack any identifying features. Diagnostic testing for 47, XYY involves karyotype analysis of chromosomes.

Autosomal Dominant Single-Gene Disorders

Huntington's disease: Huntington's disease is due to an increased number of CAG triplet repeats in the *HD* gene on chromosome 4p16. The normal number of CAG repeats ranges from 10 to 26 in unaffected individuals, where patients with Huntington's disease have between 36 and 121 repeats. The number of repeats may expand from one generation to the next, and increased severity and earlier onset of illness (known as anticipation) may be seen in subsequent generations. Psychiatric symptoms are prominent in the early presentation of this disorder and may include changes in personality, depression, and apathy. Later, progressive cognitive decline and dementia occur. Mood lability and psychosis may also be seen. A high suicide rate is reported in these patients. Early physical findings include dysarthria and clumsiness with deterioration in both voluntary and involuntary movements and the development of chorea. The abnormal movements are often treated with high-potency neuroleptics, but there is no treatment that stops the progressive neurologic decline in this disease. Characteristic atrophy of the caudate and putamen may be apparent on MRI or CT of the brain. Diagnostic testing involves molecular detection of increased number of CAG repeats in the *HD* gene.[76–78]

Tuberous sclerosis: Tuberous sclerosis is due to mutations in the *TSC1* (on chromosome 9q23) or *TSC2* (on chromosome 16p13.3) genes. Patients with tuberous sclerosis exhibit characteristic skin findings of flat hypopigmented macules (ash leaf spots), shagreen patches (raised area with dimpled texture), and angiofibromas (red papular lesions). They may have small pits in their tooth enamel. Tumors occurring in different organ systems are seen, including central nervous system (CNS) tubers, retinal hamartomas, cardiac rhabdomyomas, and renal angiomyolipomas. Seizures are a common feature of this disorder. Patients with tuberous sclerosis have been reported to have symptoms of pervasive developmental disorder and

ADHD. Mental retardation may occur, depending on the extent of CNS involvement. The diagnosis is most often made on a clinical basis, but mutation analysis of the *TSC1* and *TSC2* genes is now available.[79–81]

Neurofibromatosis type I: Neurofibromatosis type I (NF1), previously known as von Recklinghausen's disease, is due to a mutation in the *NF1* gene on chromosome 17q11.2, which is believed to result in loss of tumor suppressor function. Abnormalities of skin pigmentation *(café au lait* spots, freckling in axilla or groin), Lisch nodules (small brown spots) on the iris, bony abnormalities, neurofibromas (cutaneous, subcutaneous, or plexiform), and macrocephaly are some of the physical findings in NF1. Complications may arise depending on the size or location of neurofibromas or because of the development of malignant tumors. Psychiatric symptoms may include learning disabilities and ADHD. Diagnosis is usually made on a clinical basis; mutation analysis of the *NF1* gene is available on a limited basis.[79,82,83]

X-Linked Dominant Disorders

Fragile X syndrome: In contrast to Down syndrome, which is the most common *genetic* cause of mental retardation, fragile X syndrome is the most common *inherited* (i.e., transmitted from a parent who carries the abnormal gene) cause of mental retardation. Fragile X is the result of dysfunction of the *FMR1* gene at Xq27.3 caused by increased numbers of trinucleotide repeats. Normal alleles have approximately 5 to 44 repeats, and borderline alleles have approximately 45 to 58 repeats. Having greater than approximately 200 CGG repeats results in the full syndrome; a "premutation" allele with approximately 59 to 200 repeats may expand to the full syndrome when passed on from a mother to her children. The full syndrome is most often found in male subjects, but female subjects who carry a full-length mutation on one of their X chromosomes may have features of the disorder of variable severity. Approximately one third of female subjects with a full-length mutation are thought to be normal, one third are mildly affected, and the remaining one third have findings similar to the full syndrome in males. In addition to mental retardation in the moderate to severe range, physical features, such as large testes, connective tissue disease (loose joints), low muscle tone, and characteristic facial appearance (large head with prominent forehead and jaw, long face with large ears) may help identify males with this disorder. Of note, the facial features and testicular size may be more apparent after puberty. Psychiatric symptoms include autistic features, ADHD, oppositional defiant disorder, mood disorders, and avoidant personality disorder and traits. Although carrying a premutation-length allele has not traditionally been associated with cognitive or behavioral findings, a variety of studies have shown increased rates of psychiatric symptoms, including social phobia and mood disorders, in these women. Diagnostic testing to determine the number of trinucleotide repeats in the *FMR1* gene is widely available.[84–88]

Rett syndrome: Rett syndrome is due to a mutation in the *MECP2* gene on chromosome Xq28. This syndrome is described in girls who appear normal at birth and during the first several months or years of life. They then experience a progressive loss of developmental skills associated with acquired microcephaly. Additional features include impaired language, loss of purposeful hand movements (replaced by stereotyped hand movements), gait abnormalities, seizures, and bruxism. It is classified as a pervasive developmental disorder in DSM-IV. Mutations in the *MECP2* gene, once thought to be fatal in males, have been recognized as a cause of developmental disorders in boys. Diagnostic testing for analysis of the *MECP2* gene is available.[89–92]

METABOLIC DISEASE

Inborn errors of metabolism are a class of genetic disorders that result in dysfunction of production, regulation, or function of enzymes or enzyme co-factors. The disruption of normal metabolic processes may lead to a buildup of pathway by-products or production of alternate substances that cause toxicity. In addition, the absence of essential pathway end products may lead to disease states. Classically, disorders of metabolism have been described in children. However, presentation or recognition of disease may be delayed in patients with relative preservation of enzyme activity that is seen in milder forms of disease, and many disorders have later-onset forms. Metabolic disorders are most often classified on the basis of the abnormal substances involved or by the cell location where the enzyme dysfunction occurs.

Testing for metabolic illness begins at birth, by population screening for a variety of illnesses by state-mandated newborn screening programs. However, the number of diseases tested for varies widely by state, and even the most comprehensive testing has been available only for the past several years. Thus it is unlikely that older children and adults would have benefited from these screening programs. Furthermore, even the most comprehensive state panels do not rule out all, or even most, genetic and metabolic diseases. For this reason suspicion of a metabolic disease should be pursued vigorously. Early identification of metabolic illness is crucial to maximize good outcome.

Assessment of the Patient for Metabolic Illness

Essential to the evaluation for possible metabolic illness is careful history-taking. Questions about dietary history (e.g., food intolerances, unusual food preferences, colic or reflux), a history of decompensation associated with minor illness, or history of transient neurologic symptoms (e.g., lethargy, encephalopathy, ataxia, confusion) may lead to detection of an underlying metabolic illness. In addition, careful review of developmental history, especially a history of a developmental regression, loss of skills, or decline in cognition, is important. Because many metabolic illnesses are inherited in an autosomal recessive fashion, a review of family history should include questions about consanguinity and ethnicity. In addition, a history of stillbirths or early infant deaths may prove informative. For example, it is thought that many children who died of Reye's syndrome (manifested by vomiting, liver dysfunction with fatty infiltration, and hypoglycemia) may have had underlying problems with disorders of fatty acid oxidation.

TABLE 31–1 Laboratory Studies to Evaluate Metabolic Illness

LABORATORY TEST	METABOLIC STATE/ DISORDERS TESTED FOR
Electrolyte panel	Acidosis, calculation of anion gap
Liver function tests	Storage of abnormal substances in liver
Blood gas	Determination of pH (acidosis vs. alkalosis)
Ammonia (NH_3)	Urea cycle disorders—primary elevation organic acidemias, disorders of fatty acid oxidation—secondary elevation
Lactate, pyruvate	Disorders of energy metabolism
Plasma amino acids	Amino acid disorders (e.g., urea cycle defects, homocystinuria)
Urine organic acids	Organic acidemias
Acylcarnitine profile	Disorders of fatty acid oxidation, organic acidemias
Very long chain fatty acids	Peroxisomal disorders
Urine mucopolysaccharides	Lysosomal storage disorders
Urine oligosaccharides	Lysosomal storage disorders

Abnormal results of routine and specialized laboratory studies may indicate a primary metabolic illness. Of note, laboratory findings may be abnormal only during the period of acute illness or metabolic decompensation. For this reason following up on a suspicion of metabolic illness with prompt collection of indicated specimens is crucial for diagnosis. Some general laboratory tests to consider when evaluating a patient for metabolic illness are listed in Table 31–1. Abnormal results on preliminary testing may direct more specific assessment of certain metabolic pathways.

Many patients with metabolic illness have completely normal physical features, although characteristic findings, when applicable, are indicated later. Thorough ophthalmologic examination may prove particularly helpful when evaluating metabolic illnesses because the retina provides a window through which to observe the metabolic processes in the brain.

Many metabolic illnesses affect the brain, either directly (e.g., via destruction of white matter in metachromatic leukodystrophy) or indirectly (e.g., as encephalopathy in urea cycle disorders). For this reason neuropsychiatric symptoms associated with metabolic disease may vary widely. Conversely, many metabolic illnesses may have similar acute presentations (e.g., delirium). As is the case with genetic syndromes, some patients meet full criteria for psychiatric disorders, whereas others may exhibit nonspecific behavioral findings.

Selected Metabolic Disorders with Psychiatric Features

CASE 2

Mr. B, a 57-year-old man, was admitted to the medical service for a change in mental status. He was reported to have prominent mood lability, disorientation, and disorganized and racing thoughts. His medical history was significant for hypertension, dental surgery, and a history of hepatitis 6 months previously (attributed to alcohol intake and medication side effects). Mr. B had been consuming six beers at a time several times a week. His family history was unremarkable. On evaluation, he appeared anxious and restless, and a tremor was noted. He had difficulty with speech and had abnormal facial movements. He exhibited mood lability and had difficulty completing cognitive tasks. Laboratory studies showed a mild elevation of liver transaminases, a low serum ceruloplasmin, and a greatly increased urine copper excretion, which led to a diagnosis of Wilson's disease.

Autosomal Dominant Disorders

Porphyrias/acute intermittent porphyria: The porphyrias are a group of disorders with dysfunction of heme biosynthesis. One of the more common porphyrias is acute intermittent porphyria (AIP), which results from mutations in the *hydroxymethylbilane synthase (HMBS)* gene on chromosome 11q23.3 that causes decreased activity of porphobilinogen (PBG) deaminase. AIP is inherited in an autosomal dominant manner. Episodic neurovisceral attacks are the predominant manifestations of AIP; they consist of recurrent abdominal pain, vomiting, generalized body pain, and weakness. Photosensitivity is not a feature of AIP as it is with some types of porphyria. Psychiatric symptoms and conditions, such as delirium, psychosis, depression, and anxiety, may accompany the acute attacks. Between attacks, constitutional and psychiatric symptoms resolve, although anecdotally these patients are often described as having a distinct personality with long-standing histrionic traits. Over time, indications of demyelination may develop. Of importance to the psychiatric consultant is that medications that upregulate heme biosynthesis may worsen attacks. For this reason patients treated with medications that upregulate the cytochrome P450 system may make symptoms worse, because heme is an essential part of the cytochrome ring; these patients may be incorrectly labeled as treatment refractory. Offending agents include benzodiazepines, some tricyclic antidepressants, barbiturates, some anticonvulsants (valproate and carbamazepine), oral contraceptives, cocaine, and alcohol. Diagnostic testing focuses on identification of by-products of heme synthesis in the urine or measurement of PBG deaminase levels in the blood. Urine that is left standing may discolor, turning dark red or brown as a result of the presence of porphobilinogen and aminolevulinic acid. Treatment for AIP includes supportive care during attacks and the avoidance of offending agents. In addition, a high-carbohydrate diet, folic acid (a PBG diamine co-factor), and the use of medications that suppress heme synthesis may be helpful.[93–97]

Autosomal Recessive Disorders

Homocystinuria: Classic homocystinuria is due to mutations of the *cystathionine β-synthase (CBS)* gene on chromosome 21q22.3 that results in decreased enzymatic activity of *CBS* and problems with conversion of homocystine to cystine and remethylation of homocystine to methionine. Patients with preservation of some enzyme activity may respond to high dosages of pyridoxine (vitamin B_6), which acts as a co-factor for *CBS.* Deficiencies of other enzyme co-factors (e.g., B_{12} and folate) may also lead to symptoms. Patients with homocystinuria usually have unremarkable early histories, with development of symptoms in childhood. The patients tend to be tall and thin and are sometimes described as "marfanoid." They may have features of connective tissue disease, such as a pectus excavatum, lens dislocation, scoliosis, and a high-arched palate. Unlike patients with Marfan's syndrome, they may have restricted mobility of their joints. It is thought that high levels of homocystine may interfere with collagen cross-linking, which results in connective tissue symptoms. In addition, abnormalities in collagen can lead to disruptions of the vascular endothelium and thrombotic events with disabling or fatal consequences. High levels of homocystine or other factors are also thought to be neurotoxic and, when left untreated, lead to mental retardation and learning disabilities. During the 1960s and 1970s, these patients were reported to have increased rates of schizophrenia, which was attributed to the hypothesized central role of methionine in both disorders. More recent studies have not supported an increased risk of schizophrenia or psychosis but have shown depression, obsessive–compulsive disorder, personality disorders, and other behavioral disturbances. Urinary nitroprusside testing for disulfides and measurement of high levels of homocystine and methionine (the precursor of homocystine) in the blood help make the diagnosis. Newborn screening for homocystinuria has been available in some states for more than 30 years. Molecular testing is also available. Treatment focuses on providing a diet low in methionine and supplementation with vitamin co-factors and cystine (which becomes an essential amino acid in these patients). Use of the supplement betaine also aids in lowering homocystine levels.[98–100]

Wilson's disease: Wilson's disease is due to mutations in the *ATP7B* gene, located on chromosome 13q14.21, which lead to copper deposition in the CNS as a result of decreased levels of copper-transporting adenosine triphosphatase (ATPase). Signs and symptoms of liver dysfunction (e.g., jaundice, hepatomegaly, cirrhosis, hepatitis) may be present, along with abnormal liver function tests. Of particular importance to psychiatrists are changes in personality, mood lability (including pseudobulbar palsy), cognitive decline, and other behavioral changes that may be among the earliest symptoms of Wilson's disease. Neurologic symptoms are most often extrapyramidal in nature and can include tremor, dysarthria, muscular rigidity, parkinsonism, dyskinesia, dystonia, and chorea. Seizures may also occur. The hallmark of this disorder is the Kayser–Fleischer ring, a yellow-brown ring (a consequence of copper deposition in the cornea) that is visible on slit lamp ophthalmological examination. Accumulations of copper in other organ systems may result in a variety of complications, including arthritis, renal tubular dysfunction, and cardiomyopathy. Confirmatory diagnostic testing includes measurement of reduced bound copper and ceruloplasmin in the serum and increased copper excretion in the urine. Copper deposits may be seen on head magnetic resonance imaging (MRI) or in the liver by way of a liver biopsy. Treatment, in the form of chelation of copper (with medications such as d-penicillamine) and supplementation with antioxidants, is available. Avoidance of copper-rich foods, such as shellfish, liver, chocolate, and nuts, is recommended. Unfortunately, liver damage may progress to liver failure and necessitate liver transplantation in some patients.[101–103]

Metachromatic leukodystrophy: Metachromatic leukodystrophy is a lysosomal storage disorder with deficiency of the enzyme arylsulfatase A and mutations in the *ARSA* gene located on chromosome 22q13.31. As a result, abnormal storage of galactosyl sulfatide (cerebroside sulfate) occurs in the white matter of the central and peripheral nervous systems. The disorder may occur in infancy, childhood, or adulthood. For the later-onset forms, psychiatric symptoms may be an earlier manifestation of the disease, with a decline in cognition, personality changes, and psychotic features (including hallucinations and delusions). In some cases, psychosis may predate the onset of other symptoms by several years. Neurologic symptoms may include ataxia and walking difficulties, dysarthria and dysphagia, and pyramidal signs. Vision loss may also occur. Brain MRI may show periventricular changes; eventually white matter atrophy caused by loss of myelin may be noted. Diagnostic testing involves measurement of elevated urine sulfatides and decreased levels of arylsulfatase A in blood. No treatment is currently available, although bone marrow transplantation may delay the progression of symptoms.[93,104,105]

Niemann–Pick disease, type C: Niemann–Pick disease, type C (NPC) is a condition that results in abnormal cholesterol esterification and lipid storage in lysosomes caused by mutations in the *NPC1* gene on chromosome 18q11-q12. The disorder may appear in childhood or adolescence (and rarely in adulthood) with early findings of ataxia, coordination problems, and dysarthria. Vertical supranuclear palsy is the hallmark of the disorder. Seizures and hepatosplenomegaly may be present. Psychiatric symptoms include progressive cognitive decline and dementia. In addition, several reports have documented the initial presentation of this disorder as psychosis or schizophrenia. Diagnosis is based on demonstration of characteristic pathologic findings in the skin or bone marrow; abnormal cholesterol esterification in fibroblasts; and molecular analysis of the *NPC1* gene, which is positive in 95% of cases. Of note is that panels testing blood and urine specimens for lysosomal storage diseases will be normal in NPC, so diagnostic suspicion must direct a more comprehensive work-up.[106–109]

Tay–Sachs disease, late-onset type: Tay-Sachs disease is another lysosomal storage disease, with accumulation of GM2 gangliosides in neurons. Mutations in the *HEXA* gene on chromosome 15q23-q24, which encodes the alpha subunit of hexosaminidase A, lead to an enzyme deficiency. Most clinicians are familiar with the infantile-onset form of the disorder but may not be aware of the later-onset forms that can occur with preservation of some enzymatic activity. Patients may present with psychiatric symptoms of psychosis, mood lability, catatonia, and cognitive decline. Physical findings are those of progressive neurologic

dysfunction and include early ataxia, coordination problems, dysarthria, and progressive neurologic dysfunction (e.g., with dystonia, spasticity, and seizures). Macular cherry-red spots, the hallmark of the early-onset form, are not present in the later-onset form. Diagnosis is based on analysis of enzyme levels in the blood or mutation analysis. Tay–Sachs may occur in people of various ethnic and racial backgrounds, and prenatal screening is offered, especially to those of Ashkenazi Jewish descent, wherein the carrier rate is estimated to be 1:30, and to French Canadians, who have a carrier rate of 1:50. There is no treatment available for Tay–Sachs disease.[110,111]

X-Linked Disorders

X-linked adrenoleukodystrophy: X-linked adrenoleukodystrophy is also a disorder of abnormal storage but in the peroxisome instead of the lysosome. In this disorder deficiency of lignoceroyl-CoA ligase results from mutations in the *ABCD1* gene on Xq28 and leads to accumulation of very long chain fatty acids (VLCFAs) in the cerebral white matter and adrenal cortex. On account of its X-linked manner of inheritance, male subjects are described with the full syndrome. Female carriers, however, can also exhibit a spectrum of associated symptoms with varying degrees of severity, and they may be misdiagnosed with other disorders, including multiple sclerosis. Often, the first signs and symptoms of the disorder result in a diagnosis of ADHD for affected males. In the adult-onset form, high rates of mania and psychosis are reported. Other early signs may include difficulty with gait, handwriting, or speech. Progressive loss of motor skills, vision, and hearing, accompanied by continued decline in cognition, occurs over a period of months to years. Accumulation of VLCFAs in the adrenal cortex may cause elevation of adrenocorticotropic hormone and other findings associated with adrenal dysfunction. These adrenal abnormalities, brain MRI findings, and elevated levels of VLCFAs in the blood can lead to the diagnosis. Confirmatory molecular testing for mutations in the *ABCD1* gene is available. Treatment for adrenal dysfunction is recommended, but there is no treatment available for the neurologic sequelae of this disease, insofar as the use of Lorenzo's oil has not proven to be effective. Bone marrow transplantation has been proposed as a possible treatment for this disorder, but concerns about the high morbidity and mortality rate associated with the procedure have limited its use.[112–114]

Urea cycle defects—ornithine transcarbamylase deficiency: Disorders of the urea cycle interfere with the normal urinary excretion of excess nitrogen via conversion to urea. Several enzymes make up the urea cycle, and deficiencies of these enzymes lead to variable failure to manage nitrogenous waste from protein. Ornithine transcarbamylase (OTC) deficiency is one of the more common urea cycle disorders, and it is inherited in an X-linked manner as a result of mutations in the *OTC* gene on Xp21.1. Although male subjects with this disorder usually present in the neonatal period with marked hyperammonemia and resultant sequelae, female carriers of the *OTC* gene may have a more variable course, owing to lyonization of X chromosomes. Their presentations may occur at any age, and female carriers range from being asymptomatic to being as severely affected as their male counterparts. Psychiatric symptoms in affected female carriers may include intermittent episodes of delirium, ataxia, lethargy, and confusion.[115–120] Patients may report a history of self-restriction of protein in the diet or severe decompensations with vomiting illnesses or fasting (which may result in an endogenous protein load via catabolism of muscle). During symptomatic episodes elevations of ammonia, urine orotic acid, and liver function, accompanied by a characteristic pattern of plasma amino acids, aid in diagnosis. Confirmatory molecular diagnostic testing by mutation analysis, or enzymatic assay of liver tissue, is available. Treatment is focused on maintaining a low intake of dietary protein and providing supplemental essential amino acids and urea cycle intermediates. Acutely, medications that allow alternate excretion of nitrogen compounds may be used for high ammonia levels; in some cases hemodialysis is required for rapid control of hyperammonemic episodes. Of note, the use of valproate has been reported to cause acute liver failure in patients with OTC and also to precipitate a hyperammonemic crisis in female carriers. It is thought that valproate inhibits urea synthesis and can lead to hyperammonemia.[121–123]

Lesch–Nyhan syndrome: Lesch–Nyhan syndrome is a disorder of purine metabolism owing to deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT), caused by mutations in the *HPRT1* gene at Xq26-27.2. Hyperuricemia and hyperuricuria occur and can result in deposition of urate crystals in the joints, kidneys, and bladder. Affected males exhibit hallmark behaviors of self-injury and self-mutilation (including head-banging and biting of lips and fingers). Mutilation may be severe enough to warrant removal of teeth or the use of restraints. Mental retardation may occur, although progressive loss of cognition does not. Diagnostic testing reveals increased uric acid production and excretion, decreased HPRT activity, and confirmatory molecular analysis of the *HPRT1* gene. Although allopurinol may control sequelae of high uric acid, it does not ameliorate the neurologic or psychiatric symptoms. There is some suggestion that dysfunction of dopamine metabolism may be related to the CNS pathology in this disorder.[124–126]

Mitochondrial Disorders

Disorders that involve dysfunction of the mitochondria are diverse and include disorders of fatty acid beta-oxidation or pyruvate metabolism and dysfunction of the Krebs cycle or oxidative phosphorylation by the electron transport chain. Commonly, they may be thought of as disorders of energy metabolism. Mitochondrial disorders are inherited from the mother, in the case of those coded for by genes located in the mitochondrial genome, or from either or both parents in those coded for by genes located in the nuclear genome. Mitochondrial syndromes may be characterized as specific disorders (e.g., mitochondrial encephalopathy with lactic acidosis and strokelike episodes) or may involve dysfunction of multiple organ systems (e.g., cardiomyopathy, diabetes, and hearing loss). Body tissues with high energy demands, including the brain, may be

preferentially affected. Psychiatric symptoms and conditions in mitochondrial disorders are largely uncharacterized but may include depression, delirium, dementia, and psychosis. Mitochondrial dysfunction may be suggested by elevations of lactate or pyruvate or by presence of byproducts of fatty acid oxidation or other mitochondrial pathways. Diagnosis by analysis of specific mutations is available for some disorders, whereas others require functional analysis of pathways using skin or muscle tissue. Dietary and vitamin supplementation, prevention of lactic acidosis with acute decompensations, and management of associated medical conditions are the mainstays of treatment for mitochondrial disorders.[127–129]

Teratogen Exposure

A variety of reproducible syndromes and characteristic features are associated with prenatal exposure to prescribed medications, alcohol and drugs of abuse, maternal illnesses (e.g., diabetes) and infectious agents, chemicals, radiation, and other toxins. Observed physical, cognitive, and psychiatric findings vary depending on the amount and timing of exposure. When possible, a detailed prenatal history should be obtained as part of a comprehensive evaluation of a patient.

Fetal alcohol syndrome: Alcohol is the major teratogen to which fetuses are exposed; it can result in a wide spectrum of cognitive, behavioral, and physical findings known as fetal alcohol syndrome (FAS). The severity of symptoms appears to be dose related, although a critical threshold of alcohol intake has not been identified. High levels of blood alcohol (achieved by binge drinking) may result in more severe manifestations. Psychiatric symptoms and conditions include ADHD, depression, mood lability, anxiety, aggression, and oppositional defiant behaviors. Physical features include prenatal and postnatal growth deficiency and a characteristic facial appearance manifested by a small head, a flattened midface, the presence of epicanthal folds, a flat philtrum with a thin upper lip, and small jaw. Learning disabilities and cognitive limitations are common. Diagnosis rests on clinical features with recognition of characteristic findings in the context of a known history of prenatal alcohol exposure. Diagnosis of FAS spectrum, partial FAS, or alcohol-related

TABLE 31–2 Additional History and Physical Examination Assessment for Genetic and Metabolic Illness

PRENATAL HISTORY	MULTIORGAN REVIEW OF SYSTEMS
Any complications with pregnancy?	History of decompensation with illness?
Timing of complication(s)?	Dietary history of food intolerances, or unusual food preferences?
Maternal diabetes, systemic illness?	Episodic neurologic symptoms?
Maternal hypertension, eclampsia, or toxemia?	Problems with linear growth or weight gain? HELLP (*H*emolysis, *E*levated *L*iver enzymes, *L*ow *P*latelets)?
Maternal infection or high fevers?	
Toxic exposures (medications, illicit substances, alcohol, radiation, chemicals)?	
Any abnormalities on ultrasound?	
Any indications for amniocentesis/chorionic villus sampling (CVS)? Amniocentesis/CVS results?	
BIRTH/PERINATAL HISTORY	**PHYSICAL EXAMINATION**
Mode of delivery (vaginal vs. cesarean section, natural vs. induced vs. emergent)?	Asymmetry of features?
Complications with delivery?	Presence of dysmorphic features?
NICU or prolonged hospital stay in infancy?	Signs of neurologic dysfunction?
Issues with feeding or growth?	
DEVELOPMENTAL HISTORY	**PSYCHIATRIC REVIEW OF SYSTEMS**
Timing of major verbal and motor milestones?	Nonspecific behavioral problems (e.g., tantrums, violent behavior)?
History of speech, occupational or physical therapy?	History of developmental regression? outbursts, hyperactivity)?
Decline in school performance?	Self-injurious behaviors?
History of special education services, academic supports?	
FAMILY HISTORY	Difficulties with sleep?
Ethnicity/race of parents?	
History of consanguinity?	
Patterns of illness in family members?	
History of infertility, miscarriages?	
History of infant/child deaths?	
Family members with surgeries in childhood?	

NICU, Neonatal intensive care unit.

neurodevelopmental disorder may also be made. Exposure to multiple drugs *in utero* should also be considered in all patients evaluated for FAS. No confirmatory laboratory or imaging tests are available, although recent MRI studies have documented structural abnormalities of the brain with absence or small size of the corpus callosum being reported in FAS patients.[130–132]

CONCLUSION

Many psychiatric disorders have a substantial genetic etiology. Psychiatric disorders are also greatly influenced by the environment. Genes and the environment can interact to lead to expression of psychiatric disorders. An active area of research is identifying genes and genomic regions linked to psychiatric disorders. Discovering the genetic basis of psychiatric disorders will provide opportunities to further understand the mechanisms underlying these disorders and guide the development of new treatments. Diagnostic classifications of psychiatric disorders may be refined in light of this increased understanding of the genetic basis of psychiatric phenotypes. We anticipate that genetics, in the years to come, will be increasingly important for the diagnosis and treatment of psychiatric disorders in the general hospital.

Because the selected genetic and metabolic syndromes described in this chapter are frequently associated with psychiatric symptoms, an awareness of these disorders is important for the general psychiatrist. A comprehensive assessment that includes attention to family history (Tables 31–2 to 31–5), highlighting psychiatric and neurologic diseases, dementia, or other medical illness in family members; review of systems, including developmental and cognitive status, dietary history, and involvement of other organ systems; and noted abnormalities on physical examination, especially neurologic findings and dysmorphic features may uncover clues that can help determine which psychiatric patients may require more extensive organic work-ups. Consultation by a geneticist may help with diagnostic and management issues in individual patients with known or suspected genetic and metabolic disorders. Determination of the molecular and physiologic basis of psychiatric and behavioral symptoms of disorders in which the underlying cause is known may add to our understanding of psychiatric disorders as a whole, aid in refinement of diagnostic criteria, and offer novel treatment approaches to common psychiatric diseases.

TABLE 31–3 Selected Disorders with Associated Cognitive Decline/Dementia

GENETIC SYNDROMES	INBORN ERRORS OF METABOLISM
Rett syndrome	Wilson's disease
Huntington's disease	Homocystinuria
Down syndrome (with associated Alzheimer's disease)	X-linked adrenoleukodystrophy
	Niemann–Pick disease, type C
	Metachromatic leukodystrophy
	Tay–Sachs disease
	Mitochondrial disease

TABLE 31–4 Selected Disorders with Associated Delirium

Acute intermittent porphyria
Wilson's disease
Ornithine transcarbamylase deficiency (including female carriers)
Mitochondrial disease

TABLE 31–5 Selected Disorders with Associated Psychosis

GENETIC SYNDROMES	INBORN ERRORS OF METABOLISM
Velocardiofacial syndrome/DiGeorge syndrome	Acute intermittent porphyria
	X-linked adrenoleukodystrophy
Prader–Willi syndrome	Niemann–Pick disease, type C
Huntington's disease	Metachromatic leukodystrophy
	Tay–Sachs disease
	Wilson's disease
	Mitochondrial disease

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SUGGESTED READING

Gene Clinics: http://www.Geneclinics.org
Online Mendelian Inheritance in Man (OMIM): http://www.ncbi.nlm.nih.gov/omim/
POSSUM and software: http://www.possum.net.au/

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Coping with Illness and Psychotherapy of the Medically Ill

Steven C. Schlozman, M.D.
James E. Groves, M.D.
Anne F. Gross, M.D.
Avery D. Weisman, M.D.

Management of psychiatric illness in medically ill inpatients and outpatients requires knowledge of medicine and psychiatry as well as specialized psychotherapeutic techniques. In hospital settings, challenges to compassionate psychological care are abundant (e.g., decreasing length of stays, severe medical and surgical illnesses, prominent side effects of treatment, threats to privacy, and procedures and technology that limit a patient's ability to communicate). Nonetheless, consultation psychiatrists strive to improve the patient's ability to cope with trying circumstances that surround their illness and its treatment.

Illness is a stress that requires both the afflicted patients and the systems that surround them them to adapt (e.g., to pain, impaired cognition, loss of bodily function, threats to life, and disruptions in everyday function) via improvements in coping strategies and interpersonal relationships. Coping with illness can be a serious problem for both the patient and the physician. However, when addressing this phenomenon, it is important to recognize that few medical schools or residency programs train physicians in the management of interpersonal stress and discomfort engendered by medical illness (in patients and in themselves). This absence stands in stark contrast to the way the art of medicine was conceptualized 100 years ago. Indeed, it is ironic, and yet understandable, that we experience a profound sense of impotence when a cure cannot be found in the face of our increasing ability to heal the sick.[1,2]

Fortunately, the consultation–liaison (C-L) psychiatrist is ideally suited to assist both patient and physician with the demands of caring for the medically ill. From a psychological standpoint, the psychiatrist appreciates the powerful emotions and defense mechanisms that swirl in and around the hospital bed. These observations are relevant in both the consultative setting and in the outpatient office. In fact, specific psychotherapeutic techniques (e.g., cognitive behavior therapy [CBT] and group therapy) have been developed for work with the medically ill. This chapter addresses the fundamentals of coping, the process of adaptation to illness, as well as the art of working psychotherapeutically with the medically ill.

WHAT EXACTLY IS COPING?

Coping is best defined as problem-solving behavior that is intended to bring about relief, reward, quiescence, and equilibrium. Nothing in this definition promises permanent resolution of problems. It does imply a combination of knowing what the problems are and how to go about reaching a correct direction that will help resolution.[3,4]

In ordinary language, the term *coping* is used to mean only the outcome of managing a problem, and it overlooks the intermediate process of appraisal, performance, and correction that most problem-solving entails. Coping is not a simple judgment about how some difficulty worked out. It is an extensive, recursive process of self-exploration, self-instruction, self-correction, self-rehearsal, and guidance gathered from outside sources.

At virtually every step of patient care, physicians and patients actively assess coping ability. Though this appraisal is not always conscious, the conclusions drawn about how a patient is processing his or her illness has a tremendous impact on therapeutic decisions, on psychological well-being, and indeed on the overall course of illness. However, accurate appraisal of coping skills is hampered by muddled definitions of coping, by competing methods of assessment, by a general lack of conscious consideration of how a patient copes, and by uncertainty about whether particular coping styles are effective.[3–6]

Early conceptualizations of coping centered around the Transactional Model for Stress Management, put forth first by Lazarus[7] and colleagues in the late 1960s. This conceptualization stressed the extent to which a patient interacts with his or her environment as a means of managing the stress of illness. These interactions involve appraisals of one's medical condition in the context of psychological and cultural overlays that vary from patient to patient. Although this definition of coping persists, it may be too broad to allow for standard assessments of patients. Thus, though multiple studies of patient coping exist, most clinicians favor a more open-ended approach to evaluation that considers the unique backgrounds that the patient and the doctor bring to the therapeutic setting.[6]

Coping with illness and its ramifications cannot help but be an inescapable part of medical practice. Therefore the overall purpose of any intervention, physical or psychosocial, is to improve coping with potential problems beyond the limits of illness itself. Such interventions must take into account both the problems to be solved and the individuals most closely affected by the difficulties.

How anyone copes depends on the nature of a problem as well as on the mental, emotional, physical, and social resources one has available for the coping process. The hospital psychiatrist is in an advantageous position to evaluate how physical illness interferes with the patient's conduct of life and to see how psychosocial issues impede the course of illness and recovery. This is accomplished largely by knowing which psychosocial problems are pertinent, which physical symptoms are most distressing, and what interpersonal relations support or undermine coping.

Assessment of how anyone copes, especially in a clinical setting, requires an emphasis on the "here and now." Long-range forays into the past are relevant only if they illuminate the present predicament. In fact, more and more clinicians are adopting a focused and problem-solving approach to therapy with medically ill patients. For example, supportive therapies for medically ill children and adults in both group and individual settings have reduced psychiatric morbidity, and had measurable effects on the course of nonpsychiatric illnesses.

WHO COPES WELL?

There are few paragons who cope exceedingly well with all problems. For virtually everyone, psychiatrists included, sickness imposes a personal and social burden, threat, and risk; these reactions are seldom precisely proportional to the actual dangers of the primary disease. Therefore effective copers may be regarded as individuals with a special skill or with personal traits that enable them to master many difficulties. Characteristics of good copers are presented in Table 32–1. These characterizations are collective tendencies; they seldom typify any specific individual (except the heroic or the idealized). No one copes exceptionally well at all times, especially with problems that are associated with risk and that might well be overwhelming. However, effective copers appear able to choose the kind of situation in which they are most likely to prosper. In addition, effective copers often maintain enough confidence to feel resourceful enough to survive intact. Finally, it is our impression that those individuals who cope effectively do not pretend to have knowledge that they do not have; therefore they feel comfortable turning to experts that they trust. The better we can pinpoint which traits a patient seems to lack, the better we can help a patient cope.

WHO COPES POORLY?

Bad copers are not necessarily bad people, nor even incorrigibly ineffective people. In fact, it is too simplistic merely to indicate that bad copers have the opposite characteristics of effective copers. As was stressed earlier, each patient brings a unique set of cultural and psychological attributes that impacts the capacity to cope. Bad copers are those who have more problems in coping with unusual, intense, and unexpected difficulties because of a variety of traits. Table 32–2 lists some characteristics of poor copers.

TABLE 32–1 Characteristics of Good Copers

1. They are optimistic about mastering problems and, despite setbacks, generally maintain a high level of morale.
2. They tend to be practical and to emphasize immediate problems, issues, and obstacles that must be conquered, even before visualizing a remote or ideal resolution.
3. They select from a wide range of potential strategies and tactics, and their policy is not to be at a loss for fallback methods. In this respect, they are resourceful.
4. They heed various possible outcomes and improve coping by being aware of consequences.
5. They are generally flexible and open to suggestions, but they do not give up the final say in decisions.
6. They are composed, although vigilant, in avoiding emotional extremes that could impair judgment.

TABLE 32–2 Characteristics of Poor Copers

1. They tend to be excessive in self-expectation, rigid in outlook, inflexible in standards, and reluctant to compromise or to ask for help.
2. Their opinion of how people should behave is narrow and absolute; they allow little room for tolerance.
3. Although prone to firm adherence to preconceptions, they may show unexpected compliance or be suggestible on specious grounds, with little cause.
4. They are inclined to excessive denial and elaborate rationalization; in addition, they are unable to focus on salient problems.
5. Because they find it difficult to weigh feasible alternatives, they tend to be more passive than usual and they fail to initiate action on their own behalf.
6. Their rigidity occasionally lapses, and they subject themselves to impulsive judgments or atypical behavior that fails to be effective.

Indeed, structured investigations into the psychiatric symptoms of the medically ill have often identified many of the attributes of those who do not cope well. Problems such as demoralization, anhedonia, anxiety, pain, and overwhelming grief all have been documented in medical patients with impaired coping.

WHAT INTERFERES WITH OUR ABILITY TO ADAPT TO ILLNESS?

Adaptation to medical illness is affected by individual factors, by intrahospital factors, and by extrahospital factors[8]; understanding all three is crucial to an assessment of how an individual will adapt to illness. Individual (intrapersonal) factors include psychiatric diagnoses (including, but not limited to, depression, anxiety, delirium, dementia, substance abuse, posttraumatic stress disorder [PTSD], factitious disorders, somatoform disorders, and sleep disorders; their developmental stage, their experience with trauma, and their understanding of the illness). In addition, personality style and personality disorders (including histrionic, obsessive, paranoid, narcissistic, and borderline personality disorders) affect how a person copes with receiving bad news, how they interact with

medical staff, and how they communicate with others in their life.[8] Holland and colleagues described the "Five D's" when discussing what the illness means to a patient (e.g., distance [the interruption of interpersonal relationships], dependence [having to rely on others], disability [inability to achieve], disfigurement, and death).[9] Intrahospital factors include the characteristics of the illness (e.g., its time course, the intensity of pain, its impact on sleep, surgical interventions, and chemotherapy), whereas extrahospital variables (e.g., finances, housing, interpersonal relationships, and sociocultural/language barriers) are also key issues.[8]

THE ROLE OF RELIGION

The significance of religious or spiritual conviction in the medically ill deserves special mention. Virtually every C-L psychiatrist works with patients as they wrestle with existential issues (such as mortality, fate, justice, and fairness). Such ruminations cannot help but invoke religious considerations in both the patient and the physician; moreover, there is a growing appreciation in the medical literature for the important role that these considerations can play.

In some investigations, being at peace with oneself and with one's sense of a higher power was predictive of both physical and psychiatric recovery.[10,11] However, other studies have suggested that resentment toward God, fears of God's abandonment, and a willingness to invoke satanic motivation for medical illness were all predictive of worsening health and an increased risk of death.[12]

Because the C-L psychiatrist's role involves identification and strengthening of those attributes that are most likely to aid a patient's physical and emotional well-being, effective therapy for the medically ill involves exploration of the religious convictions of a patient; fostering those elements is most likely to be helpful. It is *never* the role of the physician to encourage religious conviction *de novo*. At the same time, ignoring religious content risks omitting an important element of the psychotherapeutic armamentarium.

THE MEDICAL PREDICAMENT—BRINGING IT ALL TOGETHER

Coping refers to how a patient responds and deals with problems within a complex of factors that relates to disease, sickness, and vulnerability. In approaching chronically ill patients, it is helpful to conceptualize *disease* as the categorical reason for being sick, *sickness* as the individual style of illness and patienthood, and *vulnerability* as the tendency to be distressed and to develop emotional difficulties in the course of trying to cope.

Given these definitions, the psychiatrist needs to first ask *why now*? What has preceded the request for consultation? How does the patient show his or her sense of futility and despair? How did the present trouble, both the medical and the corresponding coping challenges, come about? Was there a time when such problems could have been thwarted? It is also important to note that not infrequently the treatment team is even more exasperated than the patient. In these instances, one must guard against the assumption that it is only the patient who is troubled by the medical predicament.

In fact, if there is any doubt about the gap between how the staff and a patient differ in cultural bias and social expectations, one should listen to the bedside conversation. Good communication may not only reduce potential problems, but it actually help patients to cope better. Good coping is a function of empathic connection and respect between the patient and the doctor regarding the risks and points of tension related to treatment. The psychiatrist is not the sole vessel of professional concerns about coping, but has unique skills that are ideally suited to address the challenges of how patients cope. As already mentioned, much of chronic disease evokes existential issues (such as death, permanent disability, low self-esteem, dependence, and alienation); these are fundamentally psychiatric concerns.

Given all of this, it is important to remember that psychiatry does not arbitrarily introduce psychosocial problems. If, for example, a patient is found to have an unspoken, but vivid, fear of death or to be suffering from an unrecognized and unresolved bereavement, fear and grief are already there, not superfluous artifacts of the evaluation itself. Indeed, open discussion of these existential issues is likely to be therapeutic; active denial of their presence is potentially detrimental, because it risks empathic failure and the poor compliance that accompanies the course of patients who feel misunderstood or unheard.

Being sick is, of course, much easier for some patients than for others, and for certain patients, it is preferred over trying to make it in the outside world. There is too much anxiety, fear of failure, inadequacy, pathological shyness, expectation, frustration, and social hypochondriasis to make the struggle for holding one's own appealing. At key moments of life, sickness is a solution. Although healthy people are expected to tolerate defeat and to withstand disappointments, others legitimize their low self-esteem by a variety of excuses, denial, self-pity, and symptoms, long after other patients return to work. Such patients thrive in a complaining atmosphere and even blame their physicians. These are perverse forms of coping and they complicate the task of the hospital psychiatrist.

The clinician must also assess the motivation of staff and patients when a psychiatric intervention is requested. Additionally, clinicians need to be aware that the real question is not always the problem for which one is consulted. For example, the request for psychiatric consultation to treat depression and anxiety in a negativistic and passive–aggressive patient is inevitably more complicated than a simple recognition of certain key psychiatric symptoms. Those with primitive defenses can generate a profound sense of hopelessness and discomfort in their treaters. It is often an unspoken and unrecognized desire by physicians and ancillary staff that the psychiatrist shifts the focus of negativity and aggression onto himself or herself and away from the remaining treatment team. If the consulting psychiatrist is not aware of these subtleties, the intent of the consultation will be misinterpreted and the psychiatrist's efforts will ultimately fall short.

COPING AND SOCIAL SUPPORT

Every person needs, or at least deserves, a measure of support, sustenance, security, and self-esteem, even if they are not patients at all, but human beings encountered at a critical time.

In assessing problems and needs, the psychiatrist can help by identifying potential pressure points (e.g., health and wellness, family responsibility, marital and sexual roles, jobs and money, community expectations and approval, religious and cultural demands, self-image and sense of inadequacy, and existential issues) where trouble might arise.

Social support is not a hodgepodge of interventions designed to cheer up or straighten out difficult patients. Self-image and self-esteem, for example, depend on the sense of confidence generated by various sources of social success and support. In a practical sense, social support reflects what society expects and therefore demands about health and conduct.

Social support is not a "sometime" thing, to be used only for the benefit of those too weak, needy, or troubled to get along by themselves. It requires a deliberate skill that professionals can cultivate, in recognizing, refining, and implementing what any vulnerable individual needs to feel better and to cope better. In this light, it is not an amorphous exercise in reassurance, but a combination of therapeutic gambits opportunistically activated to normalize a patient's attitude and behavior. Techniques of support range from concrete assistance to extended counseling.[13,14] Their aim is to help patients get along without professional support. Social support depends on an acceptable image of the patient, not one that invariably "pathologizes." If a clinician only corrects mistakes or points out what is wrong, bad, or inadequate, then insecurity increases and self-esteem inevitably suffers.

COURAGE TO COPE

Most psychiatric assessments and interventions tend to pathologize, and to emphasize shortcomings, defects, and deviation from acceptable norms. Seldom does an examiner pay much attention to positive attributes (such as confidence, loyalty, intelligence, hope, dedication, and generosity). One of the commonly neglected virtues in clinical situations is that of courage.

Courage in a clinical sense should not be confused with "bravery under fire." The derring-do of heroes is seldom found among ordinary people, who usually have more than their share of anxiety and apprehension when facing unfamiliar, unknown, and threatening events. Threats are manifest on many levels of experience, ranging from actual injury to situations that signify failure, disgrace, humiliation, embarrassment, and so forth. In a sense, threat is "negative support" because it may do or undo everything that positive support is supposed to strengthen. It pathologizes. The courage to cope is a real but seldom recognized element in the attributes that affect the coping process. Nevertheless, in coping well, the courage to cope means a wish to perform competently and to be valued as a significant person, even when threatened by risk and anonymity.

Hope, confidence, and morale go together and can be directly asked about because most patients know what these terms mean without translation. Naturally, few people readily admit their tendency to fail, shirk, or behave in unworthy ways. Nevertheless, a skillful interview gets behind denial, rationalization, posturing, and pretense without evoking another threat to security or self-esteem.

Courage requires an awareness of risk as well as a willingness to go it alone despite a substantial degree of anxiety, tension, and worry about being able to withstand pressure and pain. Courage is always accompanied by vulnerability, but it engages itself in the courage to cope.

ASSESSMENT OF VULNERABILITY

Vulnerability is present in all humans, and it shows up at times of crisis, stress, calamity, and threat to well-being and identity.[15–21] How does a patient visualize threat? What is most feared, say, in approaching a surgical procedure, a diagnosis, anesthesia, possible invalidism, failure, pain, or abandonment (by one's physician or family)?

Coping and vulnerability have a loosely reciprocal relationship; the better one copes, the less distress he or she experiences as a function of acknowledged vulnerability. In general, a good deal of distress often derives directly from a sense of uncertainty about how well one will cope when called on to do so. This does not mean that those who deny or disavow problems and concerns are superlative copers. The reverse may be true. Courage to cope requires anxiety confronted and dealt with, not phlegmatic indifference to outcome.

Table 32–3 shows 13 common types of vulnerability. Table 32–4 describes how to find out about salient problems, the strategy used for coping, and the degree of the resolution attained.

TABLE 32–3 Vulnerability

Hopelessness:	Patient believes that all is lost; effort is futile; there is no chance at all; a passive surrender to the inevitable
Turmoil/ Perturbation:	Patient is tense, agitated, restless, hyperalert to potential risks, real and imagined
Frustration:	Patient is angry about an inability to progress, recover, or get satisfactory answers or relief
Despondency/ Depression:	Patient is dejected, withdrawn, apathetic, tearful, and often unable to interact verbally
Helplessness/ Powerlessness:	Patient complains of being too weak to struggle anymore; cannot initiate action or make decisions that stick
Anxiety/Fear:	Patient feels on the edge of dissolution, with dread and specific fears about impending doom and disaster
Exhaustion/Apathy:	Patient feels too worn out and depleted to care; there is more indifference than sadness
Worthlessness/ Self-rebuke:	Patient feels persistent self-blame and no good; he or she finds numerous causes for weakness, failure, and incompetence
Painful Isolation/ Abandonment:	Patient is lonely and feels ignored and alienated from significant others

Continued

TABLE 32–3 Vulnerability—*cont'd*

Denial/Avoidance:	Patient speaks or acts as if threatening aspects of illness are minimal, almost showing a jolly interpretation of related events, or else a serious disinclination to examine potential problems
Truculence/ Annoyance:	Patient is embittered and not openly angry; feels mistreated, victimized, and duped by forces or people
Repudiation of Significant Others:	Patient rejects or antagonizes significant others, including family, friends, and professional sources of support
Closed Time Perspective:	Patient may show any or all of these symptoms, but in addition foresees an exceedingly limited future

Seven different existential states were identified by Griffith and Gaby[22] that can be regarded as moving toward (resilience), or away from (vulnerability), assertive coping techniques (Table 32–5). They argued that an essential job of the psychiatrist is to help patients sustain characteristics of resiliency and to combat vulnerability. Confusion, defined as "an inability to make sense of one's situation," can be seen in patients who have delirium or dementia or for whom a clear medical diagnosis does not exist. Asking "How do you make sense of your experience?" can be helpful in organization, planning, and judging and can lead to the improved coherence. Communion, defined as the "felt presence of a trustworthy person," versus isolation can be assessed by asking, "Who do you believe understands your situation?" Despair, or hopelessness, has been associated with poor coping. Questions that assess hope include "What sorts of things keep you from giving up?" Feeling meaningless can be detrimental to one's ability to fight illness; questions that enhance purpose include "Who keeps you alive?" Agency, defined as "the sense that one can make meaningful choices and that one's actions matter," can combat helplessness by empowering patients to be heard by their doctors. Asking "What issues involved in your treatment concern you the most?" embraces a sense of agency and diminishes helplessness. Showing courage, as opposed to cowardice, in the face of fear, can be elicited by asking "Have there been times when you wanted to give up but you didn't?" Finally, experiencing a sense of gratitude rather than a sense of resentment can help combat feelings of depression and anxiety. The clinician can ask, "What things in your life are you most grateful for?" or "Has your illness taught you anything meaningful?"[22] While speaking with patients it is helpful to establish which of these areas of vulnerability can be improved upon.

The consulting psychiatrist frequently asks patients to fill out forms that provide an indication about their degree of anxiety, level of self-esteem, perceived illness, and so on. Although such queries are often sources of valuable information, these standardized inquiries are no substitute for careful and compassionate interviews. There is a strong element of social desirability present in any attempt to assess how a patient copes. How a patient deals with illness may not be the same as how he or she wishes to manage. Vulnerability, except in extreme forms (such as depression, anger, and anxiety), is difficult to characterize exactly, so the astute clinician must depend on a telling episode or metaphor that typifies a total reaction.

TABLE 32–4 How To Find Out How a Patient Copes

Problem:	**In your opinion, what has been the most difficult for you since your illness started? How has it troubled you?**
Strategy:	**What did you do (or are doing) about the problem?**
	Get more information (rational/intellectual approach)
	Talk it over with others to relieve distress (share concern)
	Try to laugh it off; make light of it (reverse affect)
	Put it out of mind; try to forget (suppression/denial)
	Distract myself by doing other things (displacement/dissipation)
	Take a positive step based on a present understanding (confrontation)
	Accept, but change the meaning to something easier to deal with (redefinition)
	Submit, yield, and surrender to the inevitable (passivity/fatalism)
	Do something, anything, reckless or impractical (acting out)
	Look for feasible alternatives to negotiate (if *x*, then *y*)
	Drink, eat, take drugs, and so on, to reduce tension (tension reduction)
	Withdraw, get away, and seek isolation (stimulus reduction)
	Blame someone or something (projection/ disowning/externalization)
	Go along with directives from authority figures (compliance)
	Blame self for faults; sacrifice or atone (undoing self-pity)
Resolution:	**How has it worked out so far?**
	Not at all
	Doubtful relief
	Limited relief, but better
	Much better; actual resolution

Adapted from Weisman AD: *The realization of death: a guide for the psychological autopsy*, New York, 1974, Jason Aronson Inc.

HOW TO FIND OUT MORE ABOUT COPING

Thus far, we have discussed the following: salient characteristics of effective and less effective copers, methods by which deficits in patients can be identified and how clinicians can intervene, potential pressure points that alert

TABLE 32–5 How to Assess Areas of Vulnerability Versus Resiliency

Confusion versus coherence	How do you make sense out of your experience?
Isolation versus communion	Who do you believe understands your situation?
Despair versus hope	What sorts of things keep you from giving up?
Helplessness versus agency	Who keeps you alive?
Meaninglessness versus purpose	What issues about your treatment concern you the most?
Cowardice versus courage	Have there been times when you wanted to give up but did not? What prevented you from giving up?
Resentment versus gratitude	What things in life are you most grateful for? Has your illness taught you anything meaningful?

Adapted from Griffith J, Gaby L: Brief psychotherapy at the bedside: countering demoralization from medical illness, *Psychosomatics* 46:109-116, 2005.

clinicians to different psychosocial difficulties, types of emotional vulnerabilities, and a format for listing different coping strategies, along with questions about resolutions and increasing resiliency.

The assessment and identification of ways in which a patient copes or fails to cope with specific problems requires both a description by the patient and an interpretation by the psychiatrist. Even so, this may not be enough. Details of descriptive importance may not be explicit or forthcoming. In these situations, the clinician must take pains to elucidate the specifics of each situation. If not, the result is only a soft approximation that generalizes where it should be precise. Indeed, the clinician should ask again and again about a topic that is unclear and rephrase, without yielding to cliches and general impressions.

Psychiatrists have been imbued with the value of so-called empathy and intuition. Although immediate insights and inferences can be pleasing to the examiner, sometimes these conclusions can be misleading and totally wrong. It is far more empathic to respect each patient's individuality and unique slant on the world by making sure that the examiner accurately describes in detail how problems are confronted. To draw a quick inference without being sure about a highly private state of mind is distinctly unempathic. Like most individuals, patients give themselves the benefit of the doubt and claim to resolve problems in a socially desirable and potentially effective way. It takes little experience to realize that disavowal of any problem through pleasant distortions is itself a coping strategy, not necessarily an accurate description of how one coped.

Patients who adamantly deny any difficulty tend to cope poorly. Sick patients have difficult lives, and the denial of adversity usually represents a relatively primitive defense that leaves such patients unprepared to accurately assess their options. Carefully timed and empathic discussion with patients about their current condition can help them address their treatment more effectively and avoid maladaptive approaches.

On the other hand, patients may attempt to disavow any role in their current illness. By seeking credit for having suffered so much, such patients reject any implication that they might have prevented, deflected, or corrected what has befallen them (see Table 32–4). Helping these patients does not necessarily require that they acknowledge their role in their particular predicament. Instead, the empathic listener identifies and provides comfort around the implicit fear that these patients harbor (i.e., that they somehow deserve their debilitation).

Suppression, isolation, and projection are common defenses. Effective copers seem to pinpoint problems clearly, whereas bad copers, as well as those with strong primitive defenses, seem to seek relief from further questions without attempting anything that suggests reflective analysis.

In learning how anyone copes, a measure of authentic skepticism is always appropriate, especially when it is combined with a willingness to accept correction later on. The balance between denial and affirmation is always uncertain. The key is to focus on points of ambiguity, anxiety, and ambivalence while tactfully preserving a patient's self-esteem. A tactful examiner might say, for example, "I'm really not clear about what exactly bothered you, and what you really did. …"

The purpose of focusing is to avoid premature formulations that gloss over points of ambiguity. An overly rigid format in approaching any evaluation risks overlooking individual tactics that deny, avoid, dissemble, and blame others for difficulties. Patients, too, can be rigid, discouraging alliance, rebuffing collaboration, and preventing an effective physician–patient relationship.

HOW TO BE A BETTER COPER

Coping with illness is only one special area of human behavior. It is important to recognize that in evaluating how patients cope, examiners should learn about their own coping styles and, in effect, learn from patients. Clearly, it is not enough to mean well, to have a warm heart, or to have a head filled with scientific information. Coping well requires open-ended communication and self-awareness. No technique for coping is applicable to one and all. In fact, the concept of technique may be antithetical to true understanding. A false objectivity obstructs appraisal; an exaggerated subjectivity only confuses what is being said about whom.

Psychiatrists and patients can become better copers by cultivating the characteristics of effective copers. Coping is, after all, a skill that is useful in a variety of situations, although many modifications of basic principles are called for. Confidence in being able to cope can be enhanced only through repeated attempts at self-appraisal, self-instruction, and self-correction. Coping well with illness—with any problem—does not predict invariable success, but it does provide a foundation for becoming a better coper.

ADDITIONAL PSYCHOTHERAPEUTIC TECHNIQUES IN THE MEDICALLY ILL POPULATION

Cognitive-behavioral therapy (CBT) is a structured and often short-term psychotherapeutic modality that has been effective in the treatment of many psychiatric conditions (including anxiety, depression, PTSD, and suicidal crises); it is a technique that involves assessment of the relationship among a patient's cognitive process, emotions, and behaviors. More recent literature has shown its efficacy in reducing anxiety and depression associated with a host of medical conditions (including cancer, chronic pain, and HIV infection). Typically, such research has assessed its efficacy in the outpatient setting; however, the psychiatrist in an inpatient medical setting can also use these techniques.

In a meta-analysis of various psychosocial interventions for the treatment of anxiety and depression in cancer patients, Osborn and associates[23] found that limited CBT treatment was effective for the treatment of depression and anxiety over the short term and that quality-of-life measures improved over both the short- and long-term analyses. More recently the combination of CBT and hypnosis effectively decreased negative affect and improved positive affect in breast cancer patients receiving radiation therapy.[24] CBT changed maladaptive cognitions and behaviors in these patients while leading to more adaptive cognitive process; hypnosis (involving direct suggestion of decreasing negative affect and increasing positive affect) also led to improvement. In those infected with HIV, rates of depression are high, and co-morbidity is associated with increased rates of risky behaviors, poorer disease outcome (e.g., with a decreased CD4 count, an increased viral load, an increased progression to AIDS, and an increased mortality rate), and poor treatment adherence. In a recent randomized clinical trial, CBT improved adherence and decreased depressive symptoms in a significant proportion of patients.[25] Multiple studies support the efficacy of CBT in those with chronic pain; this may result from altering perceived pain control, self-efficacy, and psychological distress (including depression and anxiety).[26]

A recent meta-analysis (by Chida and colleagues[27]) demonstrated that stress-related psychological factors led to increased rates of cancer incidence in healthy people, decreased survival in patients with cancer, and increased cancer mortality; this may be related to the chronic stress that cancer imposes on the body and to abnormalities in catecholamine and glucocorticoid secretion, with subsequent suppression in the immune response. Many psychosocial interventions (including group psychotherapy) may lead to improvements in cancer-related mortality; however, this remains controversial. Data from an 11-year follow-up study of breast cancer patients (by Anderson and associates[28]) showed that psychosocial interventions (including groups that taught about muscle relaxation, communication, diet, treatment compliance, coping with medication side effects, and problem-solving) led not only to improvements in distress level, quality of life, and health behaviors, but also led to decreased cancer recurrence and cancer mortality. Others have argued that group psychotherapy, and other psychosocial interventions, do not affect cancer recurrence or mortality rates.[29] The debate regarding the impact on mortality in cancer and other chronic medical conditions of psychosocial interventions remains; however, most authors agree that group psychotherapy helps patients as it improves depression, anxiety, and quality of life. This modality remains another critical psychotherapeutic technique to offer to the medically ill.

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Electroconvulsive Therapy in the General Hospital

33

Charles A. Welch, M.D.
Carlos Fernandez-Robles, M.D.
Cristina Cusin, M.D.

Electroconvulsive therapy (ECT) remains an indispensable treatment in the general hospital because of the large number of depressed patients who are unresponsive to drugs or intolerant of their side effects. In the largest clinical trial of antidepressant medication, only 67% of depressed patients achieved a full remission, and the rest were nonresponders or achieved only partial remission.[1] On the other hand, remission rates of 70% to 90% have been reported in clinical trials of ECT for depression.[2,3] Depression requires effective treatment because it is associated with morbidity and an increased risk of mortality (mainly due to cardiovascular events or suicide).[4] Furthermore, among all diseases, depression currently ranks fourth in global disease burden, and it is projected to rank second by the year 2020.[5] ECT is currently the most promising prospect for addressing the unmet worldwide need for effective depression treatment.

INDICATIONS

The symptoms that predict a good response to ECT are those of major depression: anorexia, weight loss, early morning awakening, impaired concentration, pessimistic mood, motor restlessness, increased speech latency, constipation, and somatic or self-deprecatory delusions.[6,7] The cardinal symptom is the loss of interest in activities that formerly gave pleasure. These are exactly the same symptoms that constitute an indication for antidepressant drugs. At the present time, there is no way to predict which patients will ultimately be drug resistant. Currently, there is little consensus on the definition of drug-resistant depression,[8] and the designation of drug failure varies with the adequacy of prior treatment.[9] Medical co-morbidities also affect this definition. Young, healthy, nonsuicidal patients can safely receive four or more different drug trials before embarking on a course of ECT, whereas older patients with depression may be unable to tolerate more than one drug trial without developing serious morbidity.

Other factors also affect the decision to move from drug therapy to ECT. Thoughts of suicide respond to ECT 80% of the time,[10] and they are an indication for an early transition from drug therapy.[11] Lower response rates to ECT have been reported in depressed patients with a co-morbid personality disorder[12] and with a longer duration of depression,[13] but there are conflicting reports as to whether a history of medication resistance is associated with a lower response rate to ECT. However, if neurovegetative signs are present, none of these factors constitutes a reason to avoid ECT.

Psychotic illness is the second indication for ECT. Although it is not a routine treatment for schizophrenia, ECT, in combination with a neuroleptic, results in sustained improvement in up to 80% of drug-resistant patients with chronic schizophrenia.[14,15] Furthermore, a recent review found preliminary evidence that supports the safety and short-term efficacy of clozapine and ECT in patients with schizophrenia or schizoaffective disorder.[16] A subgroup of young psychotics conforming to the schizophreniform profile (acute onset, affective intactness, and family history of affective disorder) appear to be more responsive to ECT, often developing a full and enduring remission of their illness, than those with chronic schizophrenia.[17–19]

Mania is also known to respond to ECT,[20,21] but drug treatment remains the first-line therapy. Nevertheless, in controlled trials, ECT has been as effective as lithium (or more so), and in drug-refractory mania, more than 50% of cases have remitted with ECT.[22] A recent review found that ECT is an effective, safe, and probably underutilized treatment for those with mixed affective states.[23] Preliminary evidence also shows that ECT stabilizes refractory bipolar disorder in adolescents and the elderly.[24,25]

Although most patients initially receive a trial of medication regardless of their diagnosis, ECT is a primary treatment for several categories of patients:

1. Mood-disordered patients who are severely malnourished, dehydrated, and exhausted. Such patients with protracted depressive illness are medically at risk and should be treated promptly after careful rehydration.
2. Patients with complicating medical illness (e.g., cardiac arrhythmias or coronary artery disease). Such patients are often more safely treated with ECT than with antidepressants.
3. Patients with delusional depression. Although most delusionally depressed patients do not improve on an antidepressant alone,[26] the reported response rate with ECT in delusional depression is 80% to 90%.[27–29] The combination of a tricyclic antidepressant (TCA) and an antipsychotic may be effective,[30] but many patients cannot tolerate the side effects of this regimen.
4. Patients who have been unresponsive to medications during previous episodes.
5. Patients with catatonia (see Chapter 21); the majority of patients with catatonia respond promptly to ECT.[31–33]

Although catatonia is most often associated with affective disorders, it may also be a manifestation of schizophrenia, metabolic disorders, structural brain lesions, or systemic lupus erythematosus. Prompt treatment is essential, because the mortality in untreated catatonia is as high as 50%; even its nonfatal complications (including pneumonia, venous embolism, limb contracture, and decubitus ulcer) are serious. ECT is effective in up to 75% of patients with catatonia, regardless of the underlying cause, and it is a primary treatment for most patients with catatonia.[34] Lorazepam has also been effective for the short-term treatment of catatonia,[35] but its long-term efficacy has not been confirmed. At times, neuroleptic malignant syndrome (NMS) may be clinically indistinguishable from catatonia,[36] although high fever, opisthotonos, and rigidity are more common in the former. More than 50 case reports suggest that ECT is effective for NMS, even when drug therapy has failed,[37] but the essential components of management are intensive (supportive) medical treatment, discontinuation of neuroleptics, and use of dantrolene and bromocriptine.

Several case reports and case series have suggested that ECT can be effective for the treatment of behavioral disturbances, aggression, and pathologic yelling associated with severe dementia (that has been unresponsive to several medication trials).[38–42] Because of the risk of cognitive impairment associated with ECT, a careful discussion of the risks and benefits of this treatment modality in those with dementia must take place before a course of ECT is attempted. Depressed patients with preexisting dementia are likely to develop especially severe cognitive deficits after ECT; fortunately, most individuals return to their baseline level of cognition after treatment, and many actually improve.[43,44]

ECT has also been useful in the treatment of myriad medical conditions. Several case reports, case series, and open trials have documented the efficacy of ECT in treatment of motor symptoms in patients with Parkinson's disease (both with and without concurrent psychiatric illnesses).[45–48]

In addition, ECT has been effective in the treatment of delirium due to toxic or metabolic encephalopathies,[49,50] and in the control of intractable pain (secondary to neuropathic pain, fibromyalgia, and complex regional pain syndrome, among other syndromes).[51–54]

RISK FACTORS FOR ADVERSE EVENTS

As the technical conduct of ECT has improved, factors that were formerly considered absolute contraindications have become relative risk factors. The patient is best served by weighing intelligently the risk of treatment against the morbidity or lethality of remaining depressed. The prevailing view is that there are no longer any absolute contraindications to ECT; however, several conditions warrant careful work-up and management when ECT is considered.[55]

Without question, the heart is physiologically stressed during ECT.[56] Cardiac work increases abruptly at the onset of the seizure, initially because of sympathetic outflow from the diencephalon, through the spinal sympathetic tract, to the heart. This outflow persists throughout the seizure and is augmented by a rise in circulating catecholamine levels that peak about 3 minutes after the onset of seizure activity.[57,58] After the seizure ends, parasympathetic tone remains strong, often causing transient bradycardia and hypotension, with a return to baseline function after 5 to 10 minutes.

The cardiac conditions that most commonly worsen under this autonomic stimulus are ischemic heart disease, hypertension, congestive heart failure (CHF), and cardiac arrhythmias., However, if properly managed, these conditions have proved to be surprisingly tolerant to ECT. Duration of the QTc in the baseline electrocardiogram (ECG) appears to be a helpful predictor of arrhythmias during ECT.[59] The idea that general anesthesia is contraindicated within 6 months of a myocardial infarction has acquired a certain sanctity; this is surprising considering the ambiguity of the original data.[60] A more rational approach involves careful assessment of the cardiac reserve, a reserve that is needed as cardiac work increases during ECT.[61] Vascular aneurysms should be repaired, if possible, before ECT[62,63]; however, more than 30 case reports have documented the safe use of ECT in the presence of intracranial and aortic aneurysms, stressing the importance of blood pressure control in this situations.[64–66] Case reports and one case series have also demonstrated safe ECT administration to patients with moderate to severe aortic stenosis and preserved left ventricular function,[67–69] but, if possible, critical aortic stenosis should be surgically corrected before a course of ECT (to avoid ventricular overload during the seizure). Patients with cardiac pacemakers are known to tolerate ECT uneventfully: safety precautions should include proper grounding of all monitoring devices, insulating the patient's stretcher, ensuring that the patient is not touched by somebody who is in ground contact during presentation of the electrical stimulus. Also a magnet should be available, in the unlikely event of pacemaker inhibition and symptomatic bradycardia, to convert the pacemaker from demand mode to fixed mode. The current recommendation for patients with an automatic implantable cardioverter defibrillator is to turn it off during ECT, to carefully monitor the rhythm, and to have an external defibrillator available.[70] Patients with compensated CHF generally tolerate ECT well, although a transient (5 to 10 minutes) decompensation into pulmonary edema may occur in patients with a baseline ejection fraction below 20%. It is unclear whether the underlying cause is a neurogenic stimulus to the lung parenchyma or a reduction in cardiac output because of increased heart rate and blood pressure. A retrospective study examining blood pressures before and after ECT in hypertensive and nonhypertensive patients concluded that a course of ECT does not worsen blood pressure in hypertensive patients beyond the time around the treatment period.[71]

The brain is also physiologically stressed during ECT. Cerebral oxygen consumption approximately doubles, and cerebral blood flow increases several-fold. Intracranial pressure increases and the blood–brain barrier becomes more permeable during ECT. These acute changes may increase the risk associated with ECT in patients with a variety of neurologic conditions.[72]

In years past, space-occupying brain lesions were considered an absolute contraindication to ECT, and case reports described clinical deterioration when ECT was given to patients with brain tumors.[73] Now, the general

consensus is that if a lesion is relatively small, solitary, and not associated with significant mass effect, edema, or increased intracranial pressure, ECT probably does not present a greater than usual risk of neurologic deterioration; however, a large mass, multiple masses (e.g., metastatic lesions), edema, increased intracranial pressure, or mass effect should be considered relative contraindications for ECT, and measures should be taken to reduce edema and the increase in intracranial pressure if treatment is undertaken.[74] The most common intracranial risk factor is probably recent cerebral infarction. Case reports of ECT after recent cerebral infarction indicate that, when the treatment is properly performed, the complication rate is low.[72] Consequently, ECT is often the treatment of choice for poststroke depression.[75] The interval between infarction and treatment with ECT should be determined by the urgency and need for depression treatment.

ECT has been safe and efficacious in patients with hydrocephalus, arteriovenous malformations, cerebral hemorrhages, multiple sclerosis, systemic lupus erythematosus, Huntington's disease, and mental retardation. ECT also appears to be safe in patients with asthma[76]; recent guidelines recommend the administration of prescribed inhalers (to patients with chronic obstructive pulmonary disease) on the morning of the ECT treatment. However, caution is recommended when performing ECT on patients taking theophylline, because this drug has been associated with prolonged seizures and status epilepticus.[77]

A severely depressed pregnant mother may require ECT to prevent malnutrition or suicide. Limited data indicate that ECT is an effective treatment for severe mental illness during pregnancy and that the risks to the fetus and to the mother from ECT are low.[78] Preparation for ECT during pregnancy should include a pelvic examination, discontinuation of nonessential anticholinergic medications, uterine tocodynamometry, IV hydration, and administration of a nonparticulate antacid. During ECT, elevation of the pregnant woman's right hip, external fetal cardiac monitoring, intubation, and avoidance of excessive hyperventilation are recommended.[79] The fetus may be protected from the physiologic stress of ECT by virtue of its lack of direct neuronal connection to the maternal diencephalon, which spares it the intense autonomic stimulus experienced by maternal end organs during the ictus.

Last, depolarizing muscle relaxants, such as succinylcholine, may generate adverse effects in patients with certain conditions (e.g., myasthenia gravis, amyotrophic lateral sclerosis, genetic or acquired pseudocholinesterase deficiency, and NMS). In such conditions, a substitute nondepolarizing agent appears indicated. Barbiturates are considered unsafe in patients with porphyria; they should receive alternative anesthetics.[80]

TECHNIQUE

The routine pre-ECT work-up should include a thorough medical history and physical examination, with a chest film, ECG, urinalysis, complete blood cell count, and determination of blood glucose, blood urea nitrogen, and electrolyte levels. Additional studies may be necessary, at the clinician's discretion. In patients with cognitive deficits, it is sometimes difficult to decide whether a CNS work-up is indicated because depression may cause this deficit. A metabolic screen, a computed tomography scan, and magnetic resonance imaging are often useful to rule out non–depression-related causes of impaired cognition. Whenever a question of primary dementia arises, neurologic consultation should be requested; neuropsychological testing does not definitively distinguish between primary dementia and depressive pseudodementia.[81]

If at all possible, the patient's medical condition should be optimized before beginning ECT. Elderly patients often arrive at the hospital severely malnourished and dehydrated, and ECT should be delayed until they have had several days of rehydration, with alimentation via feeding tube if necessary. If a patient is receiving digitalis, its serum level should be in the middle to low therapeutic range. Antihypertensive regimens should be optimized before treatment to reduce the chance of developing a severe hypertensive reaction. Most patients with diabetes are more stable if their morning dose of insulin is held until after their ECT treatment. The insulin requirement usually decreases as a diabetic patient recovers from depression, and blood glucose levels must be monitored frequently during the course of ECT.

The issue of whether to combine a psychotropic medication with ECT is a matter of much speculation; little controlled research has been conducted on this issue. In general, a patient should be taken off medications that have not been beneficial despite adequate dosage and duration of therapy. Older case reports cautioned that patients undergoing ECT who are concomitantly taking lithium may be particularly prone to severe cognitive disturbance, to prolonged time to awakening or breathing, or to prolonged or spontaneous seizures; however, a more recent case series indicated that the combination may be used safely and with optimal efficacy in certain clinical circumstances.[82] For the bipolar patient already taking lithium, the clinician must consider the risk of mania if lithium is abruptly discontinued, or that the washout of lithium in anticipation of starting ECT will delay treatment. Benzodiazepines, which are antagonistic to the ictal process, should also be decreased or discontinued whenever possible.[83] For sedation, patients receiving ECT usually tolerate a sedating phenothiazine, such as perphenazine (Trilafon) 4 to 8 mg every 6 hours, or a nonbenzodiazepine hypnotic, such as hydroxyzine (Vistaril) 50 to 100 mg, or diphenhydramine (Benadryl) 25 to 50 mg twice daily. TCAs make cardiovascular management more difficult and they should be discontinued. Monoamine oxidase inhibitors (MAOIs) are typically withheld, as the potential adverse interactions between MAOIs and ECT include effects on the induced seizure itself and interactions with the medications used for anesthesia (anticholinergic agents, anesthetic induction agents, muscle relaxants, antihypertensives, and narcotics); a washout period before ECT is unnecessary.[84] In the patient with a preexisting seizure disorder, anticonvulsants should be maintained for patient safety and the elevated seizure threshold overridden with a higher-intensity stimulus.

Because of the profound physiologic disturbances unique to this treatment, ECT should not be performed in collaboration with an anesthesiologist unfamiliar with the techniques and the cardiovascular effects of ECT. Although ECT was formerly thought to be a trivial exercise in anesthetic management, quite the contrary is true, and a careful

reading of the literature is essential for the anesthesiologist.[85,86] The use of cardiac monitoring and pulse oximetry on all patients undergoing general anesthesia has been endorsed by the American Society of Anesthesiologists. Existing ECT machines record the ECG only during the treatment itself; however, recording of baseline and postictal rhythms is essential, and a separate operating room monitor with paper recording capability is necessary to monitor the ECG adequately.

General anesthesia is induced with methohexital or propofol; succinylcholine is used to achieve muscle relaxation. Anticholinergics, such as atropine or glycopyrrolate, have long been used in ECT to eliminate parasympathetically mediated dysrhythmias. However, such agents increase heart rate and myocardial workload and may increase the risk of adverse cardiac events. Therefore, anticholinergics are not routinely administered, and their use is reserved for patients who are prone to bradycardia.[87]

For patients with coronary artery disease or hypertension, short-acting IV β-blockers effectively reduce stress on the heart. These agents attenuate hypertension, tachycardia, ectopy, and cardiac ischemia, and with proper use they rarely result in hypotension or bradycardia. Esmolol 100 to 200 mg or labetalol 10 to 20 mg given IV immediately before the anesthetic induction is usually sufficient.[88] Although these drugs may result in decompensation of CHF, this has yet to be reported. A second method of reducing cardiac work involves administration of nifedipine 10 mg sublingually, 15 minutes before treatment.[89] Nitroglycerine, infused at 0.5 to 3.0 mg/kg per min, may be used to blunt the hypertensive response of patients who are already receiving β-blockers or calcium channel blockers and who require additional antihypertensives. If an infusion is used, the patient must be observed for hypotension at the first treatment, at the very least.

Treating hypertension adequately before a course of ECT usually reduces the hypertensive response during the treatment itself. Maintenance β-blockers, such as atenolol 25 to 50 mg, orally every day, may render the use of a short-acting antihypertensive during treatment unnecessary.

Patients with cardiac disease have a significantly higher rate of cardiac complications during ECT.[90] Conduction system abnormalities during treatment have been reported in 20% to 80% of ECT patients,[91] but they are usually transient. Persistent or severe arrhythmias occasionally require treatment; the approach depends on the type of arrhythmia. Supraventricular tachycardia is generally best treated with calcium channel blockers, whereas ventricular ectopy is most rapidly stabilized with IV lidocaine. Many arrhythmias can be prevented by pretreatment with a short-acting IV β-blocker before subsequent treatments.

Decompensation of CHF is usually treatable with oxygen and elevation of the head. Occasionally, IV furosemide (Lasix) and morphine become necessary, but this is extremely rare. Most patients recompensate within 10 to 15 minutes of the treatment without aggressive intervention.

Cardiac arrest is a rare complication of ECT. Some patients have a period of asystole after the ECT stimulus that may last up to 8 seconds, and this may be mistaken for a true arrest.[56,92] Patients who receive nonconvulsive stimuli may be especially at risk, because the intense parasympathetic outflow caused by the stimulus is not counteracted by the sympathetic outflow of the seizure itself, and severe bradycardia or arrest may ensue.

There are a few large studies of the morbidity and mortality associated with ECT.[93,94] A recently published retrospective review of 2279 patients, who went through a total of 17,394 ECT treatments, reported that 21 of them (0.92%; 95% confidence interval, 0.57%-1.41%) experienced a complication at some time. Cardiac complications, mostly arrhythmias, constituted the majority, but none of the complications caused permanent injury, and none of the patients died during or immediately after ECT.

The choice of electrode placement in ECT remains controversial. Both right unilateral (RUL) and bilateral (BL) placements have advantages and disadvantages. RUL ECT causes less cognitive impairment than BL ECT, but its efficacy is not as great as that of BL ECT (the latter being indicated as first choice for those with more severe depression and for patients with poor response to RUL).[7,95] At Massachusetts General Hospital, unilateral nondominant ECT is used at the outset for all patients, with the exception of patients with treatment-resistant mania. Approximately 5% of depressed patients at this hospital prove refractory to 6 to 12 unilateral treatments; when that occurs, they are switched to ECT with a BL electrode placement. Ineffective unilateral ECT is associated with use of threshold stimulus intensity[96] and a short distance between electrodes.[97] Consequently, a unilateral stimulus should be at least 50% above the threshold with the electrodes placed in the d'Elia position.[96]

Brief-pulse waveforms have become the standard of practice in the United States. Although sine-wave stimuli were common in years past, the brief-pulse waveform more efficiently induces seizure activity and is associated with less posttreatment confusion and amnesia.[59] Ultrabrief pulse-width (0.3 msec) right unilateral (known as RUL-UB) ECT, for selected patients, can minimize cognitive effects while preserving efficacy.[98]

The schedule of administration is usually three times a week, even if a few studies postulated that ECT twice weekly was as effective in alleviating depression as ECT delivered three times weekly. Although this schedule of treatment induces less memory impairment, the improvement is slower[99]; Kellner and colleagues[100] found that decreasing the frequency of ECT administration to once a week slowed the antidepressant effect to a clinically unacceptable level.

Generalization of the seizure to the entire brain is essential for efficacy.[101] The simplest way to monitor seizure generalization is to inflate a blood pressure cuff on the arm or ankle to above the systolic pressure, just before injection of succinylcholine. The convulsion can then be observed in the unparalyzed extremity. In unilateral ECT, the cuff is placed on the limb ipsilateral to the stimulus. Most ECT instruments have a built-in, single-channel electroencephalographic monitor, but this is not a reliable indicator of full seizure generalization, because partial seizures may also generate a classic seizure tracing. No consistent relationship has ever been detected between the clinical antidepressant response to ECT and either the threshold or the duration of the induced seizure.[102]

After ECT, patients should not be left in the supine position; instead, they should be turned on their side to allow better drainage of secretions. They should be monitored

carefully by a recovery nurse; vital signs should be taken regularly and pulse oximetry monitored. About one in 20 patients, typically young, healthy individuals, develop an agitated delirium with a vacant stare, disorientation, and automatisms immediately after treatment. This clinical picture is usually the result of tardive seizures; the state clears promptly with midazolam 2 to 5 mg IV, or diazepam 5 to 10 mg IV.

The average number of ECT procedures necessary to treat major depression is consistently reported to be between 6 and 12, but occasional patients require up to 30. The customary timing is three sessions per week with one full seizure per session. The use of more than one seizure per session (multiple-monitored ECT) has not shown any advantage over conventional ECT.[103]

ADVERSE COGNITIVE EFFECTS

Although there is no evidence for structural brain damage as a result of ECT,[104] there are important effects on cognition.[105] Posttreatment confusion and general disorientation in the immediate period after ECT is a well-documented and common occurrence; it is associated with bilateral electrode placement, high stimulus intensity, inadequate oxygenation, prolonged seizure activity, older age, and the presence of neurologic disease. It has also been shown to resolve in a predictable fashion. In addition to the discrete periods of post-ECT disorientation, which are relatively frequent, longer and more severe confusional states (generally classified as delirium) can occur. Such post-ECT delirium is more common in older patients and in those with an underlying neurologic condition.[106]

The most common cognitive side effect is difficulty recalling new information (anterograde amnesia), which normally resolves within a month after the last treatment. Evidence suggests that autobiographical memory impairment also occurs as a result of ECT. Objective measures have found memory loss to be relatively short term (<6 months after treatment), whereas subjective accounts have reported amnesia to be more persistent (>6 months after ECT). ECT predominantly affects memory of prior personal events that are near the treatment date,[107] with BL ECT causing more memory disturbance than RUL ECT; this holds true for both retrograde and anterograde memory function and for both verbal and nonverbal recall.[108] The least memory deficit is seen with a unilateral brief and ultra-brief pulse stimulus.[109]

Development of a severe organic brain syndrome after ECT is rare, and it may require discontinuation of treatment. Usually, substantial improvement occurs within 48 hours of the last treatment; if symptoms become more severe after cessation of treatment, a full neurologic workup is indicated to assess whether there is an underlying cause other than ECT.

MAINTENANCE TREATMENT

After successful treatment, the risk of relapse is greater than 50% at 12 months without the use of maintenance medication.[110] A few prospective studies have provided mixed results with TCA maintenance.[111,112] The efficacy of maintenance with MAOIs, lithium, bupropion, or fluoxetine has never been evaluated in a well-controlled trial. In general, maintenance ECT (i.e., one treatment per month, on average) has been efficacious, safe, well tolerated, and cost effective compared with maintenance pharmacotherapy,[113–115] with its greatest impact consisting of reducing relapse, recurrence, and rehospitalization in treatment-resistant patients. A recently published multicenter, randomized, controlled trial showed similar efficacy for continuation ECT or nortriptyline plus lithium at 6 months, with more than half of the patients either experiencing disease relapse or dropping out of the study.[116]

SUMMARY

In recent years, the technique of ECT has become more sophisticated,[117] and this has made the treatment safer in the general hospital setting, where growing numbers of high-risk patients are seen. Increasingly, the practice of ECT is regarded as a distinct subspecialty that requires specific training and privileges.[118] In view of its efficacy in patients unresponsive to medication, it is likely that ECT will be an essential part of psychiatry in the general hospital for the foreseeable future.

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Psychopharmacology in the Medical Setting

34

Jonathan R. Stevens, M.D., M.P.H.
Maurizio Fava, M.D.
Jerrold F. Rosenbaum, M.D.
Jonathan E. Alpert, M.D., Ph.D.

The psychiatrist in the general medical setting faces many challenges posed by co-morbid medical disorders and concurrent medications that hinder the detection of psychiatric symptoms and alter the effectiveness, tolerability, and safety of psychiatric drug treatment.[1–4] Most clinical trials designed to establish the efficacy and safety of psychotropic medications exclude persons who suffer from unstable nonpsychiatric medical conditions or who take nonpsychiatric medications with appreciable central nervous system (CNS) effects. Fortunately, inroads are being created, as controlled multicenter pharmacotherapy trials are gradually extended to subjects with unstable medical illnesses[5] and large effectiveness trials in psychiatry are designed to allow participation of patients in primary care settings who have co-morbid medical illness and complex medical regimens.[6] As a guide to making informed decisions about use of psychotropic medication in the medical setting, this chapter focuses on principles of psychopharmacologic practice and on the rapidly expanding knowledge base regarding pharmacokinetics and drug–drug interactions. This chapter also reviews some of the important psychiatric uses of nonpsychiatric medications that have emerged.

PRINCIPLES OF PSYCHOPHARMACOLOGIC PRACTICE

The complicated clinical and psychosocial contexts in which psychotropic medications are often administered in the general hospital call on a sound understanding of basic principles that underlie the practice of psychopharmacology.[7] If pharmacologic efforts fail to achieve their intended goals, a review of these principles often helps to uncover potential explanations and to redirect treatment.

Initiating Treatment

The appropriate use of psychotropic medications starts with as precise a formulation of the diagnosis as possible. The use of an antidepressant alone for a depressed college student presenting to an emergency department might be appropriate if the diagnosis is of a major depressive episode; less pertinent if the diagnosis is of an adjustment disorder; and seriously inadequate and quite possibly harmful if the diagnosis is of a bipolar disorder, psychotic depression, or cocaine or alcohol abuse. As a rule, it is best to defer pharmacologic treatment until a good working diagnosis can be reached. The establishment of a psychiatric diagnosis, however, often requires longitudinal assessment of course and treatment response. Many symptoms of psychiatric disorders may be obscured or altered by co-occurring medical conditions. Therefore, in acute clinical situations, it is often not possible to defer the implementation of psychotropic medications until a diagnosis is fully clarified. In this context, it is particularly crucial to document probable and differential diagnosis, to outline the rationale for selecting a particular treatment over others, and to indicate the kind of information needed to achieve greater diagnostic certainty. When a disorder appears to present in a subsyndromal form, such as minor depression, the rationale for proceeding with psychopharmacologic treatment should be well defined.

The identification of a particular set of target symptoms plays an integral role in establishing a pretreatment baseline and in later efforts to monitor the success of treatment. These symptoms might include anger attacks, insomnia, anhedonia, delusions of reference, hallucinations, or the frequency and intensity of suicidal longings. The identification of target symptoms serves to focus attention on the symptoms that are causing greatest danger, disability, and distress to the patient while also more fully informing the patient about the core symptoms of his or her illness and the specific goals for which psychotropic medications have been recommended.

For some conditions, clinician-rated instruments, such as the Brief Psychiatric Rating Scale,[8] the Hamilton Rating Scale for Depression,[9] the Hamilton Rating Scale for Anxiety,[10] and the Young Mania Scale,[11] provide useful, well-studied templates for the serial assessment of relevant symptoms. In addition, the patient and family or other caregivers can be recruited in formal efforts to monitor progress. In the case of episodic or complex presentations, the use of daily mood charts, patient-rating scales such as the Quick Inventory for Depressive Symptomatology,[12] or behavioral logs—analogous to patient monitoring of blood pressure or glucose—can reveal temporal patterns (e.g., rapid mood cycling) and associations (e.g., to menstrual cycle or medication changes) that are not apparent cross-sectionally during office or bedside visits.

Along with the assessment of target symptoms, evaluation of current levels of function and subsequent changes with treatment relevant to quality of life are an integral part of good psychopharmacologic practice. Thus, for example, for an outpatient, the clinician might query about improvement in work or school function, family and other

social relationships, and use of leisure time, whereas for an inpatient, progress in the level of independence and reduction in the overall degree of anguish can help confirm the adequacy of treatment, because lack of improvement along these dimensions directs attention to residual symptoms or to problems not initially apparent.

The Global Assessment of Function scale, a routine part of *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) multiaxial assessment, provides a composite index of symptoms and dimensions that pertain to quality of life, which is useful for documenting treatment course over time.[13] Some clinicians also make use of the Clinical Global Impression (CGI) scale.[14] This scale, widely used in clinical trials, rates severity of disease on a scale of 1 to 7 (from normal to most extreme) and improvement on a scale of 1 to 7 (from very much improved to very much worse) and provides another simple quantitative means to document overall treatment outcome.

The understanding that a patient's psychiatric condition is influenced by psychosocial factors does not imply that psychotropic medications should be withheld. A major depression evolving in the setting of a spouse's chronic illness or panic attacks emerging in the weeks following the breakup of a significant relationship may well be as severe and as responsive to pharmacologic treatment as the same disorders that developed in other patients without similar precipitants. Vague referrals to counseling do not constitute sufficient treatment under such circumstances and may be viewed by patients as dismissive. If psychotherapy is recommended and pharmacotherapy deferred, the referral to psychotherapy—whether, for example, to individual cognitive therapy, to couples therapy, or to a pain management group (i.e., behavioral treatment)—must be viewed with the same deliberateness as the prescription of medication, and it should include a plan for follow-up. If substantial progress is not made within a clinically appropriate time frame (e.g., no more than 8 to 12 weeks for a moderately severe episode of major depression) then the adequacy of the psychotherapy should be re-evaluated. Severity, chronicity, and risk of recurrence of symptoms are often more relevant in determining the need for pharmacotherapy of psychiatric conditions than the presence of aggravating life circumstances or a caricatured description of illness as chemical or reactive.

Reciprocally, the expanding range of safe and well-tolerated psychotropic agents, such as the selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants, does not alter the imperative to explore the use of nonmedication interventions whenever medications are considered. An assessment of a patient for psychiatric medications should include an equally careful evaluation for other targeted interventions instead of, or in addition to, pharmacotherapy or psychotherapy. Often uniquely helpful are judicious referrals to parenting classes; elder care; Alcoholics Anonymous, Narcotics Anonymous, and Al-Anon; vocational assessment and rehabilitation; support groups for persons who are bereaved, who are going through separation, and who have medical disorders (e.g., epilepsy, human immunodeficiency virus [HIV] infection); and psychiatric self-help groups, such as those sponsored by the National Manic-Depressive and Depressive Association (MDDA).

Patient education and informed consent are important legal and ethical imperatives that are also critical to the success of a course of treatment with psychotropic medications. If the capacity of the patient to make his or her own decisions fluctuates or is questionable, the clinician should obtain the patient's permission to include family or other patient-appointed persons in important treatment decisions. When a patient is clearly not competent to make such decisions, formal legal mechanisms for substituted judgment should be used. Such mechanisms, however, in no way diminish the importance of educating a patient about medications and target symptoms to the fullest extent possible. When one presents recommendations to a patient about medications, information about diagnosis, target symptoms, treatment options, and anticipated means of follow-up should be included, as well as the medication's name, class, and dosing instructions. Side effects that are common (e.g., dry mouth, nausea, tremor, drowsiness, sexual dysfunction, and weight gain) should be reviewed together with side effects that are uncommon but require immediate attention, such as a hypertensive crisis on a monoamine oxidase inhibitor (MAOI), dystonia on an antipsychotic, or a rapidly progressing rash on lamotrigine. Patients should be specifically cautioned about the risks of abrupt discontinuation of a psychotropic drug. Dietary and drug restrictions must be clearly described and, particularly in the case of MAOIs, should be provided in written form as well.

In the context of urgent, life-threatening conditions (such as acute mania), counseling about some potential adverse effects, particularly those not anticipated in the foreseeable future (e.g., tardive dyskinesia or perinatal risks), can be deferred until greater clinical stability is achieved and the risks and benefits of longer-term treatment can be meaningfully addressed.

All too often omitted in discussions preceding the initiation of medications is clear information about the anticipated time course of response (whether to anticipate improvement in hours or weeks), the anticipated length of treatment, and the ready availability of strategies to address side effects or lack of efficacy. A patient's reluctance to initiate treatment might arise from a variety of concerns, including the fear that medication will be stigmatizing, might engender physical or psychological dependence, will be "mind-altering" or personality transforming, is being used to mask a problem rather than treat it, implies consignment to lifelong treatment, or reflects a narrow therapeutic philosophy. The faithfulness of a patient to a recommended course of treatment is invariably strengthened by a physician's dedicated efforts to elicit and address misgivings and potential misunderstandings at the outset. Referral to relevant pamphlets, websites, and books on diagnosis and treatment are often welcomed by patients and family members as a source of more detailed information, particularly when longer-term treatment is anticipated.

Selecting and Administering Medication

Fortunately, for the majority of psychiatric disorders, there exist at least several agents within a single class that are known to have roughly equivalent efficacy. Decisions regarding choice of a particular medication for a

patient should give considerable weight to previous treatment response and the current feasibility of the medication in terms of cost, tolerability, and complexity of dosing. Anticholinergic, hypotensive, and sedative effects of drugs must be considered carefully, particularly when prescribing medications to elderly patients or patients who are medically frail.

Once a drug is chosen, the goal should be to achieve a full trial with adequate dosages and an adequate duration of treatment. Inadequate dosing and duration count among the principal factors in treatment failure for patients with accurate diagnoses. In the service of decisions regarding a patient's care weeks or months later, it is crucial to document whether a trial of medication succeeded, failed, or was abbreviated because of clinical deterioration, medication side effects, poor adherence to treatment, or drug abuse. Suffering is unnecessarily prolonged and resources are poorly used when medications that were previously ineffective have been tried again because of inadequate documentation of failure or when medications that could have been effective are avoided because previous trials of those medications had not been flagged as having been incomplete.

Medication dosages should be adjusted to determine the lowest effective dosage and the simplest regimen. There is significant variability among individual patients with respect to response, blood levels, the expression of side effects, and the development of toxicity, such that the recommended dosage ranges provide only a general guide. Documentation of a patient's response to a particular dosage becomes a much more meaningful reference point for future treatment. As a rule, elderly patients should be started on lower dosages than younger patients, and the interval between dosage changes should be longer because the time to achieve steady-state levels is often prolonged. In the elderly, often there is also prolonged storage of medication and active metabolites in body tissues. Nevertheless, the goal of reaching an effective dosage must be pursued with equal determination in elderly as in younger patients.

For patients with chronic psychiatric conditions, exacerbation of symptoms might prompt increases in the dosages of medications or addition of other medications. So too, for patients presenting acutely with severe disorders, medication dosages may be titrated up more rapidly than usual or combined with other psychotropic medications at an early point such that the lowest effective dosage and simplest regimen is likely to be unclear. Under these circumstances, re-evaluation for cautious reduction of dosage when an appropriate interval of stability has followed should be routine. When a patient's care is likely to be transferred to another clinician or another setting, such as a chronic care facility or a community health center, it is essential that such a plan be communicated to the accepting clinical staff to avoid committing a patient to long-term treatment with dosages or regimens that are excessive.

The attentive management of side effects plays an important role in developing a therapeutic alliance and improving the quality of life for a patient who may be on psychopharmacologic treatment for months or years. Although some adverse events require immediate discontinuation of the drug (e.g., serotonin syndrome or neuroleptic malignant syndrome [NMS]), most can be addressed initially with a dosage reduction, modification in the timing or by dividing doses, taking the medication with or without food, a change in the preparation of medication (e.g., from valproic acid to divalproex sodium), or guidance about sleep hygiene, exercise, or diet (e.g., caffeine, fluids, or fiber). When such measures prove unhelpful in addressing a side effect that is causing distress or that poses a safety risk, other measures must be considered, such as prescribing bethanechol for urinary retention on tricyclic antidepressants (TCAs) or sildenafil for sexual dysfunction on SSRIs, or replacing the offending medication with a more tolerable agent. For side effects that are likely to be transient and not dangerous, a patient's understanding that a variety of straightforward strategies are available in the case of persistence or worsening may be enough to help the patient endure the side effects until they subside.

It is best to avoid responding to short-term crises with long-term changes in medication. The decision to discontinue a successful antidepressant and substitute another in the setting of despair and insomnia following a traumatic event offers the patient only the prospect of benefit from the new medication weeks hence while currently depriving the patient of active treatment known to have been effective. Although it may seem tempting to respond proportionally to a patient's marked distress with a fundamental change in established treatment, exacerbations that are thought likely to be transient are most reasonably addressed with interventions that are short term and focused coupled with adequate follow-up.

Approach to Treatment Failure

Lack of improvement, clinical worsening, or the emergence of unexpected symptoms require a concerted re-evaluation of diagnosis, dosage, drugs, and disruptions. Some patients require combined-medication regimens.

Diagnosis

Among at least one third of patients with major psychiatric disorders, initial treatment fails to bring about significant improvement despite accurate diagnosis. Nevertheless, treatment failure should motivate a careful review of history, initial presentation, and symptoms that seem incongruous with the provisional diagnosis (e.g., confusion in a patient with a seemingly mild depression; olfactory hallucinations in a patient presenting with panic attacks). A patient with fatigue out of proportion to other depressive symptoms might have a primary sleep disorder, such as obstructive sleep apnea. A depressed and cachectic elderly patient who fails to improve despite a series of adequate courses of antidepressant might turn out to have a psychotic depression, early dementia, carcinoma, or a frontal lobe tumor. An adolescent with obsessive–compulsive disorder who appears increasingly bizarre and erratic on an SSRI might have an undiagnosed bipolar disorder exacerbated by the antidepressant.

Dosage

Apparent treatment refractoriness is often the result of prescribing subtherapeutic dosages or the patient's noncompliance, and when treatment fails, the onus is on the clinician to confirm the adequacy of the dosage. Whenever

possible, blood levels of prescribed medications help establish whether a patient is taking the medications and, for medications with established dosage ranges (e.g., lithium, anticonvulsants, TCAs, but not generally antipsychotics or SSRIs or other newer-generation antidepressants), whether the medication dosages are likely to be in a therapeutic range. When adequate dosages of a drug prescribed to a conscientious patient fail to achieve consistent plasma concentrations or clinical response, the clinician must consider factors that affect drug metabolism, such as cigarette smoking, chronic alcohol use, or use of concurrent medications that result in lower levels of the drug. Less commonly, patients experience clinical deterioration after changes in their prescription brand, such as when generic preparations are substituted for brand name medications, causing variation in the bioavailability of the active agent.

Drugs

Many patients compartmentalize their use of medications and forget to mention as-needed or over-the-counter (OTC) medications or treatments prescribed in different settings. When psychopharmacologic treatments fail, a careful re-evaluation of the patient's current nonpsychiatric medication use is warranted. Thus, a patient whose panic disorder responds incompletely to full dosages of a high-potency benzodiazepine may be unaware that his or her condition is aggravated by use of a β-agonist inhaler or a sympathomimetic decongestant. So, too, a patient with bipolar disorder, previously stabilized on lithium but now presenting with hypomania, might not have realized the importance of reporting the initiation of prednisone for a flare of inflammatory bowel disease.

It has become increasingly apparent that widely consumed herbal and other natural remedies marketed as dietary supplements (e.g., St. John's wort) can participate in clinically important drug interactions[15,16]; the possibility of such interactions may be easily missed, however, because the use of alternative and complementary therapies is typically reported by patients only on direct inquiry by their clinician. Details of alcohol and illicit drug use must also be carefully elicited as factors that, when excessive, often masquerade as, and at the very least exacerbate, other psychiatric disorders and can jeopardize the safety and efficacy of pharmacotherapy.

Disruptions

Although psychosocial stressors are not an excuse for psychopharmacologic nihilism, neither can they be meaningfully ignored as potential impediments to treatment. Incomplete remission of depressive symptoms in a patient living with an alcoholic spouse or of a psychotic exacerbation in a patient with schizophrenia whose community residential treatment facility has closed should be met both by aggressive efforts to ensure the adequacy of pharmacologic treatment and by equally determined efforts to develop a plan to address the environmental factors that appear to be compromising a patient's recovery.

Combined Therapy

In clinical practice, many patients—particularly the elderly, the medically ill, or the medically complex—receive multiple medications. Moreover, general medical co-morbidity is common among patients with psychiatric disorders, elevating the likelihood of complex medication regimens and polypharmacy.[17]

The term *polypharmacy* has taken on a pejorative connotation in recent years suggesting a thoughtless, irrational, or non–evidence-based approach to the prescribing of medicine. Polypharmacy puts patients at risk due to an increased likelihood of adverse medication reactions and drug–drug interactions. In contrast, "rational" or "strategic" combined psychopharmacologic approaches can be used for the treatment of psychiatric or medical co-morbidity, as an augmentation strategy for patients with an insufficient response to a single agent, and for the management of treatment-emergent adverse effects.[18] Examples of the rational use of combined treatment include the addition of a benzodiazepine to an SSRI to hasten treatment response in panic disorder[19] or the use of lithium and a medication for attention-deficit/hyperactivity disorder (ADHD) to treat co-occurring bipolar disorder and ADHD.[20]

Therefore, a patient's use of two or more psychotropic medications ought not be viewed reflexively as in need of dismantling. One patient might arrive at a precisely adjusted, albeit complicated, regimen through a series of careful trials guided by a single experienced clinician, whereas another may accumulate multiple medications in a haphazard fashion across diverse treaters and settings. For the former patient, even a modest dosage change can result in a severe relapse that threatens the patient's safety or livelihood, whereas for the latter, a directed plan to taper medications and perhaps even to "start from scratch" is likely to be most helpful.

Discontinuing Medications

The discontinuation of psychotropic drugs must be carried out with as much care as their initiation. For patients on complicated regimens of psychotropic medications, periodic review for dosage reduction and potential discontinuation must be standard. Because data providing guidelines for drug discontinuation are scarce, the process is often empirical. Successful discontinuation, therefore, relies heavily on a good knowledge of a patient's history together with adequate follow-up.

Assessment of a patient for discontinuing a drug involves appreciating the short-term risks of rebound and withdrawal as well as the long-term risks of relapse and recurrence. Rebound effects are the transient return of symptoms for which a medication has been prescribed (e.g., insomnia or anxiety), and withdrawal effects are the development of new symptoms characteristic of abrupt cessation of the medication, such as muscle spasms, delirium, or seizures following discontinuation of high-dosage benzodiazepine; hot flushes, nausea, unusual shock-like sensations, or malaise following discontinuation of an antidepressant.

To make sound decisions regarding the re-instatement of medications, it is essential to distinguish rebound and withdrawal effects from relapse. *Relapse* is typically a persistent rather than self-limited state associated with a more-delayed onset, and the re-emergence of clinically significant symptoms of the underlying illness in the absence of (or sometimes despite the continuation of) active treatment. The return of daily panic attacks after a remission of

several months and an exacerbation of psychosis requiring hospitalization after 2 years of exclusively outpatient treatment are examples of relapse.

For disorders that can occur episodically, such as major depression, the term *relapse* refers more precisely to the recrudescence of symptoms during an initial period of remission, whereas the additional term *recurrence* refers to return of symptoms following a defined period of full remission (at least 4 to 6 months) on or off continued treatment. In the case of recurrence, the reappearing symptoms are conceptualized as denoting a new episode rather than a continuation of the one previously treated.

In parallel with the concepts of relapse and recurrence, continuation of treatment refers to the ongoing use of medication prescribed to consolidate a remission of symptoms brought about by an initial (acute) phase of treatment to prevent relapse. *Maintenance treatment* refers to a more extended course of medication thereafter aimed at preventing recurrences and is reserved for patients with an illness characterized by chronicity, past recurrences, or particular severity. For major depression, acute treatment is typically in the range of 6 to 12 weeks, whereas continuation treatment extends 4 to 6 months beyond that point, and maintenance treatment may extend a further 1 to 5 years or more depending on the clinical context. Although antidepressants appear to be more effective than placebo during long-term treatment, the number of controlled antidepressant trials focusing on treatment of depression beyond the first year remains quite limited.[21]

A taper of medications over 48 to 72 hours is typically adequate to minimize the risk of rebound or withdrawal. With respect to relapse or recurrence, however, patients at risk may well benefit from a more protracted, carefully monitored taper of medications. This allows rapid re-instatement of full-dosage treatment at the early signs of worsening to avert a more serious escalation. Analyses of discontinuation of lithium[22,23] and antipsychotic agents[24] suggest that a too-rapid cessation of psychotropic medications can, in fact, increase the risk of relapse when compared with a more gradual taper. Findings such as these suggest that for elective discontinuation of psychotropic medications, a taper lasting at least 2 to 4 weeks should be considered.

With patients for whom the consequences of relapse are likely to be severe (e.g., most patients with bipolar and psychotic disorders), an extended taper with dosage reductions of no more than 25% at intervals of no less than 4 to 6 weeks is likely to be a more prudent course. For patients who have anxiety disorders and are maintained on high-potency benzodiazepines, the introduction of a targeted course of therapy (e.g., a cognitive–behavioral panic disorder group) in preparation for a drug taper is likely to further reduce the risks of relapse (see Chapter 13).

Far from being an afterthought, decisions regarding the timing and pace of drug discontinuation should be regarded as an integral part of psychopharmacologic management and remain an important topic for further study.

PHARMACOKINETICS

Pharmacokinetic processes refer to absorption, distribution, metabolism, and excretion, factors that determine plasma levels of a drug and the local availability of drug to biologically active sites—in short, what the body does to the drug. Pharmacokinetics also refers to the mathematical analysis of these processes. Advances in analytic chemistry and computer methods of pharmacokinetic modeling[4,25,26] and a growing understanding of the molecular pharmacology of the hepatic isoenzymes responsible for metabolizing most psychotropic medications have furnished increasingly sophisticated insights into the disposition and interaction of administered drugs.

Because the pharmacokinetics of a medication are subject to myriad influences, including age, genes, gender, diet, disease states, and concurrently administered drugs, a working knowledge of pharmacokinetic principles is of particular relevance to psychopharmacology in medical settings. Although pharmacokinetics refers to only one of the two broad mechanisms by which drugs interact, pharmacokinetic interactions involve all classes of psychotropic and nonpsychotropic medications. An overview of pharmacokinetic processes is a helpful prelude to a discussion of specific drug–drug interactions.

Absorption

Factors that influence drug absorption are generally of less importance in determining the pharmacokinetic properties of psychiatric medications than factors influencing subsequent drug disposition (e.g., drug metabolism). The term *absorption* refers to processes that generally pertain to orally (rather than parenterally) administered drugs, for which alterations in gastrointestinal (GI) drug absorption can affect the rate (time to reach maximum concentration) or the extent of absorption, or both. The extent or completeness of absorption, also known as the *fractional absorption*, is measured as the area under the curve (AUC) when plasma concentration is plotted against time. The bioavailability of an oral dose of drug refers, in turn, to the fractional absorption for orally compared with intravenously (IV) administered drug. If an agent is reported to have a 90% bioavailability (e.g., lorazepam), this indicates that the extent of absorption of an orally administered dose is nearly that of an IV-administered dose, although the rate of absorption may well be slower for the oral dose.

Because the upper part of the small intestine is the primary site of drug absorption through passive membrane diffusion and filtration and both passive and active transport processes, factors that speed gastric emptying (e.g., metoclopramide) or diminish intestinal motility (e.g., opiates or cannabis) can facilitate greater contact with, and absorption from, the mucosal surface into the systemic circulation, potentially increasing plasma drug concentrations. Conversely, antacids, charcoal, kaolin-pectin, and cholestyramine can bind to drugs, forming complexes that pass unabsorbed through the GI lumen.

Changes in gastric pH associated with food or other drugs alter the nonpolar, un-ionized fraction of drug available for absorption. In the case of drugs that are very weak acids or bases, however, the extent of ionization is relatively invariant under physiologic conditions. Properties of the preparation administered (e.g., tablet, capsule, or liquid) can also influence the rate or extent of absorption and, for an increasing number of medications (e.g., lithium, bupropion, quetiapine, and methylphenidate), preparations intended for slow release are available.

The local action of enzymes in the GI tract (e.g., monoamine oxidase [MAO] and cytochrome P450 [CYP] 3A4) may be responsible for metabolism of drug before absorption. This is of critical relevance to the emergence of hypertensive crises that occur when excessive quantities of the dietary pressor tyramine are systemically absorbed in the setting of irreversible inhibition of the MAO isoenzymes for which tyramine is a substrate.

Following gut absorption, but before entry into the systemic circulation, many psychotropic drugs are subject to first-pass liver metabolism. Therefore, conditions that affect hepatic metabolism of drug (e.g., primary liver disease) or conditions that impede portal circulation (e.g., congestive heart failure) are likely to increase the fraction of drug available for distribution for the majority of psychotropic drugs, thereby contributing to clinically significant increases in plasma levels of drug.

Distribution

Drugs distribute to tissues through the systemic circulation. The amount of drug ultimately reaching receptor sites in tissues is determined by a variety of factors, including the concentration of free (unbound) drug in plasma, regional blood flow, and physiochemical properties of drug (e.g., lipophilicity or structural characteristics). For entrance into the CNS, penetration across the blood–brain barrier is required. Fat-soluble drugs (e.g., benzodiazepines, antipsychotics, and cyclic antidepressants) distribute more widely in the body than water-soluble drugs (e.g., lithium), which distribute through a smaller volume of distribution. Changes with age, typically including an increase in the ratio of body fat to lean body mass, therefore, result in a net greater volume of lipophilic drug distribution and potentially greater accumulation of drug in adipose tissue in older than in younger patients. A similar potential exists for female compared with male patients because of their generally higher ratio of adipose tissue to lean body mass.[27]

In general, psychotropic drugs have relatively high affinities for plasma proteins (some to albumin but others, such as antidepressants, to α-acid glycoproteins and lipoproteins). Most psychotropic drugs are more than 80% protein-bound. A drug is considered highly protein-bound if more than 90% exists in bound form in plasma. Fluoxetine, aripiprazole, and diazepam are examples of the many psychotropic drugs that are highly protein-bound. In contrast, venlafaxine, lithium, topiramate, zonisamide, gabapentin, pregabalin, and memantine are examples of drugs with minimal protein binding and therefore minimal risk of participating in drug–drug interactions related to protein binding.

A reversible equilibrium exists between bound and unbound drug. Only the unbound fraction exerts pharmacologic effects. Competition by two or more drugs for protein-binding sites often results in displacement of a previously bound drug, which, in the free state, becomes pharmacologically active. Similarly, reduced concentrations of plasma proteins in a severely malnourished patient or a patient with a disease that is associated with markedly lowered serum proteins (e.g., liver disease or the nephrotic syndrome) may be associated with an increase in the fraction of unbound drug potentially available for activity at relevant receptor sites. Under most circumstances, the net changes in plasma concentration of active drug are, in fact, quite small because the unbound drug is available for redistribution to other tissues and for metabolism and excretion, thereby offsetting the initial rise in plasma levels. It is important to be aware, however, that clinically significant consequences can develop when protein-binding interactions alter the unbound fraction of previously highly protein-bound drugs that have a low therapeutic index (e.g., warfarin). For these drugs, relatively small variations in plasma level may be associated with serious untoward effects.

An emerging understanding of the drug-transport proteins, of which P-glycoproteins are the best characterized, indicates a crucial role in regulating permeability of intestinal epithelia, lymphocytes, renal tubules, biliary tract, and the blood–brain barrier. These transport proteins are thought to account for the development of certain forms of drug resistance and tolerance, but they are increasingly seen as likely also to mediate clinically important drug interactions.[4,28] Little is known yet about their relevance to drug interactions involving psychiatric medications; the capacity of St. John's wort to lower blood levels of several critical medications (including cyclosporine and indinavir) is hypothesized to be related, at least in part, to an effect of the botanical agent on this transport system.[15]

Metabolism

Metabolism is the best-characterized mechanism of all of the pharmacokinetic processes implicated in drug–drug interactions. *Metabolism* refers to the biotransformation of a drug to another form, a process that is usually enzyme mediated and results in a metabolite that might or might not be pharmacologically active and might or might not be subject to further biotransformations before eventual excretion. Most drugs undergo several types of biotransformation, and many psychotropic drug interactions of clinical significance are based on interference with this process. A growing understanding of hepatic enzymes, and especially the rapidly emerging characterization of the CYP isoenzymes and other enzyme systems including the uridine-diphosphate glucuronosyltransferases (UGTs) and flavin-containing monooxygenases (FMOs),[4,29–31] has significantly advanced a rational understanding and prediction of drug interactions and individual variation in drug responses.

Phase I reactions include oxidation (e.g., hydroxylation or dealkylation), reduction (e.g., nitro reduction), and hydrolysis, metabolic reactions typically resulting in intermediate metabolites that are then subject to phase II reactions, including conjugation (e.g., glucuronide and sulfate) and acetylation. Phase II reactions typically yield highly polar, water-soluble metabolites suitable for renal excretion. Most psychotropic drugs undergo both phase I and phase II metabolic reactions. Notable exceptions are lithium, which is not subject to hepatic metabolism, and a subset of the benzodiazepines (lorazepam, oxazepam, and temazepam), which undergo only phase II reactions and are therefore especially appropriate when benzodiazepines are used in the context of concurrent medications, advanced age, or disease states in which alterations of hepatic metabolism is likely to be substantial.

The synthesis or activity of hepatic microsomal enzymes is affected by metabolic inhibitors and inducers, as well as distinct genetic polymorphisms (stably inherited traits). Table 34–1 lists enzyme inducers and inhibitors common in clinical settings. These should serve as red flags that beckon further scrutiny for potential drug–drug interactions when they are found on a patient's medication list. In some circumstances an inhibitor (e.g., grapefruit juice) or an inducer (e.g., a cruciferous vegetable, such as Brussels sprouts) is a drug but it may be another ingested substance.

Inhibitors impede the metabolism of a concurrently administered drug, producing a rise in its plasma level, whereas inducers enhance the metabolism of another drug, resulting in a decline in its plasma levels. Although inhibition is usually immediate, induction, which requires enhanced synthesis of the metabolic enzyme, is typically a more gradual process. A fall in plasma levels of a substrate might not be apparent for days to weeks following introduction of the inducer. This is particularly important to keep in mind when a patient's care is being transferred to another setting where clinical deterioration may be the first sign that drug levels have declined. Reciprocally, an elevation in plasma drug concentrations could reflect the previous discontinuation of an inducing factor (e.g., cigarette smoking or carbamazepine) just as it could reflect the introduction of an inhibitor (e.g., fluoxetine or valproic acid).

Although the CYP isoenzymes represent only one of the numerous enzyme systems responsible for drug metabolism, they are responsible for metabolizing, at least in part, more than 80% of all prescribed drugs. The capacity of many of the SSRI antidepressants to inhibit CYP isoenzymes has fueled great interest in the pattern of interaction of psychotropic and other drugs with these enzymes in the understanding and prediction of drug–drug interactions in psychopharmacology. The CYP isoenzymes represent a family of more than 30 related heme-containing enzymes, largely located in the endoplasmic reticulum of hepatocytes (but also present elsewhere, including gut and brain), which mediate oxidative metabolism of a wide variety of drugs as well as endogenous substances, including prostaglandins, fatty acids, and steroids. The majority of antidepressant and antipsychotic drugs are metabolized by or inhibited by one or more of these isoenzymes. Table 34–2 summarizes the interactions of psychiatric and nonpsychiatric drugs with a subset of isoenzymes that have been increasingly well characterized: CYP 1A2, 2D6, 2E1, 3A4, and the 2C subfamily. In addition to the numerous publications in which these interactions are cited,[4,30,31] several relevant websites are regularly updated, including www.drug-interactions.com and www.mhc.com/Cytochromes. The relevance of these and other interactions is highlighted in a later section of this chapter in which clinically important drug–drug interactions are reviewed.

TABLE 34–1 Commonly Used Drugs and Substances that Inhibit or Induce Hepatic Metabolism of Other Medications[4,30,31]

INHIBITORS	INDUCERS
Antifungals (ketoconazole, miconazole, itraconazole)	Barbiturates (e.g., phenobarbital, secobarbital)
Macrolide antibiotics (erythromycin, clarithromycin, triacetyloleandomycin)	Oxcarbazepine
Fluoroquinolones (e.g., ciprofloxacin)	Phenytoin
Isoniazid	Rifampin
Antiretrovirals	Primidone
Selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline)	Cigarettes
Nefazodone	Ethanol (chronic)
β-blockers (lipophilic), e.g., propranolol, metoprolol, pindolol	Cruciferous vegetables
Quinidine	Charbroiled meats
Valproate	St. John's wort
Cimetidine	
Calcium channel blockers (e.g., diltiazem)	
Grapefruit juice	
Ethanol (acute)	

Knowledge continues to evolve concerning genetic polymorphisms that affect drug metabolism. Within the group of CYP isoenzymes, there appears to be a polymodal distribution of metabolic activity in the population with respect to certain isoenzymes (including CYP 2C19 and 2D6). Most people are normal (extensive) metabolizers with respect to the activity of these isoenzymes. A smaller number are poor metabolizers, with deficient activity of the isoenzyme. Probably very much smaller numbers are ultrarapid metabolizers, who have more than normal activity of the enzyme, and intermediate metabolizers, who fall between extensive and poor metabolizers. Persons who are poor metabolizers with respect to a particular CYP isoenzyme are expected to have higher plasma concentrations of a drug that is metabolized by that isoenzyme, thereby potentially being more sensitive to or requiring lower dosages of that drug than a patient with normal activity of that enzyme. These patients might also have higher-than-usual plasma levels of metabolites of the drug that are produced through other metabolic pathways that are not altered by the polymorphism, thereby potentially incurring pharmacologic activity or adverse effects related to these alternative metabolites.

Studies on genetic polymorphisms affecting the CYP system suggest ethnic differences.[32,33] Approximately 15% to 20% of Asian Americans and African Americans appear to be poor metabolizers with respect to CYP 2C19 compared with 3% to 5% of whites. Conversely, the proportion of frankly poor metabolizers with respect to CYP 2D6 appears to be higher among white (approximately 5% to 10%) than among Asian Americans and African Americans (approximately 1% to 3%). Current understanding of the clinical relevance of genetic polymorphisms in drug therapy in psychiatry remains rudimentary. Commercial genotyping tests for polymorphisms of potential relevance to drug metabolism are increasingly available. For the use of certain drugs, notably carbamazepine, the U.S. Food and Drug Administration (FDA) recommends genotyping Asians for the *HLA B*1502* allele owing to data[34] implicating the allele as a marker for carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis in Han Chinese.[35]

TABLE 34–2 Selected Cytochrome P450 Isoenzyme Substrates, Inhibitors, and Inducers*[4,30,31]

ISOENZYME	SUBSTRATES	INHIBITORS	INDUCERS
1A2	Acetaminophen, aminophylline, caffeine, clozapine, cyclobenzaprine, estradiol, fluvoxamine, haloperidol, mirtazapine, olanzapine, phenacetin, procarcinogens, propranolol, ramelteon, riluzole, ropinirole, tacrine, TCAs, theophylline, verapamil, warfarin, zileuton, zolmitriptan	Amiodarone, cimetidine, fluoroquinolones, fluvoxamine, grapefruit juice, methoxsalen, ticlopidine	Charbroiled meats, cigarette smoking (tobacco), cruciferous vegetables, modafinil, omeprazole
2C	Barbiturates, diazepam, fluvastatin, glipizide, glyburide, irbesartan, losartan, mephenytoin, NSAIDs, nelfinavir, phenytoin, primidone, proguanil, propranolol, proton pump inhibitors, rosiglitazone, tamoxifen, tertiary TCAs, THC, tolbutamide, warfarin	Fluoxetine, fluvoxamine, ketoconazole, modafinil, omeprazole, oxcarbazepine, sertraline	Carbamazepine, norethindrone, prednisone, rifampin, secobarbital
2D6	Aripiprazole, atomoxetine, β-blockers (lipophilic), codeine, debrisoquine, dextromethorphan, diltiazem, donepezil, duloxetine, encainide, flecainide, haloperidol, hydroxycodone, lidocaine, metoclopramide, mexiletine, mCPP, nifedipine, odansetron, phenothiazines (e.g., thioridazine, perphenazine), propafenone, risperidone, SSRIs, tamoxifen, TCAs, tramadol, trazodone, venlafaxine	Amiodarone, antimalarials, bupropion, cimetidine, citalopram, duloxetine, escitalopram, fluoxetine, methadone, metoclopramide, moclobemide, paroxetine, phenothiazines, protease inhibitors (ritonavir), quinidine, sertraline, terbinafine, TCAs, yohimbine	Dexamethasone, rifampin
3A3, 3A4	Alfentanil, alprazolam, amiodarone, amprenavir, aripiprazole, bromocriptine, buspirone, cafergot, calcium channel blockers, caffeine, carbamazepine, cisapride, clozapine, cyclosporine, dapsone, diazepam, disopyramide, efavirenz, estradiol, fentanyl, indinavir, HMG-CoA reductase inhibitors (lovastatin, simvastatin), lidocaine, loratadine, methadone, midazolam, nimodipine, pimozide, prednisone, progesterone, propafenone, quetiapine, quinidine, ritonavir, sildenafil, tacrolimus, testosterone, tertiary TCAs, triazolam, vinblastine, warfarin, zaleplon, ziprasidone, zolpidem, zonisamide	Antifungals, calcium channel blockers, cimetidine, efavirenz, indinavir, fluoxetine (norfluoxetine), fluvoxamine, grapefruit juice, macrolide antibiotics, mibefradil, nefazodone, ritonavir, verapamil, voriconazole	Carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifampin, ritonavir, St. John's wort, troglitazone

*Drugs.com: *Drug interactions checker*. Retrieved from www.drugs.com/drug_interactions.php. Accessed February 12, 2010.

HMG-CoA, Hydroxy-methylglutaryl co-enzyme A; *mCPP*, m-chlorophenylpiperazine; *NSAID*, nonsteroidal antiinflammatory drug; *SSRI*, selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant; *THC*, tetrahydrocannabinol.

Systematic study of genetic polymorphisms and their relevance to the prediction of drug response is needed before additional testing can be meaningfully incorporated into routine psychopharmacologic practice.

Excretion

Because most antidepressant, anxiolytic, and antipsychotic medications are largely eliminated by hepatic metabolism, factors that affect renal excretion (glomerular filtration, tubular reabsorption, and active tubular secretion) are generally far less important to the pharmacokinetics of these drugs than to lithium, for which such factors can have clinically significant consequences. Conditions resulting in sodium deficiency (e.g., dehydration, sodium restriction, and use of thiazide diuretics) are likely to result in increased proximal tubular reabsorption of lithium, resulting in increased lithium levels and potential toxicity. Lithium levels and clinical status must be monitored especially closely in the setting of vomiting, diarrhea, excessive evaporative losses, or polyuria. Factors, such as aging, that are associated with reduced renal blood flow and glomerular filtration rate (GFR) also reduce lithium excretion. For this reason, as well as for their reduced volume of distribution for lithium because of the relative loss of total body water with aging, elderly patients typically require lower lithium dosages than younger patients, and a low starting dosage (i.e., 150 to 300 mg/day) is often prudent. Apparently separate from pharmacokinetic effects, however, elderly patients may also be more sensitive to the

neurotoxic effects of lithium even at low therapeutic levels. Factors associated with an increased GFR, particularly pregnancy, can produce an increase in lithium clearance and a fall in lithium levels.

For other medications, renal excretion can sometimes be exploited in the treatment of a drug overdose. Acidification of the urine by ascorbic acid, ammonium chloride, or methenamine mandelate increases the rate of excretion of weak bases such as the amphetamines and phencyclidine (PCP). Therefore, such measures may be important in the emergency management of a patient with severe phencyclidine or amphetamine intoxication. Conversely, alkalinization of the urine by administration of sodium bicarbonate or acetazolamide can hasten the excretion of weak acids including long-acting barbiturates, such as phenobarbital.

Mildly to moderately impaired renal function does not typically prompt routine changes in the dosage or dosing intervals of psychotropic medications other than lithium. Increased plasma concentrations of hydroxylated metabolites of TCAs have been measured in patients with kidney disease and patients on dialysis, and more modest increases in TCA plasma levels have been measured in patients on dialysis.[36] The clinical significance of these findings, however, appears to be limited to suggesting more cautious dosage titration and surveillance in the patient with kidney disease rather than routine dosage adjustments. A similar empirical strategy is prudent for use of SSRIs, as well as for most antipsychotic medications and anxiolytics. In patients with severe impairment of kidney function, however, there may be accumulation of metabolites and, to a lesser extent, of the parent compound across repeated doses. An increase in the dosing interval and possible reduction in drug dosage should therefore be considered in this setting, particularly in the case of chronically administered agents with active metabolites.

Renal excretion is only one contribution to the *elimination half-life*, a pharmacokinetic construct that refers to the time required for the plasma concentration of a drug to be reduced by one half. The elimination phase (also referred to as the β-phase) reflects all processes that contribute to drug removal, including renal excretion, hepatic metabolism, and, to a much lesser extent, other factors (e.g., loss of drug in sweat or biliary secretions) potentially affecting drug clearance (the volume of blood or plasma cleared of drug per unit time). For the majority of drugs, whose elimination follows first-order kinetics (i.e., their rate of elimination is proportional to the amount of drug in the body rather than equal to a constant amount), steady-state drug levels are reached in four to five elimination half-lives, whereas, on discontinuation, almost all drug is out of the body within five half-lives.

For drugs that are administered for their single-dose effects (e.g., an as-needed benzodiazepine) rather than for long-term effects of repeated administration (e.g., antidepressants), the duration of action of the drug depends not only on elimination half-life but also often more critically on the initial phase of drug redistribution from the systemic circulation to other tissues, such as muscle and fat.

DRUG INTERACTIONS

The scientific literature on psychotropic drug–drug interactions has grown immensely since first reviewed in the *Massachusetts General Hospital Handbook of General Hospital Psychiatry* in 1978.[37] Despite impressive advances in clinical and molecular pharmacology, much of the literature on drug–drug interactions remains a patchwork of case reports, postmarketing analyses, extrapolation from animal and *in vitro* studies, and inferences based on what is known about other drugs with similar properties. Fortunately, well-designed studies of drug–drug interactions are an increasingly integral part of drug development.

Drug–drug interactions refer to alterations in drug levels or drug effects (or both) attributed to the administration of two or more prescribed, illicit, or OTC agents in close temporal proximity. Although many drug–drug interactions involve drugs administered within minutes to hours of each other, some drugs can participate in interactions days or even weeks after they are discontinued because of prolonged elimination half-lives (e.g., fluoxetine) or owing to their long-term impact on metabolic enzymes (e.g., carbamazepine). Some drug–drug interactions involving psychotropic medications are life-threatening, such as those involving the co-administration of MAOIs and drugs with potent serotoninergic (e.g., meperidine) or sympathomimetic (e.g., phenylpropanolamine) effects.[38] These combinations are therefore absolutely contraindicated.

However, most drug–drug interactions in psychopharmacology manifest in somewhat more subtle ways, often leading to poor medication tolerability and compliance due to adverse events (e.g., orthostatic hypotension, sedation, or irritability), diminished medication efficacy, or puzzling manifestations such as altered mental status or unexpectedly high or low drug levels. Drug combinations that can produce these often less-catastrophic drug–drug interactions are usually not absolutely contraindicated. Some of these combinations may, indeed, be valuable in the treatment of some patients though wreaking havoc for other patients. The capacity to anticipate and to recognize both the major, but rare, and the more subtle, but common, potential drug–drug interactions allows the practitioner to minimize the impact of these interactions as an obstacle to patient safety and to therapeutic success.

It is crucial to be familiar with the small number of drug–drug interactions in psychopharmacology that, though uncommon, are associated with potentially catastrophic consequences. These include drugs associated with ventricular arrhythmias, hypertensive crisis, serotonin syndrome, Stevens–Johnson syndrome, seizures, and severe bone marrow suppression. In addition, drug–drug interactions are important to consider when a patient's drugs include those with a low therapeutic index (e.g., lithium, digoxin, or warfarin) or a narrow therapeutic window (e.g., indinavir, nortriptyline, or cyclosporine) such that relatively small alterations in pharmacokinetic or pharmacodynamic behavior can jeopardize a patient's well-being. In addition, it is worthwhile to consider potential drug–drug interactions whenever evaluating a patient whose drug levels are unexpectedly variable or extreme or a patient with a confusing clinical picture (such as clinical deterioration) or with unexpected side effects. Finally, drug–drug interactions are likely to be clinically salient for a patient who is medically frail or elderly, owing to altered pharmacokinetics and vulnerability to side effects, as well as for a patient who is heavily using alcohol, cigarettes, or illicit drugs or who is being treated for a drug overdose.

Given the increasing acceptance of combined pharmacotherapeutic regimens for many difficult-to-treat disorders,[39] the vast literature of reported and potential drug–drug interactions, and the increasingly litigious society in which physicians practice, the physician today is faced with a dilemma when evaluating the potential significance of drug–drug interactions. Fortunately, an increasing range of resources are available, including prescribing software packages and regularly updated websites (such as www.drug-interactions.com) that allow the prevention and detection of potential interactions.

Numerous factors contribute to interindividual variability in drug response.[26,40] These factors include treatment adherence, age, gender, nutritional status, disease states, and genetic polymorphisms that can influence risk of adverse events and treatment resistance**.** Drug–drug interactions are an additional factor that influences how patients react to drugs. The importance of these interactions depends heavily on the clinical context. In many cases, the practical impact of drug–drug interactions is likely to be very small compared with other factors that affect treatment response, drug levels, and toxicity. It is reasonable therefore to focus special attention on commonly used classes of drugs and the contexts in which drug–drug interactions are most likely to be clinically problematic.

Antipsychotic Drugs

The antipsychotic or neuroleptic drugs, used in the treatment of schizophrenia, schizoaffective disorder, organic psychoses, mood disorders, and an increasingly broad range of other psychiatric conditions, include the phenothiazines (e.g., chlorpromazine, fluphenazine, perphenazine, thioridazine, and trifluoperazine), butyrophenones (haloperidol), thioxanthenes (thiothixene), indolones (molindone), diphenylbutylpiperidines (pimozide), dibenzodiazepines (loxapine), and the newer atypical agents (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone). As a class, they are generally rapidly, if erratically, absorbed from the GI tract after oral administration (peak plasma concentrations ranging from 30 minutes to 6 hours). They are highly lipophilic and distribute rapidly to body tissues with a large apparent volume of distribution. Protein-binding in the circulation ranges from approximately 90% to 98%, except for molindone and quetiapine, which are only moderately protein-bound.

The antipsychotics generally undergo substantial first-pass hepatic metabolism (primarily oxidation and conjugation reactions), reducing their systemic bioavailability when given orally compared with intramuscular (IM) administration, the fractional absorption of which nearly approximates that of IV administration. Most of the individual antipsychotics have several pharmacologically active metabolites (e.g., paliperidone is 9-hydroxyrisperidone, the primary active metabolite of risperidone).[41]

Because of their propensity to sequester in body compartments, the elimination half-life of antipsychotics is quite variable, generally ranging from approximately 20 to 40 hours. For butyrophenones, however, elimination pharmacokinetics appears to be especially complex, and the disappearance of drug from the systemic circulation, and even more so from brain, can take much longer,[7,42] as it does for the newer agent, aripiprazole (and its active metabolite, dehydro-aripirazole),[41] whose half-life can exceed 90 hours.

The lower-potency antipsychotics (including chlorpromazine, mesoridazine, thioridazine, and clozapine) are generally the most sedating and have the greatest anticholinergic, antihistaminic, and α_1-adrenergic antagonistic effects, whereas the higher-potency antipsychotics (with the exception of the atypical agent, risperidone), including haloperidol, loxapine, molindone, and the piperazine phenothiazines, such as trifluoperazine, are more likely to be associated with an increased incidence of extrapyramidal symptoms (EPS), including akathisia, dystonia, and parkinsonism.

The atypical antipsychotics generally have multiple receptor affinities, including antagonism at dopamine D_1 to D_4 receptors, serotonin (5-HT) 5-HT_1 and 5-HT_2 receptors, α_1- and α_2-adrenergic receptors, histamine H_1 receptor, and cholinergic muscarinic receptors, with variations across agents. Thus, for example, clozapine and olanzapine have notably greater affinity at the muscarinic receptors than the other agents, and aripiprazole is actually a partial agonist at the D_2 receptor.

Although the more-complex pharmacologic profile of these newer atypical agents, as well as the older low-potency antipsychotics, has generally been associated with a lower risk of EPS, the same broad range of receptor activity also poses greater risk of *pharmacodynamic interactions*. Pharmacodynamic interactions refer to the pharmacologic effects that result from interactions at the same or interrelated biologically active (receptor) sites

Lower-potency drugs, as well as some atypical antipsychotics, can produce significant hypotension when combined with vasodilator or antihypertensive drugs related to α_1-adrenergic blockade (Table 34–3).[42,43] Hypotension can also occur when low-potency antipsychotics and atypical antidepressants are combined with TCA and MAOI antidepressants. Severe hypotension has been reported when chlorpromazine has been administered with the angiotensin-converting enzyme (ACE) inhibitor captopril. Hypotension can develop when epinephrine is administered with low-potency antipsychotics. In this setting, the α-adrenergic stimulant effect of epinephrine, resulting in vasodilation, is unopposed by its usual pressor effect because α_1-adrenergic receptors are occupied by the antipsychotic. A similar effect can result if a low-potency neuroleptic is administered to a patient with pheochromocytoma. Finally, hypotension can develop when low-potency antipsychotics are used in combination with a variety of anesthetics, such as halothane, enflurane, and isoflurane.

In addition, the low-potency antipsychotics (e.g., thioridazine) have quinidine-like effects on cardiac conduction and can prolong Q-T and P-R intervals. Ziprasidone may also cause Q-T prolongation, although clinically significant prolongation (QTc longer than 500 msec) appears to be rare when administered to otherwise healthy subjects.[44] Significant depression of cardiac conduction, heart block, and life-threatening ventricular dysrhythmias can result from co-administering low-potency antipsychotics or ziprasidone with class I antiarrhythmics (e.g., quinidine, procainamide, and disopyramide); it can also result from the TCAs, which have

TABLE 34–3 Selected Drug Interactions with Antipsychotic Medications

DRUG	POTENTIAL INTERACTION
Antacids (aluminum- and magnesium-containing)	Interference with absorption of antipsychotic agents; fruit juice
Carbamazepine	Decreased antipsychotic drug plasma levels; additive risk of myelosuppression with clozapine
Cigarettes	Decreased antipsychotic drug plasma levels; reduced extrapyramidal symptoms
Rifampin	Decreased antipsychotic drug plasma levels; reduced extrapyramidal symptoms
TCAs	Increased TCA and antipsychotic drug plasma levels; hypotension, depression of cardiac conduction (with low-potency antipsychotics)
SSRIs	Increased SSRI and antipsychotic drug plasma levels (see Table 34–7); arrhythmia risk with thioridazine and pimozide
Bupropion, duloxetine	Increased antipsychotic drug plasma levels (see Table 34–2); arrhythmia risk with thioridazine
Fluvoxamine, nefazodone	Increased antipsychotic drug plasma levels (see Table 34–2), arrhythmia risk with pimozide; seizure risk with clozapine
β-blockers (lipophilic)	Increased antipsychotic drug plasma levels; improved akathisia
Anticholinergic drugs	Additive anticholinergic toxicity; reduced extrapyramidal symptoms
Antihypertensive, vasodilator drugs	Hypotension (with low-potency antipsychotics and risperidone)
Guanethidine, clonidine	Blockade of antihypertensive effect
Epinephrine	Hypotension (with low-potency antipsychotics)
Class I antiarrhythmics	Depression of cardiac conduction; ventricular arrhythmias (with low-potency antipsychotics, ziprasidone)
Calcium channel blockers	Depression of cardiac conduction; ventricular arrhythmias (with pimozide)
Lithium	Idiosyncratic neurotoxicity

SSRI, Selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant.

quinidine-like activity on cardiac conduction, and when administered in the context of other aggravating factors including hypokalemia, hypomagnesemia, bradycardia, or congenital prolongation of the QTc. Pimozide also can depress cardiac conduction as a result of its calcium channel–blocking action, and the combination of pimozide with other calcium channel blockers (e.g., nifedipine, diltiazem, and verapamil) is contraindicated.

Another clinically significant pharmacodynamic interaction arises when low-potency antipsychotics, particularly clozapine or olanzapine, are administered with other drugs that have anticholinergic effects, including TCAs, benztropine, and diphenhydramine. When these drugs are combined, there is a greater risk of urinary retention, constipation, blurred vision, impaired memory and concentration, and, in the setting of narrow-angle glaucoma, increased intraocular pressure. With intentional or inadvertent overdoses, a severe anticholinergic syndrome can develop, including delirium, paralytic ileus, tachycardia, and dysrhythmias. With lower affinity for muscarinic cholinergic receptors, the high-potency agents and nonanticholinergic atypical agents (e.g., risperidone) are indicated when anticholinergic effects need to be minimized.

The sedative effects of low-potency agents and atypical antidepressants are also often additive to those of the sedative–hypnotic medications and alcohol. In patients for whom sedative effects may be especially dangerous, including the elderly, the cautious selection and dosing of antipsychotics should always take into account the overall burden of sedation from their concurrent medications. For these patients, starting with low, divided dosage is often an appropriate first step.

Because dopamine receptor blockade is a property common to all antipsychotics, they are all likely to interfere, although with varying degrees, with the efficacy of levodopa in the treatment of Parkinson's disease. When antipsychotic treatment is necessary in this setting, the low-potency antipsychotics clozapine and quetiapine have been preferred.[45] Reciprocally, antipsychotics are likely to be less effective in the treatment of psychosis in the setting of levodopa, stimulants (e.g., dextroamphetamine), and direct agonists (e.g., piribedil) that facilitate dopamine transmission. Nevertheless, these agents have been combined with antipsychotics in cautious, modestly successful efforts to treat the negative symptoms of schizophrenia (including blunted affect, paucity of thought and speech, and social withdrawal).

Elevated prolactin is common in patients on antipsychotics, particularly the higher-potency agents haloperidol, risperidone, and paliperidone. It often manifests with irregular menses, galactorrhea, diminished libido, or hirsutism. Antipsychotic-induced prolactin elevations associated with clinical symptoms can be abated by reducing the dosage of the offending agent, switching to a prolactin-sparing agent (e.g., aripiprazole, quetiapine, ziprasidone, or clozapine), or adding adjunctive amantadine (200 to 300 mg/day) or a dopamine agonist such as bromocriptine (7.5 to 15 mg/day) or cabergoline (0.5 to 4 mg/week).[46] At present, the management of sustained asymptomatic hyperprolactinemia—which is far more clinically common—is less well defined.

The risk of agranulocytosis, which occurs rarely with the low-potency antipsychotics, is much higher with clozapine, with an incidence as high as 1% to 3%. For this reason, the

combination of clozapine with other medications associated with a risk of myelosuppression (e.g., carbamazepine) should be avoided. Similarly, because clozapine lowers the seizure threshold to a greater extent than other antipsychotics, co-administration with other medications that significantly lower the seizure threshold (e.g., maprotiline) should be avoided or combined use with an anticonvulsant should be considered.

The co-administration of lithium with antipsychotic agents (most notably haloperidol) has been associated, very rarely, with potentially irreversible neurotoxicity, characterized by mental status changes, EPS, and, perhaps in some cases, cerebellar signs and hyperthermia.[47] Related to this concern is the unconfirmed suggestion that co-administering lithium with an antipsychotic can increase the risk of NMS. Other clinical variables, including dehydration and poor nutrition, are likely to be of greater significance as putative risk factors for NMS. At present, the evidence is not sufficient to warrant avoidance of the widely used combination of lithium and neuroleptics. Such a possibility, however, should be considered when a patient receiving these medications has neuropsychiatric toxicity of unclear origin.

Pharmacokinetic drug interactions are quite common among the antipsychotic drugs. Plasma levels of the antipsychotic drugs, however, can vary as much as 10-fold to 20-fold between patients even on monotherapy, and, as a class, they have a relatively wide therapeutic index.[43,48] Therefore, factors that alter antipsychotic drug metabolism might not have apparent clinical consequences. Exceptions include antipsychotics linked to risk of arrhythmia, most notably thioridazine and pimozide. Another exception has to do with patients who are maintained on antipsychotics carefully tapered to the lowest effective dosage. In these patients, a small decrease in antipsychotic levels, as can occur with the introduction of a metabolic inducer or an agent that interferes with absorption, can bring them below the threshold for efficacy.

Antipsychotic drug levels may be lowered by aluminum-containing or magnesium-containing antacids, which reduce their absorption and are best given separately. Mixing liquid preparations of phenothiazines with beverages, such as fruit juices, presents the risk of causing insoluble precipitates and inefficient GI absorption.

Carbamazepine, known to be a potent inducer of hepatic enzymes, has been associated with reduction of steady-state antipsychotic drug plasma levels by as much as 50%. This effect is especially important to bear in mind as a potential explanation when an antipsychotic-treated patient appears to deteriorate in the weeks following the introduction of carbamazepine. Oxcarbazepine can also induce antipsychotic drug metabolism, as can a variety of other anticonvulsants, including phenobarbital and phenytoin.

Cigarette smoking may also be associated with a reduction in antipsychotic drug through enzyme metabolism.[49] As inpatient units and community residential programs have widely become smoke-free, there are often substantial differences in smoking frequency between inpatient and outpatient settings. Among patients who smoke heavily, consideration should be given to the impact of these changes in smoking habits on antipsychotic dosage requirements.[48]

When an antipsychotic drug is given together with a TCA, the plasma level of each agent can rise, presumably because of mutual inhibition of microsomal enzymes. Reciprocally, when a patient with psychotic depression is tapered off an antipsychotic, the plasma level of TCAs might also decline.

SSRIs and other antidepressants with inhibitory effects on CYP isoenzymes can also produce an increase in the plasma levels of a concurrently administered antipsychotic agent (see Table 34–3). Thus, increases in clozapine, olanzapine, and haloperidol plasma levels can occur when these drugs are co-administered with fluvoxamine. Increases in risperidone, aripiprazole, and typical antipsychotic levels can follow initiation of fluoxetine, paroxetine, bupropion, duloxetine, and sertraline. Quetiapine and ziprasidone levels can rise following addition of nefazodone, fluvoxamine, or fluoxetine.

Phenothiazine drug levels may be increased when co-administered with propranolol, another inhibitor of hepatic microenzymes. Because propranolol is often an effective symptomatic treatment for neuroleptic-associated akathisia, the combined use of the β-blocker with an antipsychotic drug is common. When interactions present a problem, the use of a water-soluble β-blocker, such as atenolol, which is not likely to interfere with hepatic metabolism, provides a reasonable alternative.

Mood Stabilizers

Lithium

Lithium is absorbed completely from the GI tract; it achieves peak plasma concentrations after approximately 1.5 to 2 hours for standard preparations and 4 to 4.5 hours for slow-release preparations. It distributes throughout total body water and, in contrast to most psychotropic drugs, does not bind to plasma proteins and is not metabolized in the liver. It is filtered and reabsorbed by the kidneys, and 95% of it is excreted in the urine. Lithium elimination is highly dependent on total body sodium and fluid balance; it competes with sodium for reabsorption in the proximal tubules. To a lesser extent, lithium is reabsorbed also in the loop of Henle but, in contrast to sodium, is not reabsorbed in the distal tubules. Its elimination half-life is approximately 24 hours; clearance is generally 20% of creatinine clearance but is diminished in elderly patients and in patients with kidney disease. The risk of toxicity is increased in these patients as well as in patients with cardiovascular disease, dehydration, or hypokalemia. The most common drug–drug interactions involving lithium are pharmacokinetic. Because lithium has a low therapeutic index, such interactions are likely to be clinically significant and potentially serious (Table 34–4).[50]

Among the best-studied of these interactions are thiazide diuretics and drugs that are chemically distinct but share a similar mechanism of action (e.g., indapamide, metolazone, and quinethazone). These agents decrease lithium clearance and thereby steeply increase the risk of lithium toxicity. Thiazide diuretics block sodium reabsorption at the distal tubule, producing sodium depletion, which, in turn, results in increased lithium reabsorption in the proximal tubule. Loop diuretics (e.g., furosemide and bumetanide) appear to interact to a lesser degree with lithium excretion, presumably because they block lithium reabsorption in the loop of Henle, potentially offsetting possible compensatory increases in reabsorption more proximally.[51,52] The

TABLE 34–4 Selected Drug Interactions with Lithium

DRUG	POTENTIAL INTERACTION
Aminophylline, theophylline, acetazolamide, mannitol, sodium bicarbonate, sodium chloride load	Decreased lithium levels
Thiazide diuretics	Increased lithium levels; reduction of lithium-associated polyuria
Nonsteroidal antiinflammatory drugs, COX-2 inhibitors, tetracycline, spectinomycin, metronidazole, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors	Increased lithium levels
Neuromuscular blocking drugs (succinylcholine, pancuronium, decamethonium)	Prolonged muscle paralysis
Antithyroid drugs (propylthiouracil, thioamide, methimazole)	Enhanced antithyroid efficacy
Antidepressants	Enhanced antidepressant efficacy
Calcium channel blockers (verapamil, diltiazem)	Idiosyncratic neurotoxicity
Antipsychotic drugs	Idiosyncratic neurotoxicity, neuroleptic malignant syndrome risk

COX-2, Cyclooxygenase-2.

potassium-sparing diuretics (e.g., amiloride, spironolactone, ethacrynic acid, and triamterene) also appear to be less likely to cause an increase in lithium levels, but close monitoring is indicated when these drugs are introduced.[53] The potential impact of thiazide diuretics on lithium levels does not contraindicate their combined use, which has been particularly valuable in the treatment of lithium-associated polyuria. Potassium-sparing diuretics have also been used for this purpose. When a thiazide diuretic is used, a lithium dosage reduction of 25% to 50% and close monitoring of lithium levels are required. Monitoring of serum electrolytes, particularly potassium, is also important when thiazides are introduced because hypokalemia enhances the toxicity of lithium. Although not contraindicated with lithium, ACE inhibitors (e.g., captopril) and angiotensin II receptor antagonists (e.g., losartan) can elevate lithium levels, and close monitoring of levels is required when these agents are introduced.

Many of the nonsteroidal antiinflammatory drugs (NSAIDs) (including ibuprofen, indomethacin, diclofenac, naproxen, mefenamic acid, ketoprofen, and piroxicam) have been reported to increase serum lithium levels, potentially by as much as 50% to 60% when used at full prescription strength. This can occur by inhibition of renal clearance of lithium by interference with a prostaglandin-dependent mechanism in the renal tubule. The cyclooxygenase (COX)-2 inhibitors (e.g., celecoxib and rofecoxib), can also raise lithium levels. Limited data available suggest that sulindac,[54] phenylbutazone,[55] and aspirin[56] are less likely to affect lithium levels. A number of antimicrobials are associated with increased lithium levels, including tetracycline, metronidazole, and parenteral spectinomycin. In the event that these agents are required, close monitoring of lithium levels and potential dosage adjustment are recommended.

Conversely, a variety of agents can produce decreases in lithium levels, thereby increasing risk of psychiatric symptom breakthrough and relapse. The methylxanthines (e.g., aminophylline and theophylline) can cause a significant decrease in lithium levels by increasing renal clearance; close blood level monitoring with co-administration is necessary. A reduction in lithium levels can also result from alkalinization of urine (e.g., with acetazolamide use or with sodium bicarbonate), osmotic diuretics (e.g., urea or mannitol), or from ingestion of a sodium chloride load, which also increases lithium excretion.

A likely pharmacodynamic interaction exists between lithium and agents used clinically to produce neuromuscular blockade (e.g., succinylcholine, pancuronium, and decamethonium) during anesthesia. Muscle paralysis can be significantly prolonged when these agents are administered to the lithium-treated patient.[57] Although the mechanism is unknown, the possible inhibition by lithium of acetylcholine synthesis and release at the neuromuscular junction is a potential basis for synergism.

Lithium interferes with the production of thyroid hormones through several mechanisms, including interference with iodine uptake, tyrosine iodination, and release of triiodothyronine (T_3) and thyroxine (T_4).[7] Lithium can therefore enhance the efficacy of antithyroid medications (e.g., propylthiouracil, thioamide, and methimazole) and has also been used preoperatively to help prevent thyroid storm in the surgical treatment of Graves' disease.[58]

There have been isolated reports of various forms of neurotoxicity, which is usually, but not always, reversible, when lithium has been combined with SSRIs and other serotoninergic agents, calcium channel blockers, antipsychotics, and anticonvulsants (e.g., carbamazepine).[59–61] In some cases, features of the serotonin syndrome or NMS have been present.[62] Although it is worthwhile to bear this in mind when evaluating unexplained mental status changes in a lithium-treated patient, the combination of lithium with these classes of medication is neither contraindicated nor unusual.

Valproic Acid

Valproic acid is a simple branched-chain carboxylic acid that, like several other anticonvulsants, has mood-stabilizing properties. Valproic acid is 80% to 95% protein-bound and is rapidly metabolized primarily by hepatic microsomal glucuronidation and oxidation. It has a short elimination half-life of approximately 8 hours.[7] Clearance is essentially unchanged in the elderly and in patients with kidney disease, whereas it is significantly reduced in patients with primary liver disease.[63]

In contrast to other major anticonvulsants (such as carbamazepine or phenobarbital), valproate does not induce hepatic microsomes. Rather, it tends to inhibit oxidation reactions, thereby potentially increasing levels of co-administered hepatically metabolized drugs (Table 34–5).[63–65] A complex pharmacokinetic interaction occurs when valproic acid and carbamazepine are administered concurrently. Valproic acid not only inhibits the metabolism of carbamazepine and its active metabolite, carbamazepine-10,11-epoxide (CBZ-E), but it also displaces both entities from protein-binding sites. Although the effect on plasma carbamazepine levels is variable, the levels of the unbound (active) epoxide metabolite are increased, with a concomitant increased risk of carbamazepine neurotoxicity.[66] Conversely, co-administration with carbamazepine results in a decrease in plasma valproic acid levels. Nevertheless, the combination of valproate and carbamazepine has been used successfully in the treatment of patients with bipolar disorder who were only partially responsive to either drug alone.[67]

Cimetidine, a potent inhibitor of hepatic microsomal enzymes, is associated with decreased clearance of valproic acid, resulting in increased levels. Dosage of valproic acid may need to be reduced in the patient starting cimetidine, but not other H_2-receptor antagonists.[68] Elevated levels of valproic acid have also been reported sporadically with fluoxetine[69] and other SSRIs. Aspirin and other salicylates can displace protein binding of valproic acid, thereby increasing the unbound (free) fraction,[65] which can increase risk of toxicity from valproate even though total serum levels are unchanged. Although absence seizures have been reported with the combination of clonazepam and valproate,[70] this is likely to be rare and limited to patients with neurologic disorders.

Lamotrigine

Lamotrigine is a phenyltriazine anticonvulsant that is moderately (50% to 60%) protein-bound and metabolized primarily by glucuronidation. Its most serious adverse effect is a life-threatening hypersensitivity reaction with rash, typically, but not always, occurring within the first 2 months of use.[46] The incidence among patients with bipolar disorder is estimated at 0.8 per 1000 among patients on lamotrigine monotherapy and 1.3 per 1000 among patients on lamotrigine in combination with other agents.

The risk of adverse effects including hypersensitivity reactions and tremor is increased when lamotrigine is combined with valproic acid. As much as a twofold to threefold increase in lamotrigine levels occurs when valproic acid is added, related to inhibition of glucuronidation of lamotrigine.[65,71] Accordingly, the *Physicians' Desk Reference* (PDR) provides guidelines for more gradual dosage titration of lamotrigine and lower target dosages when introduced in a patient already taking valproate. When valproate is added to lamotrigine, the dosage of lamotrigine should typically be reduced.

Conversely, lamotrigine levels can be decreased by as much as 50% when administered with metabolic inducers, particularly other anticonvulsants (including carbamazepine, primidone, and phenobarbital). Therefore, guidelines

TABLE 34–5 Selected Drug Interactions with Valproate and Carbamazepine

DRUG	INTERACTION WITH VALPROATE
Carbamazepine	Decreased valproate plasma levels; increased plasma levels of the epoxide metabolite of carbamazepine; variable effects on plasma levels of carbamazepine
Phenytoin	Decreased valproate plasma levels; variable effects on phenytoin plasma levels
Phenobarbital	Decreased valproate plasma levels; increased phenobarbital plasma levels
Lamotrigine	Increased lamotrigine levels; hypersensitivity reaction
Aspirin	Increased unbound (active) fraction of valproate
Cimetidine	Increased valproate plasma levels
Fluoxetine	Same as above
Clonazepam	Rare absence seizures

DRUG	INTERACTION WITH CARBAMAZEPINE
Phenytoin	Decreased carbamazepine plasma levels
Phenobarbital	Same as above
Primidone	Same as above
Macrolide antibiotics	Increased carbamazepine plasma levels
Isoniazid	Same as above
Fluoxetine	Increased carbamazepine plasma levels
Danazol	Same as above
Verapamil	Same as above
Diltiazem	Same as above
Propoxyphene	Same as above
Oral contraceptives	Induction of metabolism by carbamazepine
Corticosteroids	Same as above
Thyroid hormones	Same as above
Warfarin	Same as above
Cyclosporine	Same as above
Phenytoin	Same as above
Ethosuximide	Same as above
Carbamazepine	Same as above
Valproate	Same as above
Lamotrigine	Same as above
Tetracycline	Same as above
Doxycycline	Same as above
Theophylline	Same as above
Methadone	Same as above
Benzodiazepines	Same as above
TCAs	Same as above
Antipsychotics	Same as above
Methylphenidate	Same as above
Modafinil	Same as above
Thiazide diuretics	Hyponatremia
Furosemide	Same as above

TCA, Tricyclic antidepressants.

have been developed for dosing lamotrigine in the presence of these metabolic-inducing anticonvulsants. Similar-magnitude reductions in lamotrigine levels have been reported in patients on oral contraceptives, requiring an increase in the dosage of lamotrigine.[72] Lamotrigine levels and symptom status should be monitored closely when oral contraceptives or metabolic-inducing anticonvulsants are started.

Carbamazepine and Oxcarbazepine

Carbamazepine is an iminostilbene anticonvulsant structurally related to the TCA imipramine. Carbamazepine is slowly and inconsistently absorbed from the GI tract; peak serum concentrations are achieved approximately 4 to 8 hours after oral administration. It is only moderately (60% to 85%) protein-bound. Carbamazepine, a potent inducer of hepatic metabolism, can also induce its own metabolism, such that elimination half-life can fall from 18 to 55 hours to 5 to 20 hours over a matter of several weeks, generally reaching a plateau after 3 to 5 weeks.[7]

Most drug–drug interactions with carbamazepine occur by pharmacokinetic mechanisms. Drugs whose metabolism is increased by carbamazepine include valproic acid, phenytoin, ethosuximide, lamotrigine, alprazolam, clonazepam, TCAs, antipsychotics, doxycycline, tetracycline, thyroid hormone, corticosteroids, oral contraceptives, methadone, theophylline, warfarin, and cyclosporine.[65,73] The concurrent administration of carbamazepine with any of these drugs can cause significant reductions in plasma levels and can lead to therapeutic failure. Patients of child-bearing potential who are taking oral contraceptives must be advised to use an additional method of birth control.

Several drugs inhibit the metabolism of carbamazepine, including the macrolide antibiotics (e.g., erythromycin, clarithromycin, and triacetyloleandomycin), isoniazid, fluoxetine, valproic acid, danazol, propoxyphene, and the calcium channel blockers verapamil and diltiazem.[65,73] Because of its low therapeutic index, the risk of developing carbamazepine toxicity is significantly increased when these drugs are administered concurrently. Conversely, co-administration of phenytoin or phenobarbital, both microsomal enzyme inducers, can increase the metabolism of carbamazepine, potentially resulting in subtherapeutic plasma levels. Carbamazepine has also been associated with bone marrow suppression, and its combination with other agents that interfere with blood cell production (including clozapine) should generally be avoided.[48] The combination of carbamazepine with thiazide diuretics or furosemide has been associated with severe symptomatic hyponatremia,[74] suggesting the need for close monitoring of electrolytes when these medications are used concurrently.

Oxcarbazepine, a structural derivative of carbamazepine, appears to be a less-potent metabolic inducer than its parent compound, although it still can render certain important agents (particularly CYP 3A4 substrates) less effective because of similar pharmacokinetic interactions.[7] Women of childbearing potential should therefore receive guidance about supplementing oral contraceptives with a second effective form of birth control, as with carbamazepine. Like carbamazepine, oxcarbazepine is also associated with risk of hyponatremia.

Other Anticonvulsants

Several new anticonvulsants have become available that, as with valproate, carbamazepine, and lamotrigine, are now being explored in treating bipolar disorder and other psychiatric conditions. In contrast to older anticonvulsants with demonstrated effects on mood, much less is known about the potential pharmacokinetic interactions involving these newer agents, including topiramate, zonisamide, gabapentin, and pregabalin. At present, none of these anticonvulsants can be justified as a monotherapy for any phase of bipolar disorder, but they may have a role as an adjunct treatment in some bipolar patients.[46]

Topiramate

Topiramate is a sulfamate-substituted monosaccharide, related to fructose, a rather unusual chemical structure for an anticonvulsant. Topiramate remains under study for its putative mood-stabilizing[75] and weight-reducing effects[76,77] as well as its utility in substance-abusing populations.[78]

Topiramate is quickly absorbed after oral use. Most of the drug (70%) is later excreted in the urine unchanged; therefore, it requires dosage reduction in the setting of renal insufficiency. The remainder is extensively metabolized by hydroxylation, hydrolysis, and glucuronidation. Topiramate inhibits carbonic anhydrase; therefore, the concomitant use of other carbonic anhydrase inhibitors (e.g. acetazolamide) can lead to an increased risk of forming kidney stones. Patients adhering to a ketogenic diet can also be prone to nephrolithiasis with topiramate treatment and should be instructed to stay well hydrated.[46]

In the presence of hepatic enzyme inducers (e.g., carbamazepine), the elimination of topiramate may be increased by up to 50%. Based on its properties as a weak inhibitor of CYP 2C19 and an inducer of CYP 3A4, topiramate can increase plasma levels of phenytoin but decrease plasma concentrations of estrogens in women taking oral contraceptives.[7]

Topiramate is associated with the side effects of cognitive dysfunction and sedation, both of which are limiting factors in clinical use.

Zonisamide

Zonisamide is a sulfonamide anticonvulsant used in patients with partial seizures.[79] Like topiramate, zonisamide is under investigation in psychiatry to facilitate weight loss in bipolar patients, and it might have fewer adverse cognitive effects. The FDA has warned that zonisamide can cause metabolic acidosis in some patients. As a result, patients should have their serum bicarbonate levels assessed before starting treatment and periodically during treatment with zonisamide, even in the absence of symptoms. Zonisamide is metabolized mostly by the CYP 3A4 isoenzyme; its metabolism is inhibited by ketoconazole, cyclosporin, miconazole, fluconazole, and carbamazepine (in descending order).[80]

Gabapentin and Pregabalin

Gabapentin—used at present in psychiatry for patients with anxiety, mood instability, or pain—is not a salt, but it resembles lithium because it is not hepatically metabolized, is not appreciably protein-bound, and is excreted by the kidney largely as unchanged drug. As with lithium, therefore, it is essential to adjust dosage according to changes in renal function.

Like gabapentin, pregabalin is rapidly absorbed when administered on an empty stomach, undergoes negligible metabolism in humans, has very low protein-binding, and is eliminated from the systemic circulation primarily by renal excretion unchanged. Studies have shown that pregabalin has a role in treating chronic pain disorders, such as fibromyalgia[81] and spinal cord injuries. Although *in vivo* studies have shown no significant pharmacokinetic interactions for pregabalin, it might have potential interactions with opioids (pregabalin is synergistic with opioids in lower dosages), benzodiazepines, barbiturates, alcohol, and other drugs that depress the CNS.

Antidepressants

The antidepressant drugs include the TCAs, the MAOIs, the SSRIs, the atypical agents (bupropion, trazodone, nefazodone, and mirtazapine), and the serotonin–norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine, and desvenlafaxine). Although the TCAs and MAOIs are used infrequently, they continue to serve a valuable role in the treatment of more severe, treatment-resistant depressive and anxiety disorders despite the wide range of drug–drug interactions they entail.

SSRIs and Other Newer Antidepressants

The SSRIs (e.g., fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram) share similar pharmacologic actions, including minimal anticholinergic, antihistaminic, and α_1-adrenergic blocking effects and potent presynaptic inhibition of serotonin reuptake.[7,82] There are important pharmacokinetic differences that account for distinctions among them with respect to potential drug interactions (Table 34–6).

Nefazodone, similar to trazodone, is distinguished from classic SSRIs by its antagonism of the 5-HT_2 receptor and differs from trazodone in its lesser antagonism of the α_1-adrenergic receptor. Mirtazapine blocks the 5-HT_2 receptor, 5-HT_3 receptor, and the α_2 adrenergic receptors. Venlafaxine, similar to TCAs, inhibits serotonin and norepinephrine reuptake, but, in contrast to TCAs, it is relatively devoid of postsynaptic anticholinergic, antihistaminic, and α_1-adrenergic activity. Similarly, duloxetine is an inhibitor of serotonin and norepinephrine reuptake, although whereas venlafaxine is predominantly serotoninergic at low to moderate dosages, duloxetine is a potent inhibitor of both the norepinephrine and serotonin transporters across its clinical dosage range.

Although not an approved antidepressant, the SNRI atomoxetine, indicated for the treatment of ADHD, might have a role in depression pharmacotherapy as a single agent or adjunctive treatment. It is neither a significant inhibitor nor inducer of the CYP system, but owing to its adrenergic effects, the risk of palpitations or pressor effects is likely to be greater than with serotoninergic agents when combined with prescribed and OTC sympathomimetics, and its use with MAOIs is contraindicated.

All of the SSRIs (except for fluvoxamine [77%], citalopram [80%], and escitalopram [56%]) as well as nefazodone are highly protein-bound (95% to 99%). Venlafaxine is minimally protein-bound (20% to 30%), whereas duloxetine is highly protein-bound (90%). All of the antidepressants are hepatically metabolized, and all of them except paroxetine and duloxetine have active metabolites. The major metabolites of sertraline and citalopram, however, appear to be minimally active.

Elimination half-lives range from 5 hours for venlafaxine and 11 hours for its metabolite, *O*-desmethylvenlafaxine, to 2 to 3 days for fluoxetine and 7 to 14 days for its metabolite, norfluoxetine. Nefazodone, similar to venlafaxine, has a short half-life (2 to 5 hours), with fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram in the intermediate range of 15 to 35 hours.[7] Food can have variable effects

TABLE 34–6 Potential Drug Interactions with the Selective Serotonin Reuptake Inhibitors and Other Newer Antidepressants

DRUG	POTENTIAL INTERACTION
MAOIs	Serotonin syndrome
Secondary amine TCAs	Increased TCA levels when co-administered with fluoxetine, paroxetine, sertraline, bupropion, duloxetine
Tertiary amine TCAs	Increased TCA levels with fluvoxamine, paroxetine, sertraline, bupropion, duloxetine
Antipsychotics (typical) and risperidone, aripiprazole	Increased antipsychotic levels with fluoxetine, sertraline, paroxetine, bupropion, duloxetine
Thioridazine	Arrhythmia risk with CYP 2D6–inhibitory antidepressants
Pimozide	Arrhythmia risk with CYP 3A4–inhibitory antidepressants (nefazodone, fluvoxamine)
Clozapine and olanzapine	Increased antipsychotic levels with fluvoxamine
Diazepam	Increased benzodiazepine levels with fluoxetine, fluvoxamine, sertraline
Triazolobenzodiazepines (midazolam, alprazolam, triazolam)	Increased fluvoxamine, nefazodone, sertraline
Carbamazepine	Increased carbamazepine levels with fluoxetine, fluvoxamine, nefazodone
Theophylline	Increased theophylline levels with fluvoxamine
Type 1C antiarrhythmics (ecainide, flecainide, propafenone)	Increased antiarrhythmic levels with fluoxetine, paroxetine, sertraline, bupropion, duloxetine
β-blockers (lipophilic)	Increased β-blocker levels with fluoxetine, paroxetine, sertraline, bupropion, duloxetine
Calcium channel blockers	Increased levels with fluoxetine, fluvoxamine, nefazodone

CYP, Cytochrome P450; *MAOI*, Monoamine oxidase inhibitor; *TCA*, tricyclic antidepressant.

on antidepressant bioavailability, including an increase for sertraline, a decrease for nefazodone, and no change for escitalopram.

The growing knowledge about the interaction of the newer antidepressants with the CYP isoenzymes has revealed differences among them in their pattern of enzyme inhibition that are likely to be critical to the understanding and prediction of drug–drug interactions.[4,31]

Cytochrome P450 2D6

Fluoxetine, norfluoxetine, paroxetine, bupropion, duloxetine,[83] sertraline (to a moderate degree), and citalopram and escitalopram (to a minimal degree)[4] all inhibit CYP 2D6, which accounts for their potential inhibitory effect on TCA clearance and the metabolism of other CYP 2D6 substrates. Other drugs metabolized by CYP 2D6—and whose levels can rise in the setting of CYP 2D6 inhibition—include the type 1C antiarrhythmics (e.g., encainide, flecainide, and propafenone) as well as β-blockers (e.g., propranolol, timolol, and metoprolol), antipsychotics (e.g., risperidone, haloperidol, aripiprazole, thioridazine, and perphenazine), TCAs, and trazodone. CYP 2D6 converts codeine into its active analgesic form.

These observations underscore the need to exercise care and to closely monitor when prescribing these SSRIs, bupropion, or duloxetine in the setting of complex medical regimens. Plasma TCA levels do not routinely include levels of active or potentially toxic metabolites, which may be altered by virtue of shunting to other metabolic routes when CYP 2D6 is inhibited. Therefore, particularly in the case of patients at risk for conduction delay, electrocardiography and blood level monitoring are recommended when combining TCAs with SSRIs, duloxetine, or bupropion.

Cytochrome P450 3A4

Fluoxetine's major metabolite (norfluoxetine), fluvoxamine, nefazodone, and, to a lesser extent, sertraline, desmethylsertraline, citalopram, and escitalopram inhibit CYP 3A4. All of these agents therefore have the potential for elevating levels of pimozide and cisapride (arrhythmia risks), calcium channel blockers, the statins, carbamazepine, midazolam, and many other important and commonly prescribed substrates of this widely recruited CYP enzyme.

Cytochrome P450 2C

Serum concentrations of drugs metabolized by this subfamily may be increased by fluoxetine, sertraline, and fluvoxamine. Reported interactions include decreased clearance of diazepam on all three SSRIs, a small reduction in tolbutamide clearance on sertraline, and increased plasma phenytoin concentrations reflecting decreased clearance on fluoxetine. Warfarin is also metabolized by this subfamily, and levels may be increased by the inhibition of these enzymes. SSRIs can interact with warfarin by still other, probably pharmacodynamic mechanisms (such as depletion of platelet serotonin). Although the combination is common, increased monitoring is recommended when SSRIs are prescribed with warfarin.

Cytochrome P450 1A

Among the SSRIs, only fluvoxamine appears to be a potent inhibitor of CYP 1A2. Accordingly, increased serum concentrations of theophylline, haloperidol, clozapine, olanzapine, and the tertiary amine TCAs including clomipramine, amitriptyline, and imipramine can occur.[4] Because theophylline and TCAs have a relatively narrow therapeutic index and because the degree of elevation of antipsychotic blood levels appears to be substantial (e.g., up to fourfold increases in haloperidol concentrations), additional monitoring and consideration of dosage reductions are necessary when fluvoxamine is co-administered with these agents.

Additional Interactions

Mirtazapine, although neither a potent inhibitor nor inducer of the CYP cytochrome isoenzymes, has numerous pharmacodynamic effects including antagonism of the histamine, α_2-adrenergic, 5-HT_2 and 5-HT_3, and muscarinic receptors, creating the possibility of myriad pharmacodynamic interactions (including blockade of clonidine's antihypertensive activity).[84] It also has the possible benefit of attenuated nausea and sexual dysfunction that can occur with SSRIs.[85]

The serotonin syndrome is a potentially life-threatening condition characterized by confusion, diaphoresis, hyperthermia, hyperreflexia, muscle rigidity, tachycardia, hypotension, and coma.[86,87] Although this can arise whenever an SSRI is combined with a serotoninergic drug (e.g., L-tryptophan, clomipramine, or venlafaxine) and drugs with serotoninergic properties (e.g., lithium, mirtazapine, dextromethorphan, tramadol, meperidine, and pentazocine), the greatest known risk is associated with the co-administration of an SSRI with an MAOI; this is absolutely contraindicated. In view of the long elimination half-life of fluoxetine and norfluoxetine, at least 5 weeks must elapse after fluoxetine discontinuation before an MAOI can be safely introduced. With the other SSRIs, an interval of 2 weeks appears to be adequate.

The weak, reversible MAOI antimicrobial linezolid, used for treatment of multidrug-resistant gram-positive infections, has been implicated in a small number of postmarketing cases of serotonin syndrome in patients on serotoninergic antidepressants, typically patients on SSRIs, as well as other medications, including narcotics.[88] Patients on serotoninergic antidepressants receiving linezolid should be monitored for the occurrence of symptoms suggesting serotonin syndrome. The co-administration of SSRIs with other serotoninergic agents is not contraindicated, but it should prompt immediate discontinuation in any patient on this combination of drugs who presents with mental status changes, fever, or hyperreflexia of unknown origin.

Tricyclic Antidepressants

TCAs are thought to exert their pharmacologic action by inhibiting the presynaptic neuronal reuptake of norepinephrine and serotonin in the CNS with subsequent modulation of both presynaptic and postsynaptic α-adrenergic receptors. TCAs also have significant anticholinergic, antihistaminic, and α-adrenergic activity as well as quinidine-like effects on cardiac condition, and in these respects they resemble the low-potency antipsychotic drugs, which are structurally similar.[82]

TCAs are well absorbed from the GI tract and subject to significant first-pass liver metabolism before entry into the systemic circulation, where they are largely protein-bound, ranging from 85% (trimipramine) to 95% (amitriptyline).

Peak plasma concentrations are reached approximately 2 to 6 hours after oral administration. They are highly lipophilic, with a large volume of distribution. TCAs are extensively metabolized by hepatic microsomal enzymes, and most have pharmacologically active metabolites.[89]

With two methyl groups on the terminal nitrogen of the TCA side-chain, imipramine, amitriptyline, trimipramine, doxepin, and clomipramine are called *tertiary amines*. The demethylation of imipramine, amitriptyline, and trimipramine yields the secondary amine TCAs, desipramine, nortriptyline, and protriptyline, which are generally less sedating and have less affinity for anticholinergic receptors. The demethylation of imipramine relies on cytochrome CYP isoenzymes 1A2, 3A3, and 3A4, whereas that of amitriptyline appears to rely primarily on 1A2. These tertiary amines as well as their secondary amine offspring are then hydroxylated via CYP 2D6, a step sensitive to inhibition by a wide variety of other drugs.[2] The hydroxymetabolites of the most commonly prescribed TCAs can be active. Furthermore, the hydroxymetabolite of nortriptyline can block the antidepressant effect of the parent drug,[90] and some hydroxymetabolites of the TCAs may be cardiotoxic.[91]

Additive anticholinergic effects can occur when the TCAs are co-administered with other drugs possessing anticholinergic properties (e.g., low-potency antipsychotics, antiparkinsonian drugs), potentially resulting in an anticholinergic syndrome. SSRIs, atypical antidepressants, and MAOIs are relatively devoid of anticholinergic activity, although the MAOIs can indirectly potentiate the anticholinergic properties of atropine and scopolamine. Additive sedative effects are not uncommon when TCAs are combined with sedative–hypnotics, anxiolytics, or narcotics or alcohol (Table 34–7).

TCAs possess class 1A antiarrhythmic activity and can lead to depression of cardiac conduction, potentially resulting in heart block or ventricular arrhythmias when combined with quinidine-like agents (including quinidine, procainamide, and disopyramide as well as the low-potency antipsychotics).[92–94] The antiarrhythmics quinidine and propafenone, inhibitors of CYP 2D6, can additionally produce clinically significant elevations of the TCAs, thus increasing the risk of cardiotoxicity through both pharmacodynamic and pharmacokinetic mechanisms.[95,96]

The arrhythmogenic risks of a TCA are enhanced in a patient with underlying coronary or valvular heart disease, a patient with a recent myocardial infarction or hypokalemia, and in a patient receiving sympathomimetic amines, such as amphetamine stimulants.[92,93]

TCAs also interact with several antihypertensive drugs. TCAs can antagonize the antihypertensive effects of guanethidine, bethanidine, debrisoquine, or clonidine via interference with neuronal reuptake by noradrenergic neurons. Conversely, TCAs can cause varying degrees of postural hypotension when co-administered with vasodilator drugs, antihypertensives, or low-potency neuroleptics.

Hypoglycemia has been observed with secondary and tertiary TCAs, particularly in the presence of sulfonylurea hypoglycemic agents,[2] suggesting the need for close monitoring.

Pharmacokinetic interactions involving the TCAs are often clinically important. The antipsychotic drugs (including haloperidol, chlorpromazine, thioridazine, and perphenazine) are known to increase TCA levels by 30% to 100%.[97,98] Cimetidine can also raise tertiary TCA levels as predicted by microsomal enzyme inhibition,[99] as can methylphenidate. The antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and calcium channel blockers (e.g., verapamil and diltiazem) as inhibitors of CYP 3A4 can also impair the clearance of tertiary amine TCAs, thereby requiring a reduction in TCA dosage. SSRIs have been associated with clinically significant increases in TCA plasma levels, believed to be the result of inhibition primarily, but not exclusively, of CYP 2D6.[25] Similar elevations of TCA levels would be expected with other potent CYP 2D6 inhibitor antidepressants (e.g., duloxetine and bupropion). Inducers of CYP enzymes can increase the metabolism of TCAs. Thus, plasma levels of TCAs may be significantly reduced when carbamazepine, phenobarbital, rifampin, or isoniazid are co-administered or in the setting of chronic alcohol or cigarette use.

TABLE 34–7 Selected Drug Interactions with Tricyclic Antidepressants

DRUG	POTENTIAL INTERACTION
Carbamazepine Phenobarbital Rifampin Isoniazid	Decreased TCA plasma levels
Antipsychotics Methylphenidate SSRIs Quinidine Propafenone Antifungals Macrolide antibiotics Verapamil Diltiazem Cimetidine	Increased TCA plasma levels
Class I antiarrhythmics	Depression of cardiac conduction; ventricular arrhythmias
Guanethidine Clonidine	Interference with antihypertensive effect
Sympathomimetic amines	Arrhythmias, hypertension (e.g., isoproterenol, epinephrine)
Antihypertensives Vasodilator drugs Low-potency antipsychotics	Hypotension
Anticholinergic drugs	Additive anticholinergic toxicity
MAOIs	Delirium, fever, convulsions
Sulfonylurea hypoglycemics	Hypoglycemia

MAOI, Monoamine oxidase inhibitor; *SSRI*, selective serotonin reuptake inhibitor; *TCA*, tricyclic antidepressant.

Monoamine Oxidase Inhibitors

Monoamine oxidase is an enzyme located primarily on the outer mitochondrial membrane and is responsible for intracellular catabolism of the monoamines. It is found in

high concentrations in brain, liver, intestines, and lung. In presynaptic nerve terminals, MAO metabolizes cytoplasmic monoamines. In liver and gut, MAO catabolizes ingested bioactive amines, thus protecting against absorption into the systemic circulation of potentially vasoactive substances, particularly tyramine.

Two subtypes of MAO have been distinguished: Intestinal MAO is predominantly MAO_A, whereas brain MAO is predominantly MAO_B. MAO_A preferentially metabolizes norepinephrine and serotonin. Phenylethylamine and benzylamine are the prototypic substrates for MAO_B. Both MAO subtypes metabolize dopamine and tyramine. The currently available MAOIs—phenelzine, tranylcypromine, and isocarboxazid—are nonspecific inhibitors of both MAO_A and MAO_B. Selegiline, available in transdermal form, has been approved for the treatment of depression. At low dosages selegiline is primarily an inhibitor of MAO_B, though it is a mixed MAO_A and MAO_B inhibitor at higher dosages.

When patients are using MAOIs, dietary[100,101] and medication restrictions must be closely followed to avoid serious interactions. The MAOIs are, therefore, generally reserved for use in responsible or supervised patients when adequate trials of other classes of antidepressants have failed. The two major types of MAOI drug–drug interaction are the serotonin syndrome and the hypertensive (also called hyperadrenergic) crisis.[102]

Hypertensive Crisis

Hypertensive crisis is an emergency characterized by an abrupt elevation of blood pressure, severe headache, nausea, vomiting, and diaphoresis; intracranial hemorrhage or myocardial infarction can occur. Prompt intervention to reduce blood pressure with the α_1-adrenergic antagonist phentolamine or the calcium channel blocker nifedipine may be lifesaving.[38]

Potentially catastrophic hypertension appears to be due to release of bound intraneuronal stores of norepinephrine and dopamine by indirect vasopressor substances. The reaction can therefore be precipitated by the concurrent administration of vasopressor amines, stimulants, anorexiants, and many OTC cough and cold preparations; these include L-dopa, dopamine, amphetamine, methylphenidate, phenylpropanolamine, phentermine, mephentermine, metaraminol, ephedrine, and pseudoephedrine.[103,104] By contrast, direct sympathomimetic amines (e.g., norepinephrine, isoproterenol, and epinephrine), which rely for their cardiovascular effects on direct stimulation of postsynaptic receptors, rather than on presynaptic release of stored catecholamines, appear to be somewhat safer when administered to patients on MAOIs (although they are also contraindicated).[101]

Hypertensive crises may also be triggered by ingestion of naturally occurring sympathomimetic amines (particularly tyramine), which is present in various food products, including aged cheeses (e.g., stilton, cheddar, bleu cheese, or camembert, rather than cream cheese, ricotta cheese, or cottage cheese), yeast extracts (e.g., Marmite, brewer's yeast tablets), fava (broad) beans, overripe fruits (e.g., avocado), pickled herring, aged meats (e.g., salami, bologna, and many kinds of sausage), chicken liver, fermented bean curd, sauerkraut, many types of red wine and beer (particularly imported beer), and some white wines. Although gin, vodka, and whiskey appear to be free of tyramine, their use should be minimized during the course of MAOI treatment, as with other antidepressants, because of the risk of exaggerated side effects and reduced antidepressant efficacy. Other, less-stringent requirements include moderate intake of caffeine, chocolate, yogurt, and soy sauce. Because MAO activity can remain diminished for nearly 2 to 3 weeks following the discontinuation of MAOIs, a tyramine-free diet and appropriate medication restrictions should be continued for at least 14 days after an MAOI has been discontinued.[38]

The lowest dose available of transdermal selegiline has been shown to have minimal risks of hypertensive crisis on a normal diet and therefore does not require the same level of restriction; however, dosages of at least 9 mg in 24 hours carry the same dietary recommendations as oral MAOIs.[38,100] Reversible inhibitors of MAO_A, such as moclobemide and brofaromine (not approved in the United States), and novel delivery systems (e.g., transdermal selegiline) are being developed, offering some promise that MAOIs will be devised that provide antidepressant benefits with fewer dietary and medication restrictions.

Serotonin Syndrome

The serotonin syndrome, the other major drug–drug interaction involving the MAOIs, occurs when MAOIs and serotoninergic agents are co-administered.[105] Potentially fatal reactions most closely resembling the serotonin syndrome can also occur with other drugs with less-selective serotoninergic activity, most notably meperidine and dextromethorphan, a widely available cough suppressant. Both of these medications, similar to the SSRIs, SNRIs, and clomipramine, are absolutely contraindicated when MAOIs are used. Other serotoninergic medications (e.g., buspirone and trazodone) are not contraindicated but should be used with care.

The 5-HT_1 agonist triptans, used in the treatment of migraine, have been implicated in serotonin syndrome when administered to patients on MAOIs. Other narcotic analgesics (e.g., propoxyphene, codeine, oxycodone, morphine, alfentanil, or morphine) appear to be safer alternatives to meperidine, but, in conjunction with MAOIs, their analgesic and CNS-depressant effects may be potentiated and rare serotonin syndrome–like presentations have been reported.[30,44,106] If opioid agents are necessary, they should be started at one fifth to one half of the standard dosages and gradually titrated upward, with monitoring for untoward hemodynamic or mental status changes.

Extremely adverse, although reversible, symptoms of fever, delirium, convulsions, hypotension, and dyspnea were reported on the combination of imipramine and MAOIs.[107] This has contributed to avoidance of the once-popular TCA–MAOI combinations. Nevertheless, although incompletely studied, the regimen has been observed in some instances to be successful for exceptionally treatment-refractory patients.[46,107–110] When TCAs and MAOIs are combined, simultaneous initiation of a TCA–MAOI or initiation of the TCA before, but never after, the MAOI is recommended, as is avoidance of the more serotoninergic TCAs (including clomipramine, imipramine, and amitriptyline).[111,112]

The sedative effects of CNS depressants (including the benzodiazepines, barbiturates, and chloral hydrate) may be potentiated by MAOIs. MAOIs often cause postural hypotension, and severe additive effects have occurred when co-administered with vasodilator or antihypertensive medications or low-potency antipsychotics.[30] The MAOIs, similar to the TCAs, have also been observed to potentiate hypoglycemic agents, including insulin and sulfonylurea drugs, suggesting the need for more frequent glucose monitoring when MAOIs are co-administered with hypoglycemic medications.[30]

Phenelzine has been associated with lowered serum pseudocholinesterase levels and prolonged neuromuscular blockade.[113] When possible, phenelzine may be discontinued 10 to 14 days before elective procedures requiring succinylcholine.[30] Nevertheless, the concurrent use of MAOIs is not a contraindication to surgery or electroconvulsive therapy (ECT), although it requires a detailed pre-procedure consultation with the anesthesiologist.

St. John's Wort

Although the efficacy of St. John's wort for depression remains to be confirmed, it has emerged as the most carefully studied herbal preparation when it comes to drug–drug interactions. Initial concerns about the generally weak, though potentially variable, MAOI activity of this botanical and the associated risk of serotonin syndrome when combined with serotoninergic agents have only been weakly borne out, with few cases of serotonin syndrome reported despite widespread concurrent use of St. John's wort with serotoninergic antidepressants. However, case reports and clinical trials indicate that some critical medications may be rendered less effective in some patients concurrently taking St. John's wort.[114,115] These medications include immunosuppressants (such as cyclosporine and tacrolimus), coumarin anticoagulants, antiretrovirals, theophylline, digoxin, amitriptyline, and oral contraceptives. Although the precise mechanisms and herbal constituents responsible for these effects remain to be elucidated, the primary focus has been on CYP 3A4 and P-glycoprotein. A paucity of systematic information exists concerning potential drug interactions and adverse effects of other herbal products, including a possible risk of increased bleeding in patients on ginkgo biloba and warfarin and of hepatotoxicity in patients on certain kava preparations.[116]

Psychostimulants and Modafinil

Psychostimulants

Psychostimulants have provided an often rapidly effective treatment of depressive symptoms among elderly and medically frail patients, including those with heart disease or HIV infection, who would be at particular risk from anticholinergic, hypotensive, sedative, or quinidine-like effects of the TCAs.[117–120] Although the broader range of options presented by the newer antidepressants has limited the need for stimulants in these settings, stimulants continue to be recruited as antidepressants and antidepressant adjuncts to the SSRIs, TCAs, and bupropion in the management of treatment-refractory depression. In addition, the cautious combination of methylphenidate and dextroamphetamine with MAOIs has been found to be effective in a subset of treatment-refractory depressed patients[121,122] and in efforts to treat particularly severe postural hypotension from the MAOIs. In view of the high risk of hypertensive crises, the addition of stimulants to MAOIs for antidepressant augmentation should remain an option only in exceptional cases in which other options (e.g., ECT) have been carefully weighed.

Methylphenidate, one of the most commonly used stimulants in modern psychiatric practice, has low bioavailability (20% to 30%) in orally administered forms and undergoes extensive presystemic metabolism through hydrolysis or de-esterification with limited oxidation.[123,124] Carboxylesterase-1A1 (CES-1), located in the stomach and liver, is the primary enzyme involved with first-pass methylphenidate metabolism. Difference in an individual's hydrolyzing enzyme activity, linked to variants in human CES-1 gene,[125] can lead to wide variations in methylphenidate metabolism (and corresponding methylphenidate blood concentrations) in certain persons. Improved, long-acting forms of methylphenidate and amphetamine have become available, thereby circumventing the short duration of action of the older immediate-release stimulant preparations (e.g., 3 to 4 hours of effectiveness for ADHD symptoms with immediate-release methylphenidate). A transdermal preparation of methylphenidate, which avoids much of the first-pass metabolism through CES-1, is also available.

In combination with other drugs, psychostimulants such as methylphenidate have been linked to increased plasma levels of TCAs and possibly other antidepressants; increased plasma levels of phenobarbital, primidone, and phenytoin; increased prothrombin time on anticoagulants; attenuation or reversal of the guanethidine antihypertensive effect; and increased pressor responses to vasopressor drugs.[30] Methylphenidate has been implicated in putative drug interactions more often than dextroamphetamine or mixed amphetamine salts.[126] At present, methylphenidate and other psychostimulants have been insufficiently studied to draw firm conclusions about their comparative suitability for use among patients following more-complex medical regimens.

Modafinil

The relatively benign side-effect profile of modafinil, together with its stimulant-like properties but differing mechanism, have motivated efforts to define the potential role of this wakefulness-promoting agent currently approved for treatment of narcolepsy. Its success as a treatment for fatigue in neurologic conditions (e.g., multiple sclerosis) [127] suggests the possibility of usefulness as a treatment for drowsiness related to other causes, including medications (e.g., antipsychotic-induced sedation). In addition, it has shown some promise in initial studies as an agent, like the psychostimulants, useful for treating depression co-morbid with medical illness[128] and as an antidepressant adjunct in refractory depression.[129] Likewise, several studies have suggested efficacy for children[130,131] and adults[132] with ADHD, though the use of modafinil for this purpose remains an off-label practice.

Clinical and preclinical studies have suggested that modafinil may be less likely than methylphenidate or dextroamphetamine to generate euphoria[133]; nevertheless it is a Schedule IV drug and its abuse liability is not yet known

to be less than the psychostimulants in real-world clinical settings. In addition, the risks of exacerbating psychosis or unmasking motor tics in predisposed persons, as can occur on psychostimulants, is not well defined. Modafinil interacts with the CYP isoenzymes as a minimal to moderate inducer of 3A4 and as an inhibitor of the 2C isoforms.[134] Modafinil can thereby engage in drug–drug interactions with common substrates, including oral contraceptives (the levels of which can decrease) and β-blockers and warfarin (the levels of which can increase), which requires monitoring and patient education.

Benzodiazepines

The benzodiazepines are a class of widely prescribed psychotropic drugs that have anxiolytic, sedative, muscle-relaxant, and anticonvulsant properties. Their rate of onset of action, duration of action, presence of active metabolites, and tendency to accumulate in the body vary considerably and can influence both side effects and the success of treatment. Most benzodiazepines are well absorbed on an empty stomach, with peak plasma levels achieved generally between 1 and 3 hours, although with more rapid onset of some (e.g., diazepam and clorazepate) than others (e.g., oxazepam). Duration of action of a single dose of benzodiazepine generally depends more on distribution from systemic circulation to tissue than on subsequent elimination (e.g., more rapid for diazepam than lorazepam). With repeated doses, however, the volume of distribution is saturated, and elimination half-life becomes the more important parameter in determining duration of action (e.g., more rapid for lorazepam than diazepam). A benzodiazepine that is comparatively short-acting on acute administration can therefore become relatively long-acting on long-term dosing. Benzodiazepines are highly lipophilic and distribute readily to the CNS and to tissues. Plasma protein-binding ranges from approximately 70% (alprazolam) to 99% (diazepam).[7]

Of the benzodiazepines, only lorazepam, oxazepam, and temazepam are not subject to phase I metabolism. Because phase II metabolism (glucuronide conjugation) does not produce active metabolites and is less affected than phase I metabolism by primary liver disease, aging, and concurrently used inducers or inhibitors of hepatic microsomal enzymes, the 3-hydroxy substituted benzodiazepines are much preferred in older patients and patients with liver disease. Perhaps the most common and clinically significant interactions involving benzodiazepines are the additive CNS-depressant effects, which can occur when a benzodiazepine is administered concurrently with barbiturates, narcotics, or ethanol. These interactions can be serious because of their potential to cause excessive sedation, cognitive and psychomotor impairment, and, at higher dosages, potentially fatal respiratory depression. An interesting pharmacodynamic interaction exists between benzodiazepines and physostigmine, which can act as a competitive inhibitor at the benzodiazepine receptor, antagonizing benzodiazepine effects. The specific benzodiazepine antagonist, flumazenil, however, is now more commonly the treatment of choice in managing a severe benzodiazepine overdose.

Pharmacokinetic interactions include a decreased rate of absorption, but not extent of absorption, of benzodiazepines in the presence of antacids or food. This is more likely to be a factor in determining the subjective effects accompanying the onset of benzodiazepine action for single-dose rather than repeated-dose administration. Carbamazepine, phenobarbital, and rifampin can induce metabolism, lowering levels of benzodiazepines that are oxidatively metabolized. In contrast, potential inhibitors of CYP 3A4 (including macrolide antibiotics, antifungals such as ketoconazole and itraconazole, nefazodone, fluvoxamine, and cimetidine) have been associated with decreased clearance and therefore increased levels of the triazolobenzodiazepines. A similar reaction occurs with several nonbenzodiazepine sedative–hypnotics (e.g., zolpidem, zaleplon, and eszopliclone), which are also metabolized through this pathway. The metabolism of diazepam depends in part on CYP 2C19. Decreased diazepam clearance has been reported with concurrent administration of a variety of agents including fluoxetine, sertraline, propranolol, metoprolol, omeprazole, disulfiram, low-dose estrogen-containing oral contraceptives, and isoniazid.[30]

PSYCHIATRIC USES OF NONPSYCHIATRIC MEDICATIONS

In the general hospital, consideration of the psychiatric complications of nonpsychiatric medications[135] is an integral part of the evaluation of alterations in mood, behavior, or mental status. A selected array of nonpsychiatric medications that are associated with neuropsychiatric symptoms are listed in the text in the differential diagnosis of mood changes (see Chapter 9), delirium (see Chapter 10), psychosis (see Chapter 12), and anxiety (see Chapter 13) in the medical setting. Nevertheless, whether by extrapolation from known *in vitro* mechanisms or through serendipity, nonpsychiatric drugs have also been found to be useful in the treatment of psychiatric illness. These include medications that ameliorate the side effects of psychotropic drugs as well as the growing number of nonpsychiatric medications studied for the treatment of mood, anxiety, psychotic, substance abuse, attentional, and tic disorders.

Medications for Psychotropic Drug Side Effects

The importance of attentive management of psychotropic drug side effects for alleviating the patient's suffering, for developing a therapeutic alliance, and for increasing the likelihood of the patient's adherence to necessary treatment continues to fuel the search for effective pharmacologic strategies when more-conservative measures fail to reduce dangerous or difficult-to-tolerate side effects.[7] Anticholinergic agents (benztropine 1 to 2 mg twice a day, biperiden 1 to 3 mg twice a day, and trihexyphenidyl 1 to 3 mg twice a day) and, less often, anticholinergic antihistamines (diphenhydramine 25 to 50 mg twice a day) and amantadine (100 mg two to three times a day) are widely used for managing the parkinsonian side effects of antipsychotics. Benztropine 2 mg and diphenhydramine 50 mg are also used IM or IV for the acute management of dystonia. Anticholinergic side effects are not uncommon, however, and combination of these drugs with other highly anticholinergic agents (e.g., tertiary amine TCAs) invites the risk

of frank toxicity. In this regard, IV physostigmine has been used in the emergency management of the anticholinergic syndrome, which includes delirium and tachyarrhythmias. β-blockers (including propranolol starting at 10 to 20 mg one to two times a day or the less centrally active atenolol (approximately 50 mg/day) have been useful for akathisia from antipsychotics and antidepressants, for lithium-associated tremor, and, less commonly, for jitteriness on antidepressants. Although the risk of depression on β-blockers is likely to be quite small, it is still reasonable nevertheless to monitor for alterations in mood whenever moderate to high dosages of the more lipophilic CNS active agents are used (e.g., propranolol dosages greater than 80 mg/day).[135,136]

Diuretics, including amiloride 5 to 10 mg one to three times a day and hydrochlorothiazide 50 to 100 mg/day, have been successful in treating disruptive polyuria on lithium, albeit potentially requiring reduction of lithium dosage and close monitoring of lithium levels and serum potassium. Anticholinergic side effects, including urinary retention, constipation, blurred vision, and dry mouth, may be treated with bethanechol 10 to 25 mg one to three times a day; dry mouth and blurred vision can also be treated with 1% pilocarpine ophthalmic solution. Excessive sweating on antidepressants is infrequently treated with the α_1-adrenergic agents terazosin (1 mg for every hour of sleep) and doxazosin (1 to 2 mg for every hour of sleep) as well as with anticholinergic agents, such as benztropine (0.5 to 1.0 once or twice daily) or glycopyrrolate (1 to 2 mg once daily to three times a day).

Pharmacologic attempts to reduce orthostatic hypotension on antidepressants have included caffeine or cautious introduction of T_3 (25 to 50 µg/day), T_4 (50 to 200 µg/day), the mineralocorticoid fludrocortisone (0.05 to 0.5 mg/day), salt tablets (600 to 1800 mg/day), methylphenidate, or dextroamphetamine (5 to 20 mg/day). These measures tend to be used after other measures have failed, including efforts to maximize hydration and to improve venous return from the lower extremities by calf muscle exercises or surgical support stockings.

Nausea or indigestion that is not responsive to change in dosing strategy or a change in preparation has been successfully treated with nizatidine (150 to 300 mg/day), famotidine (20 to 40 mg/day), or metoclopramide (5 to 10 mg one to two times a day). Metoclopramide, a cholinergic agonist and dopamine antagonist, has been associated rarely with extrapyramidal and dyskinetic effects, akathisia, and a case of mania, and because it increases gastric motility, it can potentially affect the absorption of co-administered medications. With respect to the H_2 antagonists, although all are capable of producing mood and cognitive changes, including delirium, cimetidine, which has been most closely associated with these effects, is also a potent inhibitor of CYP metabolism, rendering it least preferable among these agents for use in patients on multiple psychotropic medications. Similarly, omeprazole, an inhibitor of the gastric proton pump, appears to be an inducer of CYP 1A2 and an inhibitor of CYP 2C,[4] and its potential impact on the metabolism of concurrent medications should therefore be considered when it is prescribed. Agents that block 5-HT_3 receptors also may be helpful in reducing nausea related to serotoninergic agents. Although odansetron is an option, a less-expensive, albeit less-selective, alternative for appropriate candidates is mirtazapine.

Diarrhea not responsive to changes in preparation or dosing is often responsive to standard agents, such as loperamide or diphenoxylate. Acidophilus (1 capsule/meal) and cyproheptadine (2 to 4 mg one to three times a day) have also been used as antidiarrheal strategies.

Weight gain on psychotropic medications is common, distressing, and associated with risk of diabetes and hyperlipidemia. In addition to behavioral strategies for weight reduction, attention has also been directed toward pharmacologic strategies. These have included exploratory use of the anticonvulsants topiramate (25 to 100 mg one to three times a day) and zonisamide (up to 600 mg once daily). Both agents have carbonic anhydrase inhibitory properties and have been linked to an increased risk of nephrolithiasis. The H_2 antagonists, including nizatidine (up to 300 mg/day) have also showed promise in curbing weight gain, as have dopaminergic agents and bupropion.

Sexual dysfunction has proved to be a particularly common and troublesome side effect of antidepressants, especially the SSRIs, including diminished libido, erectile dysfunction, ejaculatory delay, and anorgasmia. As an alternative to switching medications (e.g., to bupropion, nefazodone, or mirtazapine), a variety of partly effective strategies have been marshaled for when dosage reductions or drug holidays[137] have not been feasible. These include sildenafil (25 to 100 mg/day)[138–140]; yohimbine (2.5 mg as needed up to 5.4 mg three times a day), potentially complicated by jitteriness, dizziness, or irritability; cyproheptadine (4 to 16 mg/day), with the potential, although apparently quite small, risk of interfering with efficacy of serotoninergic antidepressants; bethanechol (10 to 25 mg one to three times a day); neostigmine (7.5 to 15 mg/day); and amantadine (100 mg two to three times a day). Psychotropic medications have also been used in an effort to treat sexual dysfunction, including bupropion (75 to 150 mg/day),[141] nefazodone (50 to 200 mg/day), methylphenidate (5 to 10 mg one to four times a day), trazodone (25 to 100 mg/day), and buspirone (5 to 20 mg two to three times a day), as have dopamine agonists, such as ropinirole.[142] Improvement may be limited not only by the lack of more-effective pharmacologic strategies but also by the impact of depressive illness on sexual interest and by the influence of relevant psychosocial factors (e.g., marital conflict) that can accompany the depression.

α_1-Adrenergic Antagonists

Prazosin, the α_1-adrenergic receptor antagonist used for many years to treat hypertension, has been demonstrated in several open-label trials, chart reviews, and two placebo-controlled trials[143] to offer possible benefit at dosages of up to 10 mg at bedtime in the treatment of core symptoms of posttraumatic stress disorder (PTSD), particularly nightmares, insomnia, and hyperarousal.[144] Side effects include orthostatic blood pressure changes and dizziness, and particular caution does need to be observed when administered concurrently with other agents with α_1-adrenergic blocking properties, including low-potency antipsychotics.

α_2-Adrenergic Agonists

The antihypertensive clonidine is highly lipophilic and readily crosses the blood–brain barrier, where it stimulates α_2-adrenergic receptors. In 1980 it was first reported to be

an effective pharmacotherapy for Gilles de la Tourette's syndrome of chronic multiple motor and phonic tics,[145] and, as such, an alternative to antipsychotic drugs (such as haloperidol and pimozide and, more recently, risperidone), which have been the mainstays of treatment for this disabling condition arising in childhood. Clonidine alone or with naltrexone has been useful in suppressing the signs and symptoms of autonomic hyperactivity associated with inpatient detoxification from narcotic substances, including heroin, methadone, narcotic analgesics, and propoxyphene.[145] Although generally more likely to cause sedation and hypotension than other treatments for akathisia (e.g., anticholinergic medications, β-blockers, and benzodiazepines), clonidine has also been used to reduce akathisia refractory to other agents.[146] Clonidine has been shown effective in the treatment of ADHD in children and adolescents,[147] particularly in cases in which there is a marked hyperactive or aggressive component.

Although controlled trials are generally lacking, guanfacine, another α_2-adrenergic receptor agonist antihypertensive drug, appears to be useful for many of the same indications as clonidine but with the potential advantages of a longer half-life and generally less sedation.[148,149]

β-blockers

In addition to their role in the treatment of akathisia and tremor, the nonselective β-adrenergic receptor antagonists, which block the β_1-adrenergic receptors in heart and brain and β_2-adrenergic receptors in lung, blood vessels, and brain (including glial cells), have been among the first-line treatments for organically based aggressive behavior.[150] Anti-aggression β-blockers include the lipid-soluble agents propranolol and pindolol and the water-soluble agent nadolol.[151] Dosages used are generally high (e.g., propranolol up to about 12 mg/kg per day), and there may be a response latency of as long as 6 to 8 weeks. High dosages of propranolol can have modest adjuvant antipsychotic properties[152] and anti-manic effects[153]; however, the need for dosages as high as 800 to 2000 mg or more has limited the utility of this treatment approach.

Much lower dosages of β-blockers (e.g., propranolol 10 to 40 mg or the equivalent) have been used widely to reduce symptoms associated with performance anxiety[154] and are not uncommonly used for this purpose by musicians and public speakers. β-blockers are less likely to be effective pharmacotherapy for more generalized forms of social phobia, however, when compared with benzodiazepines, MAOIs, or SSRIs. The β-blockers have also had limited use for treatment of autonomic arousal associated with other anxiety states, including PTSD, generalized anxiety disorder, and panic disorder.

The prescription of β-blockers is potentially hazardous in a variety of common clinical conditions, including bronchospastic pulmonary diseases, insulin-dependent diabetes, hyperthyroidism, significant peripheral vascular disease, and congestive heart failure. In addition, β-blockers entirely or primarily eliminated by liver (e.g., propranolol, metoprolol, and pindolol) may be inhibitors of, as well as substrates for, hepatic microsomal enzymes and are therefore more likely to be subject to pharmacokinetic drug interactions than β-blockers primarily cleared by kidney (e.g., atenolol, nadolol, and sotalol).[155]

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Psychopharmacological Management of Children and Adolescents

35

Boris A. Lorberg, M.D.
Jefferson B. Prince, M.D.

Similar to adults, hospitalized children develop psychiatric illness as a result of psychosocial stresses of hospitalization (e.g., loss of control, threat of illness, separation from caregivers), effects of general medical conditions (e.g., infections), use of medications or substances (e.g., drug–drug interactions, drug withdrawal), and exacerbation of preexisting psychiatric vulnerabilities. The decision to use psychotropics in this population should be based on a careful diagnostic formulation and consideration of the strikingly limited database on the risks and benefits of using, as well as not using, psychotropics. Since the National Institute of Mental Health (NIMH) conference "Medication Safety Monitoring 2000: Developing Methodologies for Monitoring Long-Term Safety of Psychotropic Medications in Children," researchers on pediatric psychopharmacology have continued to emphasize the need for collecting safety data in children.[1,2] Despite increasing research efforts, expanding clinical experience, and a continued rise in prescriptions for psychoactive medications to pediatric patients, a large gap remains between empirical support and clinical practice.[3] General guidelines for the use of psychoactive medications in children and adolescents are provided in Table 35–1; they are consistent with the American Academy of Child and Adolescent Psychiatry's (AACAP) policy statement on prescribing psychotropic medications for children and adolescents (AACAP Policy Statement October 21, 2001).

ISSUES IN CLINICAL MANAGEMENT

Use of psychotropics in pediatric patients raises a variety of concerns. The first of these issues is the off-label use of medications. The Food and Drug Administration (FDA) approves the use of medications in specified clinical situations. However, the FDA allows practitioners to use medications in clinical situations not included in the official labeling—that is, practitioners may use a medication for clinical situations other than the approved use or use it in age groups in which it has not been formally studied. Medical advances are often made with use of drugs in conditions that are not yet approved by the FDA.

A second issue deals with obtaining consent to use medications. Except in emergency situations, consent must be obtained from the custodial parent or the legal guardian before any compounds can be used in pediatric patients. This consent process involves a discussion of the diagnosis being treated, the prognosis with or without treatment, the potential risks and benefits of the proposed intervention, and a discussion of treatment alternatives. The practitioner also needs to assess the reliability of the parents before initiation of outpatient treatment because it will be their responsibility to administer the drugs on an outpatient basis. If the parents cannot reliably administer the medication, this type of intervention may be precluded.

A third issue involves developmental factors. Both pharmacodynamic and pharmacokinetic factors may influence the safety, tolerability, and efficacy of medications in the pediatric population.[4] Pharmacodynamic factors, such as the ongoing development of neural networks, may affect response to medications. Similarly, pharmacokinetic factors may influence the absorption, distribution, metabolism, and excretion of medications. Pediatric patients often require higher doses of medication to achieve the same benefit as adults, perhaps as a result of more extensive or rapid metabolism by the liver or increased renal excretion (owing to a higher glomerular filtration rate). Furthermore, the pharmacokinetics in children and adolescents may be different for short- and long-term exposures. Clinicians must keep these factors in mind as they monitor the use of medications in children and adolescents.

MEDICAL PRECAUTIONS AND CONTRAINDICATIONS

In the presence of active pediatric illness, special precautions apply when using psychotropics (Table 35–2). For example, in the presence of preexisting cardiac disease that might impair cardiac conduction, tricyclic antidepressants (TCAs) either alone or in combination with antipsychotics should be used cautiously; a cardiac evaluation should be considered before initiating treatment. In 2008 the American Heart Association re-issued an official scientific statement regarding how to decide on cardiovascular monitoring of children and adolescents receiving psychotropics, specifically stimulants.[5,6] Clinicians should refer to these recommendations when selecting and monitoring psychotropics.

TABLE 35–1 General Guidelines for the Use of Psychoactive Medications in Children and Adolescents

1. The use of psychotropics should follow a careful evaluation of the child and the family (including psychiatric, medical, and social considerations).
2. Consideration should be given to the child's nonpsychiatric disorders, and an exclusionary differential diagnosis should be considered, particularly in an acute medical setting.
3. Children who manifest transient symptoms related to an adjustment to a medical illness or to a loss should be considered for nonpharmacologic treatment; pharmacologic care should be reserved for severe or refractory cases.
4. Pharmacotherapy should be considered as part of a comprehensive treatment plan that includes individual and family psychotherapy, educational and behavioral interventions, and careful medical management; it should not be presented as an alternative to these interventions. However, pharmacotherapy should be considered as an initial treatment when it is known to be superior to other modalities.
5. If a patient has a psychiatric disorder that may respond to a psychotropic, the clinician should decide which psychotropic to use and take into consideration the age and weight of the child and the severity and nature of the clinical picture. The diagnosis and target symptoms should be defined before the initiation of pharmacotherapy.
6. The family and the child should be familiarized with the risks and benefits of this intervention, the availability of alternative treatments, the possible adverse effects, the potential for interactions with other medications, the realization that unforeseeable adverse events may arise, and the prognosis with or without treatment. Permission to use medications should be obtained from the custodial parent or from the patient's legal guardian.
7. Ongoing assessment of pharmacologic interventions is necessary. When a medication is thought to be either ineffective or inappropriate to the current clinical situation, it should be tapered and discontinued under careful clinical observation. Appropriate alternatives should be reviewed with the family before initiation.
8. Pediatricians, family practitioners, other medical staff, mental health professionals, and child psychiatrists should work collaboratively in the pharmacologic management of children.

TABLE 35–2 Medical Precautions for and Contraindications to Use of Stimulants

MEDICATION	MECHANISM	PRECAUTIONS/ACTIVE MEDICAL CONDITIONS	RECOMMENDATIONS
Tricyclic antidepressants (TCAs); TCAs + antipsychotics	May impair cardiac function	Preexisting cardiac disease	If indicated, cardiac evaluation before the initiation of treatment; use with caution
β-blockers	Bradycardia	Congestive heart failure (CHF), sinus bradycardia, first-degree atrioventricular block, and Wolff–Parkinson–White syndrome	Contraindicated Note: Should not be used with β-adrenergic medications (Clonidine, Tenex) because of heart block risk.
β-blockers	Bronchoconstriction	Asthma	Contraindicated
β-blockers	Risk of masking the symptoms of hypoglycemic crisis	Diabetes mellitus	Use with caution
β-blockers	Risk of masking the symptoms of thyrotoxicosis	Hyperthyroidism	Use with caution
TCAs, bupropion, antipsychotics, stimulants	Risk of lowering the seizure threshold	Epilepsy	Use with caution
Stimulants	Risk of lowering the seizure threshold	Epilepsy	Use with caution
Antidepressants, antipsychotics, and antianxiety agents	Central nervous system (CNS) depression	Chronic respiratory disease.	Use with caution
Antidepressants, antipsychotics, and antianxiety agents	Anticholinergic properties	Acute narrow-angle glaucoma and untreated open-angle glaucoma	Contraindicated

Because β-blockers may cause severe bronchoconstriction and bradycardia, they are contraindicated in patients with asthma, congestive heart failure, sinus bradycardia, first-degree atrioventricular block, and Wolff–Parkinson–White syndrome. Similarly, β-blockers should not be used in conjunction with α-adrenergic medications because of concerns over heart block. β-blockers can mask the symptoms of hypoglycemic crisis and thyrotoxicosis and therefore should be used with caution in patients with diabetes and hyperthyroidism.

Atypical antidepressants (e.g., bupropion), antipsychotics, and TCAs have each been reported to lower the seizure threshold. Although the *Physicians' Desk Reference* (PDR)[7,8] notes that stimulants are associated with seizures, clinical experience and recent investigations do not support this assertion. Furthermore, stimulants do not appear to exacerbate well-controlled epilepsy. Recently published guidelines for the evaluation of attention-deficit/hyperactivity disorder (ADHD) do not recommend a baseline electroencephalogram (EEG) as part of the work-up, and recent data indicate that patients with ADHD and a normal EEG are at minimal risk for seizures. However, patients with ADHD and an epileptiform EEG do have an increased risk of seizures.[9]

Antidepressants, antipsychotics, and antianxiety agents can produce central nervous system (CNS) depression; therefore these agents should be used with caution in patients with a chronic respiratory disease.

Known drug interactions should also be considered. Psychostimulants generally do not generate significant interactions with other agents, with the exception of monoamine oxidase inhibitors (MAOIs); however, many antidepressants, antipsychotics, and anticonvulsants can interact with a wide array of drugs. Clinicians are encouraged to have ready access to databases that can provide up-to-date information about their metabolism and interactions with other medications. For instance, antidepressants, antipsychotics (particularly those with strong anticholinergic properties), and antianxiety agents are contraindicated in patients with acute narrow-angle glaucoma and in untreated patients with open-angle glaucoma.

Psychotropics should be used with caution in pediatric patients with renal or hepatic dysfunction. In these patients psychotropics with specific metabolic pathways (i.e., renal or hepatic) should be selected or the dose decreased and serum levels closely monitored.

EMERGENCY INTERVENTIONS: TREATMENT OF ACUTE AGITATION OR AGGRESSION

Typically, the request for the emergency use of psychotropics deals with the initial management of acutely assaultive or self-injurious behaviors. Use of emergency psychotropics should be conducted in concert with behavioral interventions and aimed at addressing the crisis situation, its causes, and its psychosocial impact.[10] If reduced stimulation and general calming measures are ineffective, pharmacotherapy should be considered. Low doses of a short-acting benzodiazepine (e.g., lorazepam 0.5 to 1 mg) or a sedating antihistamine (e.g., diphenhydramine 25 to 50 mg) can be used to reduce acute anxiety, agitation, and insomnia with few side effects. These agents can be administered orally, intravenously (IV), or intramuscularly (IM). Behavioral disinhibition can occur among children and should be monitored. In severe or agitated psychotic states, low doses of a sedating antipsychotic (e.g., chlorpromazine or thioridazine 25 to 50 mg, olanzapine 2.5 to 10 mg, or quetiapine 25 to 300 mg) may be very effective in reducing concomitant anxiety, agitation, or psychosis. For children with active hallucinations or severe disturbances of reality, a higher-potency antipsychotic (e.g., risperidone at 0.25 to 4 mg orally) may be necessary. Often a combination of a benzodiazepine and an antipsychotic may be necessary for severe agitation. Medications used for crisis management should not be continued indefinitely, unless they are indicated for the treatment of a co-existing psychiatric disorder.[10]

DELIRIUM

Delirium is a transient derangement of cerebral function with global impairment of cognition and attention. It is frequently accompanied by disturbances of the sleep–wake cycle and changes in psychomotor activity. Delirium may be an early warning of a deteriorating medical condition, a toxic insult, or a brain injury, and it may be accompanied by self-injurious behaviors, such as pulling out IV lines. In adolescents clinicians should consider substance intoxication and drug interactions (between prescribed medications and illicit substances, such as marijuana and TCAs) in the differential.[11]

Treatment is usually directed at both the cause and the symptoms. Correction of metabolic abnormalities, removal of agents that may be exacerbating the symptoms, or treatment of the underlying injury or infection is generally followed by reversal in the delirium. After attempting to re-orient and decrease the sensory input, the practitioner may need to implement pharmacologic intervention. Generally, antipsychotics are useful if hallucinations or delusions are present, whereas anxiolytics (i.e., benzodiazepines) help reduce anxiety and apprehension. As mentioned previously, antihistamines (e.g., diphenhydramine 25 to 50 mg orally or IM every 6 to 8 hours) or benzodiazepines (e.g., lorazepam 0.5 to 1 mg orally, IM, sublingually [SL], or IV every 4 to 6 hours) generally are considered to be the most benign choices for agitation and anxiety. In older children or adolescents who do not respond to these treatments or in those with psychosis, severe dyscontrol, or agitation, haloperidol can be used, with the dose repeated every 6 hours if needed. Psychotropic medications should be withdrawn with resolution of the delirium.

CHILDHOOD ANXIETY DISORDERS

Children tend to be anxious when receiving care in any medical setting. When the level of anxiety impairs the child (or practitioner) and is unremitting, a child should be assessed for an anxiety disorder. Anxiety problems may also manifest in children as multiple somatic complaints, such as headaches and stomachaches. Childhood anxiety disorders are relatively common and tend to persist into adult life.[12,13] The three most common childhood anxiety disorders seen in medical settings are separation anxiety disorder (SAD), generalized anxiety disorder (GAD) of childhood, and acute stress disorder (ASD). Other anxiety disorders, such as posttraumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), and tic disorders may be present in hospitalized children.

In SAD the predominant disturbance is a developmentally inappropriate excessive anxiety on separation from familial surroundings. It is called *separation anxiety* because it is assumed that the main disturbance is the child's inability to separate from the parent or major attachment figures. When separation occurs or is anticipated, the child may

experience severe anxiety to the point of panic. Although it may develop during the preschool age, it more commonly appears in older children.

Similar to GAD in the adult patient, the essential feature of childhood GAD is excessive worry and fears that are not focused on a specific situation or a result of psychosocial stressors. Affected children may manifest an exaggerated or unrealistic response to the comments or criticisms of others.

At this time no medication is FDA-approved for use in childhood anxiety disorders. Based on the efficacy and safety of multiple randomized controlled trials (RCTs), the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, and fluvoxamine appear to be the first-line medications for the treatment of SAD and GAD in children.[14] The literature on benzodiazepines, TCAs, buspirone, and β-blockers is mixed at best.[15]

Acute stress disorder develops within 1 month of an acute traumatic event and lasts for a maximum of 1 month. It is manifested by anxiety, dissociative symptoms, persistent re-experiencing of the trauma, and avoidance of stimuli that evoke recollections of the trauma. The Screening Tool for Early Predictors of PTSD (STEPP) is a 12-item questionnaire that obtains information from the child, parents, and medical record. A score of 4 or greater from the child or 3 or greater from the parent demonstrates sensitivity in predicting PTSD of 0.88 for children and 0.96 for parents.[16] Because of its high sensitivity, brevity, and ease of scoring, STEPP offers a quick way to identify children and families at high risk of developing PTSD in the acute care setting. The nature, severity, duration, and proximity to the trauma are factors that influence the development of ASD. In a number of patients, ASD may continue beyond 1 month and develop into PTSD. Effective management is focused on ensuring safety and reducing pain, anxiety, and fear. Recent investigations of children with burns suggest that aggressive management of pain with morphine may reduce and secondarily prevent PTSD.[17] Pediatric patients with PTSD are likely to have co-morbidity with other psychiatric disorders, a history of neglect or abuse, or both.[18,19]

In adults with PTSD, SSRIs have been shown to be useful in reducing symptoms of anxiety, depressed mood, rage, and obsessional thinking.[20,21] In fact, both sertraline and paroxetine are approved for treatment of PTSD in adults and are often used in pediatric patients.[20]

β-blockers, in particular propranolol, have been studied as a means of reducing arousal symptoms of PTSD. Similarly, α_2-adrenergic agents, such as clonidine or guanfacine, may likewise reduce anxiety, hyperarousal, and impulsivity and improve attention.[20,21]

In patients with dissociation, medications that enhance gamma-aminobutyric acid (GABA), such as the benzodiazepines or gabapentin (Neurontin), may reduce the severity of anxiety. In patients with fear or terror, the short-term use of atypical antipsychotics in low doses may be useful. Long-term treatment of ASD and PTSD uses both pharmacologic and psychotherapeutic modalities.[22]

High-potency (e.g., alprazolam 0.25 to 1 mg three times per day or clonazepam 0.25 to 1 mg three times per day) or medium-potency (e.g., lorazepam 0.25 to 1 mg three times per day) benzodiazepines can be effective for short-term relief of anxiety. A short-acting compound (e.g., lorazepam) can be very effective in managing more acute situations (e.g., anxious or agitated reactions to psychosocial crises). Doses of 0.5 to 1 mg of lorazepam given orally or SL are often effective. Lorazepam may be administered IM in an emergency. Use of short-acting benzodiazepines requires multiple daily doses. Long-term use should be avoided whenever possible.

In general, the clinical toxicity of benzodiazepines is low, but higher rates of disinhibition are observed in the pediatric population than in adults. Children who become disinhibited on high-potency benzodiazepines may respond more favorably to the mid- or low-potency agents (e.g., clorazepate or diazepam). The most commonly encountered short-term adverse effects of benzodiazepines are sedation, disinhibition, and depression.

When long-term treatment in older adolescents is warranted, long-acting benzodiazepines (such as clonazepam) may be preferable. For clonazepam an initial dose of 0.25 to 0.5 mg can be given at bedtime. The dose may be increased by 0.5 mg every 5 to 7 days depending on the clinical response and the side effects. Typically, doses between 0.25 and 2 mg per day are effective. Potential benefits of the longer-acting compounds are single-daily dosage and a decreased risk of withdrawal symptoms on discontinuation of treatment.

Buspirone is a nonbenzodiazepine anxiolytic without anticonvulsant, sedative, or muscle-relaxant properties. Clinical experience with this drug suggests limited antianxiety efficacy.[14] The effective daily dose is estimated to range from 0.3 to 0.6 mg/kg.

One controlled study with high-dose imipramine demonstrated efficacy under controlled conditions.[23] However, TCAs have had only limited usefulness for management of anxiety disorders given their narrow therapeutic window.[14]

AKATHISIA

Akathisia is a movement disorder experienced as inability to sit still (the term is derived from the Greek and literally means "not to sit").[24] In children and adolescents, it is most often seen as a side effect of antipsychotics or antidepressants. Akathisia may be confused with ADHD or agitation. Historically, patients are free from akathisia before starting an antidepressant or antipsychotic or reducing an anticholinergic medication. Treatment of akathisia involves reducing the dose of the offending medication to the lowest effective dose and then adding either β-blockers or benzodiazepines (0.5 to 1 mg three times per day of lorazepam). Although all β-blockers are likely to be effective, propranolol has good CNS penetration and is typically used. Propranolol should be initiated at 10 mg two times per day and the dose increased every several days to effect.

Studies in adults have demonstrated the efficacy of the potent selective β-1 blocking agent betaxolol in reducing akathisia. Betaxolol is a selective and potent β-1 blocker with a long half-life (allowing a dose once daily) with minimal medication interactions. Betaxolol is generally initiated at 5 mg and can be titrated as tolerated to doses between 10 to 20 mg per day.

OBSESSIVE–COMPULSIVE DISORDER

The best studied of the juvenile anxiety conditions, OCD often develops early in life. Nearly one third of adults with obsessions report the onset of symptoms before the age of 15; cases of the disorder have been described as early as age 3. It is characterized by persistent ideas or impulses (obsessions) that are intrusive and irrational (e.g., thoughts of having caused violence, becoming contaminated, or severely doubting oneself) that may lead to persistent repetitive, purposeful behaviors (compulsions, e.g., handwashing, counting, checking, touching) in order to neutralize the obsessive worries.[25] In the medical setting, this disorder is often associated with an exaggerated, persistent, and impairing obsession with an organ, disease process, or treatment. This disorder has been estimated to affect 1% to 2% of the adult population; it has been shown to be familial and associated with Tourette's syndrome (TS) and ADHD.

The treatment of OCD with serotonergic medications has been promising. Studies suggest that children with OCD respond in a similar fashion to these agents as adults. Currently, the SSRIs, (e.g., sertraline [Zoloft, initiated at 12.5 to 25 mg daily and titrated to 50 to 200 mg daily], fluvoxamine [Luvox, a more sedating drug that is initiated at 25 mg at bedtime and increased to 25 to 150 mg twice per day], and fluoxetine [Prozac, initiated at 5 to 10 mg and increased to 60 mg per day]) are FDA-approved for OCD in the pediatric population.[26–30] The SSRIs paroxetine (Paxil), citalopram (Celexa), escitalopram (Lexapro), and the mixed agent venlafaxine (Effexor) may also be useful in the management of OCD.

In addition, the TCA clomipramine (Anafranil) has been shown under controlled conditions to be useful for this chronic disorder. These studies suggest a clomipramine dosage of up to 250 mg per day, a fluoxetine dose of approximately 10 to 40 mg per day, and a sertraline dose of 50 to 200 mg per day, although anecdotal information indicates that some children may require higher dosages. Treatment with these agents should be initiated at a low dose (e.g., 25 mg per day of clomipramine) and increased slowly according to clinical response and side effects.

Recently, researchers have shown increased interest in a syndrome that resembles both OCD and tic disorders: pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Investigators have studied plasma exchange, IV immunoglobulin, and penicillin to treat OCD and tics associated with PANDAS. Although many of these patients responded favorably to the treatments, the numbers studied remain small and the study designs were open.[31,32] These treatments appear effective only for those patients whose OCD and tics were associated with streptococcal infections.

TIC DISORDERS

The best-known tic disorder is TS, a childhood-onset neuropsychiatric disorder that often persists throughout the patient's lifetime; it is manifested by multiple motor and vocal tics and other behavioral and psychological symptoms. TS is commonly associated with OCD (in about 30% of cases) and ADHD (in about 50% of cases). It is noteworthy that in many cases it is not the tics but rather the co-morbid disorders that are the major source of distress and disability. Much interest has been expressed in the overlap of TS with ADHD. Some interesting associations include the findings that ADHD appears earlier in life than tics, and stimulants may exacerbate tics. For many patients with tics and ADHD, the symptoms of ADHD appear to be associated with the most severe impairment.

Several typical antipsychotics (e.g., haloperidol, pimozide) have been considered the drugs of choice in TS; however, antipsychotics have limited effects on the frequently associated co-morbid disorders of ADHD and OCD, and they are associated with short-term (e.g., extrapyramidal side effects [EPS]) and long-term adverse effects (e.g., tardive dyskinesia [TD]). Recently, pilot studies of the atypical antipsychotics, risperidone (Risperdal) and ziprasidone (Geodon), have been completed in the treatment of TS. These studies show that both ziprasidone (initially dosed at 20 mg per day and increased to a mean dose of approximately 60 mg per day) and risperidone (titrated to a maximum dose of 0.06 mg/kg per day in one study and a maximum of 3 mg per day in another) were effective and generally well tolerated.[33–36] Both these medications are potent blockers of D_2 and 5-HT_{2A} receptors, thereby reducing the theoretical risk of EPS and TD. Of note, dysphoria and depression are reported to occur in adolescents with TS who are treated with risperidone.[37]

Clonidine has been shown to be highly effective in reducing the severity and frequency of tics and is considered a first-line drug for tic disorder and TS. Clonidine is usually begun at very low doses (i.e., 0.025 mg per day) to reduce the initial adverse effect of sedation, and it is increased upward as necessary.

Comparison of clonidine and risperidone and risperidone and pimozide demonstrated similar improvements in tic severity.[34,38] In addition, clonidine alone and in combination with methylphenidate was recently studied for effects on tics and ADHD.[39] Compared with placebo, clonidine and methylphenidate, clonidine alone, and methylphenidate alone were associated with reductions in tic severity. Although some patients experience an exacerbation of tics during treatment with stimulants (and it is still listed as a contraindication in the PDR), many patients appear to benefit from treatment of their ADHD symptoms.

Recently, the TCAs have been found to be effective in some children with TS. There have been promising results in open and controlled investigations of TCAs (desipramine and nortriptyline) for ADHD and tic symptoms in juveniles with tic disorders and TS.[40]

Given concerns over cardiac safety with the TCAs, atomoxetine (ATMX) may be an effective treatment for patients with ADHD and TS, although this remains to be formally studied.

Additional recent reports suggest that a variety of medications may prove useful in patients with TS with or without ADHD, including the selective type B, irreversible MAOI, L-deprenyl, the mixed $D_1/D_2/D_3$ dopamine agonist pergolide,[41,42] the hypotensive agent mecamylamine,[43,44] and medications that enhance cholinergic neurotransmission (e.g., donepezil and nicotine).[45,46]

Cannabinoids have also been investigated as a potential treatment for TS, although their use is not currently recommended.[47] Patients with co-morbid OCD may need additional pharmacotherapy with serotonergic agents (e.g., clomipramine or the SSRIs).

UPDATES ON SAFETY OF MEDICATIONS USED TO TREAT ADHD

In 2006 the FDA's Pediatric Drugs Advisory Committee (PDAC) reviewed data regarding the cardiovascular (CV) effects of medications used to treat ADHD as well as concerns regarding psychosis, mania, and suicidal thinking. However, currently the only black box warning for stimulants concerns the potential for substance abuse.

Cardiovascular Safety of ADHD Treatments

The PDAC cited the baseline rate of sudden unexplained death in the pediatric population as 0.6 to 6 occurrences per 100,000 patient-years.[48] According to the PDAC's and FDA's research, the rates of sudden unexplained death in pediatric patients (between 1992 and 2005) treated with methylphenidate (MPH), amphetamine, or ATMX were 0.2, 0.3, and 0.5 cases per 100,000 patient-years, respectively. On the basis of these data, the PDAC *rejected* adding a black box warning but recommended that current labeling language (regarding the CV risks to patients with structural cardiac abnormalities) for amphetamine drugs should be extended to all medications approved for the treatment of ADHD.[49,50]

The American Heart Association noted that it is prudent to monitor symptoms referable to the CV system (e.g., syncope, palpitations, chest pain) and vital signs at baseline in young patients taking psychotropics[51]; despite the generally benign CV effects of these medications, caution is warranted in the presence of a compromised CV system (e.g., with untreated hypertension, arrhythmias, or known structural heart defects). For most pediatric patients, it is not necessary to check an electrocardiogram (ECG) at baseline or with treatment. In patients at risk for CV symptoms, collaboration with the patient's primary care physician (PCP) is recommended to ensure that hypertension is not problematic. Recent data from an open-label study of adults being treated for ADHD suggested that if hypertension is well controlled, stimulants may be used safely[52]; however, in each case the physician and patient must weigh the risks against the benefits of treatment.

Aggression During Treatment with ADHD Medications

According to the PDAC's and FDA's research, all ADHD medications have been associated with episodes of aggression during clinical trials and in postmarketing surveillance. However, aggression in patients with ADHD usually responds to stimulant treatment.[53] During clinical trials rates of aggression have been similar whether the subject receives active treatment or placebo. The PDAC noted that the decision as to whether therapy is continued after an act of aggression is complex and that the physician and the parents should evaluate whether the risks of treatment outweigh the benefits to the child.

Psychotic Symptoms with ADHD Agents

The FDA has received hundreds of reports of psychotic or manic symptoms, particularly hallucinations, associated with use of medications for ADHD in children and adolescents. FDA drug-safety analysts recommended the addition of warnings to ADHD medication labels advising that ADHD medications be stopped if a patient experiences signs and symptoms of psychosis or mania. A recent review of stimulant trials found that psychotic-like or manic-like symptoms occur in approximately 0.25% of children (or 1 in 400) treated with stimulants.[54]

In summary, the PDAC concluded that potential episodes of psychosis, aggression, suicidality, and cardiac events during treatment with ADHD medications in children do not warrant a black box warning.

ADHD DISORDER

A common psychiatric condition, ADHD is found in 3% to 10% of school-age children.[55] ADHD is characterized by the classic triad of impaired attention, increased impulsivity, and excessive motor activity, although many children manifest only inattentiveness.[56] With developmental variations, ADHD affects children of all ages (as early as age 3), and it persists into adulthood about half of the time.[57–59] Within the medical setting, ADHD needs to be differentiated from environmental stimulation, iatrogenic causes (e.g., use of β-agonists), or other psychiatric disorders (e.g., anxiety, depression, mania, or intoxication). Pharmacotherapy remains the cornerstone of ADHD treatment (Table 35–3).[60–76]

FDA-APPROVED TREATMENTS FOR ADHD

Stimulants

Since the 1940s, stimulants have been used safely and effectively in the treatment of ADHD. There are three main stimulant families (see Table 35–3): methylphenidate (MPH) (e.g., short-acting Ritalin and Metadate, long-acting Concerta and Metadate-CD), dextroamphetamine (DEX) (e.g., short-acting Dexedrine tablets and long-acting Dexedrine spansules), and a mixture of dextroamphetamine salts (DEX) plus mixed amphetamine salts (MAS) (e.g., short-acting Adderall and long-acting Adderall-XR).

Stimulants increase intrasynaptic (extracellular) brain concentrations of dopamine; norepinephrine; and, to a lesser extent, serotonin (5-HT).[77,78] After oral administration, stimulants are rapidly absorbed and preferentially taken up into the CNS. Stimulants bind poorly to plasma proteins; this partially explains their relative paucity of drug–drug interactions. MPH is metabolized primarily by plasma-based esterases to ritalinic acid that is excreted in the urine. The amphetamines are 80% excreted in the urine unchanged; 20% undergo hepatic metabolism. Acidification of the urine may enhance excretion of the amphetamines. MPH is not usually detected on routine drug screening.

Methylphenidate

Originally formulated in 1954, methylphenidate was produced as an equal optical isomer mixture of d, l-threo-MPH and d, l-erythro-MPH. Because the erythro form of MPH

TABLE 35–3 FDA-Approved Treatments for Attention-Deficit/Hyperactivity Disorder

GENERIC NAME (BRAND NAME)	FORMULATION AND MECHANISM	DURATION OF ACTIVITY	HOW SUPPLIED	USUAL AND FDA-APPROVED ABSOLUTE MAXIMUM DOSING RANGE
Dex-MPH (Focalin)*	Tablet, 100% d-threo-MPH	3-5 hr	2.5-, 5-, and 10-mg tablets; 2.5 mg Focalin equivalent to 5 mg Ritalin	(0.15-1 mg/kg per day) 20 mg per day
MPH (Ritalin)* (Methylin)*	Tablet, 50 : 50 racemic mixture d,l-threo-MPH (50:50 d,l-t-MPH)	3-4 hr	5-, 10-, and 20-mg tablets	(0.3-2 mg/kg per day) up to 60 mg per day
MPH-SR (Ritalin-SR)* MPH (Metadate ER)*	Wax-based matrix tablet, 50:50 d,l-t-MPH	3-8 hr	Variable 20-mg tablets (amount absorbed appears to vary)	
MPH (Methylin ER)*	Hydroxypropyl methylcellulose-based tablet, (50:50 d,l-t-MPH); no preservatives	8 hr	10- and 20-mg tablets; 2.5-, 5-, and 10-mg chewable tablets; 5 mg/5 mL and 10 mg/5 mL oral solution	
MPH (Ritalin LA)*	Two types of beads give bimodal delivery (50% immediate release and 50% delayed release) of 50:50 d, l-t-MPH		20-, 30-, and 40-mg capsules; can be sprinkled	
MPH (Metadate CD)*	Two types of beads give bimodal delivery (30% immediate release and 70% delayed release) of 50:50 d, l-t-MPH		20-mg capsule; can be sprinkled	
MPH (Daytrana)*	MPH transdermal system	12 hr (patch worn for 9 hr)	10-, 15-, 20-, and 30-mg patches	(0.3 to 2 mg/kg per day) 30 mg per day
MPH (Concerta)*	Osmotic pressure system delivers 50:50 d,l-t-MPH		18-, 27-, 36-, and 54-mg tablets	(0.3 to 2 mg/kg per day) 72 mg per day
AMPH† (Dexedrine tablets)	d-AMPH tablet	4-5 hr	5-mg tablets	(0.15-1 mg/kg per day) 40 mg per day
AMPH† (Dextrostat)			5- and 10-mg tablets	
Mixed salts of AMPH† (Adderall)	Tablet of d,l-AMPH isomers (75% d-AMPH and 25% l-AMPH): -d-amphetamine saccharate, -d,l-amphetamine asparate, -d-amphetamine sulfate, and -d,l-amphetamine sulfate	4-6 hr	5-, 7.5-, 10-, 12.5-, 15-, 20-, and 30-mg tablets	
AMPH† (Dexedrine spansules)	Two types of beads in a 50 : 50 mixture immediate and delayed absorption of d-AMPH	8 (6-9) hr	5-, 10-, and 15-mg capsules	
Mixed salts of AMPH*‡ (Adderall-XR)	Two types of beads give bimodal delivery (50% immediate release and 50% delayed release) of 75 : 25 racemic mixture d,l-AMPH	At least 8 hr (but appears to last up to 12 hr in certain patients)	5-, 10-, 15-, 20-, 25-, and 30-mg capsules; can be sprinkled	
Lisdexamfetamine (Vyvanase)*	Tablets of dextroamphetamine and L-lysine	12 hr	30-, 50-, and 70-mg tablets	(0.15-1 mg/kg per day) 30 mg per day in children; recommended dose is 20 mg per day in adults
Atomoxetine*‡ (Strattera)	Capsule of atomoxetine	5 hr plasma half-life, but CNS effects appear to last much longer	10-, 18-, 25-, 40-, 60-, and 80-mg capsules	70 mg per day 1.2 mg/kg per day to 1.4 mg/kg per day or 100 mg

*Approved to treat attention-deficit/hyperactivity disorder age 6 years and older.
†Approved to treat attention-deficit/hyperactivity disorder age 3 years and older.
‡Specifically approved for treatment of attention-deficit/hyperactivity disorder in adults.

was linked with CV side effects, MPH is now manufactured as an equal mixture of d, l-threo-MPH. Later studies found that the d-threo MPH isomer was twice as active as the l-threo one. The d-threo isomer or MPH called Focalin (d-threo-MPH or dex-MPH) has been a recent addition. With regard to conversion and potency, 10 mg of Ritalin is biologically equivalent to 5 mg of Focalin.

The time to peak plasma concentration with oral administration of immediate-release d, l-threo-MPH (e.g., generic MPH, Ritalin, Metadate, Methylin) is variable (1 to 2 hours); its half-life is 2 to 3 hours. Behavioral effects of immediate-release MPH peak 1 to 2 hours after administration and tend to dissipate in 3 to 5 hours. Although generic MPH has a similar pharmacokinetic profile to Ritalin, it is more rapidly absorbed and peaks sooner.[79]

Plasma levels of the sustained-release preparations of MPH (Ritalin-SR) peak in 1 to 4 hours and have a half-life of 2 to 6 hours.[80] Peak behavioral effects of this preparation are noted 2 hours after ingestion, and effects last up to 8 hours. Because of the wax-matrix preparation, absorption of the sustained release (SR) preparation is variable; it is less often used now that better alternative extended-delivery systems are available.

Recently, several novel methods of delivering MPH and amphetamine have become available; each is intended to extend the clinical effectiveness of stimulants. Although these medications all deliver a stimulant, their pharmacokinetic profiles differ. Concerta (OROS methylphenidate), the first of these novel delivery systems, has been available since August 2000. Concerta uses the OROS technology to deliver a 50:50 racemic mixture of d, l-threo-MPH. An 18-mg caplet of Concerta delivers the equivalent of 15 mg MPH (5 mg MPH three times per day) providing 12-hour coverage. Initially the 18-mg caplet provides 4 mg MPH and delivers the additional MPH in an ascending profile over 12 hours.[81] The recommended dose of Concerta is between 18 to 54 mg per day, although a trial in adolescents studied doses up to 72 mg per day.[82] If Concerta is cut or crushed, its delivery system is compromised.

Metadate-CD (MPH-MR) capsules (10, 20, and 30 mg; may be sprinkled) contain d, l-threo-MPH with 30% of immediate-release beads and 70% of extended-release beads.[83] Metadate-CD delivers 30% or 6 mg of d, l-threo-MPH initially and is designed for 8-hour coverage.

Ritalin-LA (MPH-ERC) capsules (10, 20, 30, and 40 mg; may be sprinkled) deliver 50% of its d, l-threo-MPH initially and another bolus approximately 3 to 4 hours later, thereby providing approximately 8 hours of coverage.

The primarily active form of MPH is the d-threo isomer,[84] which has become available in both immediate-release tablets (Focalin 2.5, 5, and 10 mg) and extended-delivery capsules (Focalin XR 5, 10, 15, and 20 mg). The efficacy of D-MPH is well established in children, adolescents, and adults under double-blind conditions.[85,86] D-MPH is approved to treat ADHD in children, adolescents, and adults in doses of up to 20 mg per day and has been labeled to provide 12 hours of coverage.[8] Although the research is not definitive, 10 mg of MPH appears to be approximately equivalent to 5 mg of D-MPH, and clinicians can reasonably use this estimate in clinical practice.[87]

For patients who have difficulty swallowing or tolerating an oral stimulant formulation or for patients who need flexibility in the duration of medication effect, there is a new treatment option. The MPH Matrix Transdermal System (MTS; Daytrana; 10-, 15-, 20-, and 30-mg patches[88,89]) delivers MPH through the skin. The patches are applied once daily and are intended to be worn for 9 hours, although in clinical practice they can be worn for shorter or longer periods. The MTS usually takes effect within 2 hours and provides coverage for 3 hours after removal of the patch. Because the MPH is absorbed through the skin, it does not undergo first-pass metabolism in the liver; therefore patients require lower doses with the patch compared with oral preparations (10 mg MTS is equivalent to 15 mg extended-release oral MPH).

Amphetamines

Mixed amphetamine salts (MAS; Adderall) are a racemic mixture of approximately 3:1 of d- to l-amphetamine.[8] The two isomers have different pharmacodynamic properties, and some patients with ADHD preferentially respond to one isomer over another. Recent data on children with ADHD suggest that, when compared with immediate-release MPH, the peak behavioral effects of Adderall occur later and are more sustained.[90]

The extended-delivery preparation of MAS is a capsule containing two types of Micotrol beads (MAS XR; Adderall XR). The beads are present in a 50:50 ratio, with immediate-release beads designed to release MAS in a fashion similar to that of MAS tablets, and delayed-release beads designed to release MAS 4 hours after dosing.[8] A single dose of MAS-XR 20 mg is bioequivalent to 10 mg of an MAS tablet dosed twice per day. The efficacy of MAS XR is well established in youth with ADHD.[90–92]

Dextroamphetamine (DEX; Dexedrine) tablets contain only the d-isomer of amphetamine. DEX tablets achieve peak plasma levels 2 to 3 hours after oral administration and have a half-life of 4 to 6 hours. Behavioral effects of DEX tablets peak 1 to 2 hours after administration and last 4 to 5 hours. When DEX spansules are used, behavioral effects last 6 to 9 hours.

Lisdexamphetamine dimesylate (LDX; Vyvanase), previously known as NRP-104, was recently approved by the FDA for treatment of ADHD in children between the ages of 6 and 12 years. LDX is an amphetamine prodrug in which L-lysine, a naturally occurring amino acid, is co-valently linked to d-amphetamine. After oral administration, the prodrug is hydrolyzed in the body to release d-amphetamine. Although lisdexamfetamine appears to have less abuse liability and overdose protection, the FDA has recommended a CII schedule. It is available in doses of 30, 50, and 70 mg that appear to be comparable to MAS XR doses of 10, 20, and 30 mg, respectively.[93]

Pemoline

Pemoline (Cylert) is a CNS stimulant that enhances central dopaminergic transmission, while being structurally different from MPH, DEX, and MAS. Since receiving FDA approval for the treatment of ADHD and narcolepsy in the 1970s, it has been linked with 21 cases of liver failure (13 of them fatal). In 2005 the FDA withdrew its approval for pemoline. Since our last edition, Abbott Laboratories has discontinued the production of Cylert for economic reasons (March 2005).

Guidelines on the Use of Stimulants in Children

The AACAP released guidelines on the use of stimulants in children and adolescents in 2007[60]; these included starting with a longer-acting preparation in most cases. Clinicians can initiate therapy at 18 mg Concerta or 20 mg Metadate-CD or Ritalin-LA for MPH products or 5 to 10 mg Adderall-XR or Dexedrine spansules. However, in the hospital setting, clinicians may prefer short-acting stimulants, starting with lower doses (2.5 to 5 mg per day for children and adolescents, 5 to 10 mg per day for adults), given in the morning with food. The dose is titrated upward every 3 to 5 days until a beneficial effect is noted or adverse effects emerge. Typically, the half-life of the short-acting stimulants necessitates at least twice-daily dosing, with the addition of similar or smaller afternoon doses, based on breakthrough symptoms. Although the PDR lists maximum dosages for amphetamine products at 40 mg per day and 60 mg per day for MPH, patients often benefit from suggested daily doses that range from 0.3 to 1.5 mg/kg per day for amphetamine products and from 0.5 to 2 mg/kg per day for MPH products. Thus an older adolescent may need immediate-release MPH up to 30 mg three to four times daily or amphetamine 15 to 20 mg three to four times a day.

Numerous short-term (less than 12 weeks) clinical trials show that approximately 70% of patients with ADHD respond to stimulants. A positive dose–response relationship of stimulants is present for both hyperactivity and inattention. Longer-term trials have demonstrated the tolerability and continued efficacy of stimulants in patients treated continuously over 2 years.

Despite the vast literature and excellent safety profile of stimulants, studies indicate that approximately one third of children and adolescents with ADHD either do not respond or manifest intolerable adverse effects; these outcomes necessitate alternative treatments. Fortunately, ATMX and other off-label treatments (including antidepressants and antihypertensives) are available.

Side Effects of Stimulants

Although generally well tolerated, stimulants can cause clinically significant side effects (e.g., anorexia, nausea, insomnia, nightmares, headaches, dizziness, dry mouth, anxiety, irritability, dysphoria, rebound phenomena).[62–64,94] Rates and types of stimulant-induced side effects appear to be similar in all ADHD patients, regardless of age. In patients with a current co-morbid mood or anxiety disorder, clinicians should consider whether a presenting complaint reflects the co-morbid disorder, a side effect of the treatment, or an exacerbation of the co-morbidity. Moreover, although stimulants can cause these side effects, many ADHD patients experience these problems before treatment; therefore it is important for clinicians to document these symptoms at baseline.[63] Although tolerance to the effects of stimulants has been debated, data from the NIMH Multimodal Treatment of ADHD study demonstrated the persistence of stimulant-associated medication effects. Recommendations about management of common side effects are listed in Table 35–2.

Appetite Suppression

Youth treated with stimulants often experience a dose-related reduction in appetite (in some cases, weight loss); thus it often is useful to administer stimulants during or after meals.[65] Although appetite suppression has been observed to decrease over time,[66] clinicians should give guidance on improving the patient's nutritional options with higher caloric intake to balance the consequences of decreased food intake.[62] Cyproheptadine, in doses of 4 to 8 mg, has recently been reported to improve appetite in ADHD patients with stimulant-associated appetite suppression.[67]

Sleep

Stimulant-induced sleep disturbances are common. Modifications in behavior and sleep hygiene (e.g., adjusting the timing of sleep or type of stimulant used) may be helpful.[68] Symptomatic treatments include use of melatonin (1 to 3 mg, while monitoring for over-the-counter [OTC]–related variability),[70] clonidine (0.05 to 0.2 mg, monitoring for hypotension),[69] diphenhydramine (25 to 50 mg, with the understanding that its effectiveness is often short-lived), trazodone (25 to 50 mg, monitoring for priapism), mirtazapine (3.75 to 15 mg, especially useful with co-morbid anorexia), imipramine (25 to 100 mg, especially useful with enuresis).[62] Although not yet studied, another consideration for insomnia is ramelteon, a synthetic melatonin receptor agonist.[71]

Mood, Anxiety, and Substance Abuse

A majority of patients with ADHD experience at least one additional co-morbid psychiatric disorder. ADHD is co-morbid with anxiety disorders (in approximately 40%), mood disorders (in approximately 33%), substance abuse disorders, oppositional defiant disorder (ODD; in up to 70%), and conduct disorder (CD) (in approximately 25%).[95] These co-morbid disorders may alter a stimulant's effectiveness. For instance, patients with ADHD and co-morbid mood or anxiety disorders may respond differently to a stimulant, depending on the clinical state of their co-occurring disorders. In addition, stimulants may exacerbate tics, obsessions, or compulsions, although they are frequently used in patients with these conditions. Irritability or dysphoria may occur 1 to 2 hours after administration of stimulants, which suggests an absorption peak phenomenon that may respond to lower and more frequent doses. Occasionally, they may elicit a depressive reaction or psychosis.

DEX, MAS, and MPH are all Schedule II controlled substances that have the potential for abuse. The order of addictive liability with available preparations from most to least addictive is MAS, DEX, then MPH. Although the rates of substance abuse in patients with ADHD are increased, the use of stimulants does not appear to increase the risk of substance abuse; recent data suggest that successful stimulant treatment of children with ADHD may delay or decrease the risk of substance abuse in adolescence. When administered orally in their intended dosages, stimulants do not appear to cause euphoria, nor do they appear to be addictive. The design of the extended-delivery preparations makes abuse of stimulants less likely. Recent meta-analytic data show that in patients with ADHD treated for years with stimulants, the risk of substance abuse is halved compared with patients who

have ADHD but are not treated with stimulants.[94] Although no physical withdrawal is associated with stimulants, patients who have used high doses for a prolonged period may experience fatigue, hypersomnia, hyperphagia, dysphoria, and depression when the drug is discontinued. Given the abuse potential of these medications, it is important to inquire about concomitant use of drugs and alcohol.

Medication Interactions with Stimulants

The interactions of stimulants with other prescription and OTC medications are generally mild and not a major source of concern.[78,96,97] Co-administration of stimulants with MAOIs is the only true contraindication to their use: It may result in a potentially life-threatening hypertensive crisis. Concomitant use of sympathomimetic agents (e.g., pseudoephedrine or caffeine) may potentiate the effects of both substances and exacerbate sleep difficulties. Stimulants are associated with small increases in heart rate and blood pressure that are usually insignificant. Although data on the co-administration of stimulants with TCAs suggest little interaction between these compounds,[98] careful monitoring is warranted when prescribing stimulants with either TCAs or anticonvulsants because of potential CV and CNS effects. Although administration of stimulants with ATMX is common in clinical practice and appears to be well tolerated and effective, to date only small samples have been studied; therefore patients who take this combination should be monitored closely.[99]

Growth

The long-term impact of stimulants on growth velocity remains a concern, and data are conflicting. The current consensus is that height and weight should be monitored prospectively because stimulants may have a mild negative impact on growth velocity (possibly related more to ADHD than to its treatment).[100] In the vast majority of patients, growth delay does not pose a significant problem. However, if a decrease in growth rate occurs while a child is taking a stimulant, consideration should be given to either a medication "holiday" or alternative treatments.

Some studies support significant growth delay. For instance, in the MTA study, ADHD youth treated with a stimulant continuously over 2 years experienced a deceleration of about 1 cm per year. Despite this slowing, the children remained within the normal curves, except for those subjects in the lowest percentile for height. Other studies have not detected a significant growth delay. In a study by Faraone and associates[72] of the growth deficit in girls with ADHD, deficits were modest, only evident in early adolescence, unrelated to weight deficits or stimulant treatment, and not significant after correction for age and parental height. The finding of small height differences in preadolescent girls was consistent with results from other long-term studies.[66,72]

Atomoxetine

A highly selective norepinephrine reuptake inhibitor, ATMX (Strattera) increases intrasynaptic norepinephrine. ATMX was initially developed as an antidepressant but became FDA-approved as a nonstimulant (hence, not a controlled agent) for the treatment of ADHD.

In the initial trials, ATMX was dosed twice a day (up to 2 mg/kg per day). However, its CNS effects appeared to last more than 24 hours, even though its plasma half-life appeared to be only 5 hours. As expected, later studies demonstrated its efficacy and tolerability when dosed once a day,[101] with its best tolerability occurring when dosed in the evening.[102] ATMX should be initiated at 0.5 mg/kg per day; after several days, it can be increased to 1.2 mg/kg per day. Current guidelines recommend a maximum once-daily dose of 1.4 mg/kg per day. It may take up to 10 weeks to see the full benefits of ATMX treatment (although some patients achieve an early response).[103–105]

To date, plasma levels of ATMX have not been used to guide dosing. However, Dunn and colleagues[106] found that patients with a plasma level of ATMX greater than 800 ng/mL had more robust responses, although those treated with higher doses also had more side effects. Laboratory monitoring aside from routine medical care has not been necessary. Recently, concerns have been raised that treatment with ATMX may increase the risk of hepatitis. During post-marketing surveillance, two patients (out of 3 million exposures) developed hepatitis during treatment with ATMX.[107] Patients should consult with their doctors if symptoms of hepatitis develop.

Although generally well tolerated, the most common side effects in children and adolescents taking ATMX include dyspepsia, dizziness, and reduced appetite.[108] Height and weight are unaffected by long-term use.[104] In older adolescents ATMX may be associated with dry mouth, insomnia, nausea, decreased appetite, constipation, decreased libido, dizziness, and sweating.[109] When patients experience nausea, the dose of ATMX should be divided and administered with food. Sedation is often transient, but it may be helped by either administering the dose at night or dividing the dose. If mood swings occur, patients should be evaluated and their diagnosis reassessed.

The impact of ATMX on the CV system appears to be minimal.[110] ATMX was associated with a mean increase in the heart rate of 6 beats per minute and an increase in both the systolic and diastolic blood pressure of 1.5 mm Hg. Extensive ECG monitoring indicates that ATMX has no apparent effect on QTc intervals, and ECG monitoring aside from routine medical care is not indicated.

Recently, the FDA issued a public health advisory, and the manufacturer later added a black box warning regarding the development of suicidal ideation in patients treated with ATMX.[8] As with the SSRIs, there was a slight increase in suicidal thinking in controlled trials of ATMX. Parents should monitor for any such occurrences and for unexpected changes in mood or behavior.

ATMX is metabolized primarily in the liver to 4-hydroxyatomoxetine by the cytochrome CYP P450 2D6 enzyme, and it is primarily excreted in the urine.[111,112] ATMX does not appear to inhibit 2D6. Although patients identified as poor metabolizers (i.e., having low 2D6 activity) appear to tolerate ATMX, they seem to have more side effects; a reduction in the dose may be necessary. Therefore in patients who are also on strong 2D6 inhibitors (e.g., fluoxetine, paroxetine, and quinidine), it may be necessary to reduce the dose of ATMX. Use of ATMX is contraindicated with MAOIs.

Alternative (Non-FDA-Approved) Treatments for ADHD

Bupropion Hydrochloride (Wellbutrin, Zyban)

Bupropion hydrochloride (Wellbutrin, Zyban) is a unicyclic aminoketone (unrelated to other antidepressants) that modulates both norepinephrine and dopamine. Bupropion is approved for the treatment of depression and as an aid for smoking cessation in adults,[8] and it has improved ADHD symptoms in children, adolescents,[113–117] and adults.[118–120] Although helpful, the magnitude of bupropion's effect is less than that seen with either stimulants or ATMX. Bupropion can be particularly useful in patients with ADHD and co-morbid conditions (e.g., ADHD and nicotine dependence,[121] substance use and mood disorders,[118] substance abuse and conduct disorder,[122] depression,[114] and bipolar disorder [BPD]).[123] In light of the high rates of marijuana use in patients with ADHD,[124] it is important for clinicians to note that adolescents treated with bupropion may experience increased irritability during marijuana withdrawal.[125]

Bupropion appears to be more stimulating than other antidepressants, and it may cause irritability, exacerbate tics,[126] and induce seizures (more often than do other antidepressants).[8] Seizures appear to be dose-related (above 450 mg per day) and are more likely to occur in patients with bulimia or a seizure disorder.

Treatment should be initiated at 37.5 mg per day of the immediate-release (IR, tid dosing), 100 mg sustained-release (SR, bid dosing), or 150 mg extended release (XL, once-daily dosing) and titrated gradually as indicated. Although dosage guidelines are not available for children, in one study doses of 3 to 6 mg/kg per day were given. As in adults, no single dose of the IR preparation should exceed 150 mg, SR 200 mg, or XL 450 mg. A recent open trial found the SR form of bupropion (mean dose 2.2 mg/kg in the morning and 1.7 mg/kg in the afternoon) was helpful for the reduction of symptoms of depression and ADHD in adults.[127]

Tricyclic Antidepressants

Although controlled trials in ADHD youth[128] and adults[129] demonstrate the efficacy of TCAs, their effects are less robust than are those of stimulants. On the other hand, possible advantages of TCAs over stimulants include once-daily dosing, the option of monitoring plasma drug levels, and a negligible abuse liability. TCAs may be particularly useful in patients with co-morbid anxiety; ODD[130]; tics[131]; and, theoretically, depression (in adults). However, given concerns about potential cardiotoxicity and the availability of ATMX, use of the TCAs has been significantly curtailed.

Desipramine (DMI) and nortriptyline are associated with lower risks of adverse effects (e.g., sedation, dry mouth, and impairment in cognition) than imipramine and other tertiary amine TCAs and therefore may be better tolerated.[129]

Dosing for ADHD appears to be similar to that for depression. ECGs should be obtained at baseline and as the dose is increased (as well as when there is a family history of early-onset or sudden cardiac arrhythmias).[5] Treatment with a TCA should be initiated with 10 mg or 25 mg depending on the size of the child (approximately 1 mg/kg per day) and increased slowly (every 4 or 5 days) by increments of 20% to 30%. For imipramine and DMI, an upper dose limit of 5 mg/kg per day has been suggested for children, and for nortriptyline 2 mg/kg per day is suggested. When a daily dose of 2 to 3 mg/kg per day (or a lower effective dose for imipramine and DMI or 1 mg/kg per day for nortriptyline) is reached, steady state serum levels and an ECG should be obtained. A steady state serum level obtained 10 to 14 hours after the last dose is usually achieved after at least 1 week on the same daily dose. Monitoring serum levels of TCAs is more helpful in preventing toxicity than it is in determining optimal levels for response.

Common short-term adverse consequences of the TCAs include anticholinergic effects (e.g., dry mouth, blurred vision, orthostasis, and constipation). To date, no known deleterious effects have been associated with chronic administration of these drugs. After the sudden death of a number of children receiving DMI, concerns were raised regarding the possible cardiac toxicity of TCAs in children.[132] However, epidemiologic evaluation of the association between DMI and sudden death in children has not supported a causal relationship.[133] TCAs predictably increase heart rate and are associated with conduction delays that generally affect the right bundle and thus require ECG monitoring.[134] However, these effects, when small, rarely seem to be pathophysiologically significant in patients with a normal baseline ECG. In children with documented congenital or acquired cardiac disease, pathologic rhythm disturbances (i.e., atrioventricular block, supraventricular tachycardia, ventricular tachycardia, and Wolff–Parkinson–White syndrome), family history of sudden cardiac death or cardiomyopathy, or diastolic hypertension (> 90 mm Hg) or when the cardiovascular status of the patient is unknown, a complete (noninvasive) cardiac evaluation is indicated before initiating treatment with a TCA to help determine the risk–benefit ratio of such an intervention. A serious adverse event associated with use of TCAs is overdose, either by the patient or by a sibling. Thus parents should closely supervise the storage and administration of these medications.

α-Adrenergic Agonists

Clonidine

Clonidine is an imidazoline derivative with α-adrenergic agonist properties; it has been primarily used in the treatment of hypertension.[135] At low doses it appears to stimulate inhibitory, presynaptic adrenergic autoreceptors in the CNS.[136] Clonidine has achieved an increasing prominence in pediatric psychopharmacology because of its wide range of uses and relative safety.[137] Although clonidine ameliorates symptoms of ADHD,[138] its overall effect is less than the stimulants[139] and likely smaller than ATMX, TCAs, and bupropion. Clonidine appears particularly helpful in patients with ADHD and co-morbid conduct disorder or ODD,[140,141] tic disorders,[142,143] and ADHD-associated sleep disturbances.[144,145] In addition, clonidine has been increasingly reported to be useful in developmentally disordered patients to control aggression toward self and others.[146] Furthermore, clonidine appears to reduce anxiety and hypervigilance in traumatized children.[20]

Clonidine is a relatively short-acting compound with a plasma half-life ranging from approximately 5.5 hours (in children) to 8.5 hours (in adults). Usual dose ranges from 3 to 10 µg/kg per day given generally in divided doses, once, twice, three, or four times per day; there is also a transdermal preparation.[147] Therapy is usually initiated at the lowest manufactured dose of a half (0.05 mg) or a quarter (0.025 mg) of a 0.1-mg tablet, depending on the size of the child (approximately 1 to 2 µg/kg per day) and increased depending on the clinical response and adverse effects. The initial dosage can more easily be given before bedtime because nocturnal sedation will not adversely affect daytime function.

The most common short-term adverse effect of clonidine is sedation, which tends to subside with continued treatment. It can also produce hypotension, dry mouth, vivid dreams, depression, and confusion. Overdoses of clonidine in children under the age of 5 may have life-threatening consequences.[148] Except in overdose, clonidine is not known to be associated with long-term serious adverse effects. Because abrupt withdrawal of clonidine has been associated with rebound hypertension, slow tapering is advised.[149,150] In addition, extreme caution should be exercised with the co-administration of clonidine with β-blockers or calcium channel blockers because adverse reactions, including complete heart block, have been reported.[151] After reports of several sudden deaths related to clonidine use, concerns about the safety of co-administration of clonidine with stimulants were raised.[152,153] However, these cases were thoroughly examined, and no causative link between use of the combination and sudden death was found. Additional discussion of these issues can be found in the work of Wilens and coworkers.[154] Current guidelines are to monitor blood pressure when initiating and tapering clonidine, but ECG monitoring is not usually necessary.[5]

Guanfacine (Tenex)

Recently, the clonidine-like but more selective, α_2-adrenergic agonist compound guanfacine (Tenex) has been used as an alternative to clonidine for the same indications.[155–157] Possible advantages of guanfacine over clonidine include less sedation and a longer duration of action. Anecdotal information suggests that guanfacine may be more useful in improving the cognitive (inattention) symptoms of ADHD (and less effective in reducing the behavioral symptoms of impulsivity, aggressiveness, and hyperactivity). In open pilot trials, school-age children with ADHD and co-morbid tic disorder treated with guanfacine (in doses ranging from 0.5 mg twice per day to 1 mg three times per day) showed reduction in both tics and ADHD.[158] Controlled data also demonstrated the benefit of guanfacine in reducing tic severity and ADHD symptomology.[159]

Guanfacine treatment is associated with minor, clinically insignificant decreases in blood pressure and pulse rate. The adverse effects of guanfacine include sedation, irritability, and depression. Several cases of apparent guanfacine-induced mania have been reported, but the impact of guanfacine on mood disorders remains unclear.[160] New guanfacine extended-release formulation at doses of 2, 3, and 4 mg per day was more effective than placebo and was generally well tolerated in a multicenter, 8-week, fixed-dose escalation study in children with ADHD who were 6 to 17 years of age.[157]

Novel Treatments for ADHD

Modafinil

Modafinil, a novel stimulant that is distinct from amphetamine, is approved for the treatment of narcolepsy.[161] Unlike the broad brain area activation observed with amphetamine, modafinil appears to activate specific hypothalamic regions.[162,163] Although initial trials in adults were negative, in three recent pediatric trials, modafinil demonstrated efficacy in the treatment of ADHD.[164–166] The FDA PDAC voted that modafinil is "not approvable" for pediatric ADHD owing to possible Stevens–Johnson syndrome in pediatric patients (see www.fda.gov). It may be reasonable to consider combining modafinil with stimulants,[167,168] but clinicians should be aware of the potential to exacerbate mania.[169]

Selegiline

Selegiline (l-deprenyl), an irreversible type B MAOI that is metabolized into amphetamine and methamphetamine, has been compared with MPH in two trials of ADHD youth[170,171] and in adults.[172] Previous work with selegiline in children with ADHD and TS suggested that it may reduce symptoms of ADHD.[173,174] Although to date its role in the treatment of ADHD has been limited by both the availability of alternative treatments and potential for the "cheese reaction," its recent formulation as a patch,[175] which may diminish this reaction, may increase interest in its use.

MOOD DISORDERS

Depression

Children and adolescents may develop a variety of depressive disorders (including major depressive disorder [MDD], dysthymia or mood disturbances that are primary or associated with medical conditions, substance use or abuse, and as a result of psychosocial problems).[176] In the medical setting, clinicians are challenged to differentiate transient symptoms of depression from true depressive disorders. Children often manifest worry, hopelessness, and sadness as primary symptoms related to their own illness, whereas adolescents typically display anxiety, anger, or withdrawal. If the symptoms are episodic and associated with limited impairment, they are generally considered an adjustment disorder with depressed or anxious mood. These patients usually respond to reassurance, environmental intervention, or interpersonal or cognitive-behavioral therapy (CBT). In the outpatient medical setting, children and adolescents with depression may present for evaluation for medical symptoms of unclear etiology. During routine examination these patients may appear sad, withdrawn, apathetic, anxious, angry, or irritable. Although an increasing number of families seek care from PCPs for depression, most family physicians and pediatricians believe they are inadequately trained to screen for, evaluate, and manage pediatric depression.[177,178]

The prevalence of MDD increases with advancing age. Epidemiologic studies from community and clinical samples estimate that the prevalence of MDD is approximately 0.3% in preschoolers, 2% in children, and between 1.5% to 9% in adolescents.[179–187] By the end of

adolescence, the cumulative incidence of MDD is estimated at 20%.[182,185,186,188,189] Although the gender ratio appears equal in children with MDD, by the age of 14, girls appear twice as likely to experience depression as boys.[190] However, additional data suggest that boys and girls who develop depression during prepubescence experience similar symptoms, rates of recovery, relapse, and co-morbidity.[191] Depressive disorders in older children and adolescents commonly co-occur with anxiety, ADHD, and conduct and substance use disorders.[192] The challenge to the clinician is to recognize the developmental progression of co-morbidity. Children initially may be evaluated and treated for ADHD, only to develop depression several years later during their treatment for ADHD.

Pediatric depressive disorders are recognized by their core symptoms (which are similar to those found in adults but with developmentally specific associated features, including sudden-onset school difficulties, school refusal, irritability, sad faces, low energy, isolation, withdrawal, negativism, and aggression or prolonged irritability).[193,194] Diagnostic criteria for MDD include at least a 2-week period of symptoms that represent a change from previous function, with at least one of the symptoms being either depressed mood (which may manifest as irritability in pediatric patients) or loss of interest or pleasure. Other symptoms include decreased or increased appetite, weight loss (or in children, failure to make expected weight gains), weight gain, insomnia or hypersomnia, psychomotor retardation or agitation, fatigue or loss of energy, feelings of worthlessness, inappropriate or excessive guilt (which may be manifest in children as extreme sensitivity to rejection or requests), diminished ability to concentrate (which may be manifested in children as indecisiveness), and recurrent thoughts of death or suicide with intent or a plan.[176] Assessing depression in preschoolers may require some adjustment from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (*DSM-IV*) criteria, and it remains an area of active investigation.[195]

On average, the duration of pediatric depression appears to be approximately 7 months; in the course of a first episode, as many as 40% appear to recover without specific treatment.[193,196] However, patients who do not recover are at high risk for chronic depression, and those who do recover have high rates of recurrence and dysthymia.[197,198] Evidence suggests that children of parents who suffered from depression, especially before the age of 30, have a significantly increased risk for recurrent bouts of depressions.[199,200] Mood disorders in children tend to be chronic compared with the more episodic nature that is typical of adult mood disorders. Furthermore, children and adolescents with depression have a higher rate of conversion to BPD. In follow-up, almost half of the children who initially had single-episode, nonpsychotic MDD converted to BPD that lasted into their early 20s.[201,202] Similarly, as many as 20% of adolescents who had MDD converted to BPD during follow-up.[203] Risk factors for switching from MDD to BPD include history of BPD in parents and grandparents or a family history of antidepressant-induced mania. Other warning signs for conversion to mania include a rapid onset of depression associated with psychosis, psychomotor retardation, and hypersomnia.[204] Afflicted patients may be at increased risk for self-injurious behaviors or suicide.

Suicidal ideation, threats, and behaviors are commonly seen among children and adolescents with psychiatric disorders. These behaviors are of great concern to clinicians who need to ensure the safety of patients within the medical setting and identify patients at increased risk for self-injurious behaviors. The American Academy of Pediatrics (AAP) and the AACAP published reviews and guidelines for the evaluation and management of suicidal behaviors in children and adolescents.[205,206] Suicide remains a leading cause of death in adolescents 15 to 19 years of age; in fact, the number of adolescent suicides has increased dramatically in the past few decades. Overall, male subjects are at increased risk compared with female subjects; in particular, boys with previous suicide attempts, a mood disorder (MDD or BPD), and associated substance abuse are at higher risk. Female subjects at greatest risk also have mood disorders (MDD or BPD) and a history of suicidal behaviors. After a suicide attempt, patients at greatest risk to repeat an attempt have a history of suicidal behaviors; continue to think about suicide; are agitated, irritable, and socially isolated; and have associated MDD, BPD, or substance abuse. In addition to medical care, these patients require close monitoring (which may include restraint, seclusion, or observation by a sitter). Information should be obtained from outside sources (e.g., family, school, the patient's therapist), and the patient must be evaluated for an underlying psychiatric disorder and treated appropriately. In outpatient settings approximately half of children referred for depression are suicidal. Pharmacotherapy should be considered for children with malignant symptoms, significant impairment, suicidality, or lack of response to psychotherapy.

Similar to adults, children with subsyndromal depressive disorders, that are long-standing and often associated with anhedonia and negativity, may have dysthymic disorder. Dysthymia in children and adolescents is manifested by chronically depressed mood for at least 1 year, in association with a change in appetite (too little or too much), a sleep disturbance (insomnia or hypersomnia), low energy, easy fatigability, low self-esteem, indecisiveness, poor concentration, and feelings of hopelessness.[25] Juveniles with dysthymia are often self-critical and feel easily criticized or rejected. Although dysthymic disorder is a major risk factor for future episodes of MDD,[207] juveniles with dysthymia have fewer melancholic symptoms and thoughts of suicide. In contrast to adults, children and adolescents must manifest their symptoms for at least 1 year rather than 2 years.[176]

Updates on Antidepressant-Associated Suicidality

Patients with MDD, both adult and pediatric, may experience worsening of their depression, suicidal thoughts, and behavior, regardless of whether they are taking antidepressants. Antidepressants may also cause emergence of suicidality during initial treatment. The controversial issue of SSRIs causing suicidal behaviors is not new.[208] On the one hand, a 2003 analysis of a large FDA database (N = 48,277 patients) failed to show any increase in suicide rates for patients treated with SSRIs.[209] On the other hand, analysis of nine pooled studies (three for depression) of paroxetine treatment in pediatric patients showed that

1.5 to 3.2 times as many patients on paroxetine as on placebo described severe mood changes, including suicidal ideation (www.medicines.mhra. gov.uk). As a result, in June 2003 the FDA recommended that paroxetine not be used for the treatment of depression in patients younger than 18 years of age.

The next study analyzed more than 4100 pediatric patients pooled from 24 placebo-controlled trials for eight drugs (citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine). It showed that about 2 out of every 100 pediatric patients became more suicidal on placebo. On antidepressants 4 out of every 100 pediatric patients became suicidal—an additional 2 per 100 patients. Although no one committed suicide in these studies, the FDA issued a black box warning[210] for all antidepressants in children to raise public awareness regarding the potential of increased suicidality based on this data in October 2004.

A more recent *Journal of the American Medical Association* analysis (Apr 18, 2007)[211] covered data on 5310 children and teenagers from 27 studies, including 7 that were part of an FDA review in 2004 that led to the black box warning. The researchers found that for every 100 children treated with antidepressants, only approximately 1 more child experienced worsening suicidal feelings above what would have happened without drug treatment in contrast to the FDA analysis that found an added risk affecting about 2 in 100 patients.

The FDA changed their black box label in 2007[212] on the basis of its pooled analysis of placebo-controlled trials in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 short-term trials of 9 antidepressant drugs in more than 4400 patients). This analysis showed that among youth younger than 18 years of age, antidepressant treatment led to 14 additional cases of suicidality per 1000 patients. Among 18- to 24-year-olds, antidepressant treatment led to 5 additional cases of suicidality per 1000 patients. Among 25- to 64-year-olds, antidepressant treatment led to 1 fewer case of suicidality per 1000 patients. Among those 65 years old, antidepressant treatment led to 6 fewer case of suicidality per 1000 patients.

The TADS 2004 Study (Treatment of Adolescents with Depression Study) sponsored by the NIMH compared the effectiveness of fluoxetine, CBT, and placebo in the treatment of adolescents with MDD.[213] It showed that although a number of adolescents started the study with suicidal thoughts, there was a significant reduction in the incidence of such thoughts with treatment. The reduction was most marked in the adolescents who received a combination of medication and therapy.

A study published in the *Archives of General Psychiatry* in October 2003[214] showed an inverse relationship between regional change in the use of antidepressants in individuals 10 to 19 years of age and the incidence of completed suicide. In other words, if the area showed an increase in the use of antidepressants, there was a decrease in the incidence of completed suicides.

Lastly, it is unknown whether the suicidality risk extends to longer-term use (i.e., beyond several months). However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.[210] All patients being treated with antidepressants for any indication should be monitored appropriately and observed for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial 1 to 2 months of a course of drug therapy or whenever the dose is increased or decreased.

Pharmacotherapy

Prescription of antidepressants for children and adolescents has increased dramatically in recent years.[215–218] However, this increase must be put into the context of the prevalence of pharmacologically responsive depression in this population.[219] Fortunately, research investigating the safety, tolerability, and efficacy of antidepressants in juveniles has expanded significantly.

Tricyclic Antidepressants Versus Selective Serotonin Reuptake Inhibitors

Initial studies of the pharmacotherapy of pediatric depression focused on the use of TCAs.[220] Despite solid methodology, thorough assessment, diagnosis, and treatment-controlled trials of TCAs in children and adolescents with depression have demonstrated a minimal advantage of TCAs over placebo. Because pediatric depression appears refractory to treatment with TCAs, researchers have investigated the safety, tolerability, and efficacy of the SSRIs. Currently, SSRIs appear to be the medications of choice for the treatment of pediatric depression and dysthymia.[187,221,222]

FDA-Approved Treatments for Pediatric Major Depressive Disorder

Fluoxetine

As a result of two large, double-blind, placebo-controlled trials that demonstrated the short-term safety, tolerability, and efficacy of fluoxetine, it was the first FDA-approved medication for the treatment of MDD in children and adolescents between 7 and 17 years of age.[223–225] In the first trial (single site, NIMH-sponsored), 583 subjects with MDD were screened and 96 randomized to either placebo or fluoxetine (20 mg). With use of the primary outcome measures of reduction on Childhood Depression Rating Scale (CDRS) scores, by week 5 fluoxetine separated from placebo. By the end of the study period, 56% (N = 27) of the fluoxetine-treated patients and 33% (N = 16) of the placebo-treated patients were rated as "much" or "very much" improved on the Clinical Global Impression (CGI) scale. Response rates were similar in adolescents and latency-age children, as well as in males and females. Although patients responded well to the treatment, only 31% of the fluoxetine-treated patients achieved full remission, compared with 23% of placebo-treated patients. Lifetime co-morbidities with anxiety disorders (N = 54, 55%), dysthymia (N = 34, 35%), ADHD (N = 29, 30%), and ODD (N = 29, 30%) were common in this sample.

In the second trial (multisite, industry-sponsored), 420 pediatric subjects with MDD were screened and 219 randomized to either placebo (N = 110) or 20 mg of fluoxetine (N = 109). In this sample co-morbidity with ADHD (N = 31,

14%), oppositional defiant disorder (ODD) (N = 34, 16%), CD (N = 4, 2%), and anxiety disorders (none reported, and baseline HAM-A scores in clinically insignificant range) appeared relatively low. Compared with patients randomized to placebo, patients treated with fluoxetine showed significant reductions in CDRS scores as early as the first week of treatment and they were maintained on the treatment throughout the 9 weeks of the trial. Although significantly more fluoxetine-treated patients achieved remission (41.3% versus 19.8%; $p < 0.05$), based on the predefined definition of response (> 30% reduction in CDRS scores) the percentage of patients responding to fluoxetine was not significantly different than placebo (65.1% versus 53.5%; p = .093). Compared with placebo, fluoxetine treatment was associated with significantly greater improvements in CGI severity (52.3% vs. 36.8%; p = 0.028) scores. The most common side effect observed with fluoxetine treatment was headache, although difficulty paying attention and dizziness were also commonly reported.

Since our last edition, the TADS study (Treatment of Adolescents with Depression Study) compared the effectiveness of fluoxetine, CBT, and placebo in the treatment of adolescents with MDD.[213] It involved 439 adolescents with moderate to severe depression. The teens were randomly assigned to receive medication alone, placebo pills alone, CBT alone, or a combination of medication and CBT. The rates of improvement were 34.8% for placebo, 43.2% for therapy alone, 60.6% for medication alone, and 71% for the combination of medication and psychotherapy. Those on medication alone or psychotherapy alone did not do significantly better than those on placebo. However, the adolescents on medication alone did significantly better than those who received psychotherapy alone.

Escitalopram

In March 2009 escitalopram became the second antidepressant to be approved by the FDA for the acute and maintenance treatment of MDD in adolescents 12 to 17 years of age. Escitalopram was approved on the basis of data from two flexible-dose, placebo-controlled trials that each lasted 8 weeks. One trial was conducted in children and adolescents (6 to 17 years of age) and compared escitalopram with placebo.[226] Only in a *post hoc* analysis of adolescent (12 to 17 years of age) completers, but not in the primary (last observation carried forward) analysis of all participants, escitalopram significantly improved Childhood Depression Rating Scale-Revised (CDRS-R) scores compared with placebo.

The other trial was conducted in children and adolescents 7 to 17 years of age; the difference using CDRS-R was significant beginning at week 1 through week 8 between placebo (24%) and citalopram (36%) at week 8. The greatest benefit was observed in the adolescent group.

Two additional flexible-dose, placebo-controlled MDD studies—one with escitalopram in patients 7 to 17 years of age and one with citalopram in adolescents—failed to demonstrate a significant benefit in the primary end point.

Non-FDA-Approved Treatments for Pediatric MDD

On the basis of results of large controlled trials, other SSRIs appear to be efficacious in the treatment of pediatric depression.

Sertraline

Wagner and associates reported on pooled results of two 10-week (industry-sponsored multisite) double-blind, placebo-controlled trials of sertraline for pediatric depression.[227] In this protocol 377 outpatients (177 children 6 to 11 years of age and 189 adolescents 12 to 17 years of age) were randomized to treatment with placebo or sertraline. Based on a 40% decrease in the adjusted CDRS-R total score at study end point, 69% of sertraline-treated patients compared with 59% of placebo patients were considered responders ($P = .05$). Although generally well tolerated, sertraline treatment was associated with higher rates of diarrhea, vomiting, anorexia, and agitation. In an open trial of sertraline in depressed adolescents (N = 53), Ambrosini and associates[228] observed significant improvements in efficacy (measured using various rating scales) by ensuring adherence to the prescribed dose of sertraline between weeks 6 and 10. These results suggested that in clinical practice the acute phase of treatment for depression in adolescents should extend for at least 10 weeks.

Citalopram

Wagner and colleagues[229] also reported on the efficacy of citalopram in the treatment of MDD in children and adolescents. In this trial 174 pediatric patients (83 children 6 to 11 years of age and 91 adolescents 12 to 17 years of age) were randomized in a double-blind manner to treatment with either placebo or citalopram. Citalopram was initiated at 20 mg and increased to 40 mg after 4 weeks if clinically indicated. In patients treated with citalopram, significant reductions in mean CDRS-R scores were observed by week 1 ($p < 0.02$) and maintained thorough the end of the study (week 8, $p < 0.04$). By the end of the study, significantly more patients treated with citalopram responded compared with those taking placebo (36% vs. 24%; $p < 0.05$). Patients treated with citalopram more commonly reported nausea, influenza-like symptoms, and rhinitis.

Fluvoxamine

Although well studied in pediatric anxiety disorders,[230] we are not aware of any controlled trials that have investigated the efficacy of fluvoxamine in the treatment of pediatric depression.

Paroxetine

An early report compared the efficacy of paroxetine, imipramine (Tofranil), and placebo in the treatment of adolescent depression. In this 8-week, double-blind, placebo-controlled, parallel design trial, 425 adolescents (12 to 17 years of age) were screened and 275 randomized (93 to paroxetine, 95 to imipramine, and 87 to placebo). Co-morbidity with anxiety disorders (N = 73, 26.5%) and externalizing disorders (i.e., ADHD, ODD, and CD) (N = 71, 25.8%) commonly were observed in this cohort. Paroxetine was started at 20 mg per day, which could have been titrated up to 30 mg at week 5 and to 40 mg at weeks 6 to 8. Imipramine was initiated at 50 mg and titrated up weekly to a target dose of 200 mg per day (but which could have been increased to 250 mg at week 5 or 300 mg during weeks 6 to 8 as clinically indicated). Although paroxetine was associated with significant improvements in CGI scores, it did not separate from imipramine or placebo on

the total score of the primary outcome measure (Hamilton Rating Scale for Depression-17 item [HAM-D-17]). However, the HAM-D-17 was designed for adult patients, and it may not be the best way to measure change in adolescent depression. For this reason most current trials in pediatric depression use the CDRS-R to measure medication effect.[221] Nearly half of the paroxetine-treated patients were maintained on 20 mg per day. The most frequent side effects observed in the paroxetine-treated group included dry mouth, nausea, dizziness, insomnia, somnolence, and headache. Although 11 paroxetine-treated patients experienced serious adverse events, including emotional lability (N = 5), conduct problems or hostility (N = 2), worsening depression (N = 2), euphoria and expansive mood (N = 1), and headache during discontinuation (N = 1), investigators believe that only the discontinuation-related headache was directly related to paroxetine treatment.

Venlafaxine

Several other antidepressants are used in juvenile depression. Venlafaxine (Effexor) possesses both SSRI and noradrenergic properties. Venlafaxine is effective in refractory adult depression and may be useful in the treatment of juvenile mood disorders and children with ADHD that is co-morbid with their depression. The adverse effect profile of venlafaxine is similar to that of the SSRIs, except for significant nausea that can be reduced by using very low doses for the first 1 to 2 weeks. Venlafaxine also led to an increase in diastolic blood pressure, pulse, and skin problems.[231] Venlafaxine did not show benefit over placebo in one published trial, although low doses (75 mg per day) were used.[232]

Bupropion

Bupropion hydrochloride is a novel antidepressant with noradrenergic and dopaminergic properties. Bupropion may be helpful in children with prominent mood lability, dysthymia, and co-morbid ADHD.[114] Similar to the management of ADHD (discussed previously), bupropion should be started between 37.5 to 75 mg per day of the immediate-release preparation or 100 mg of the sustained-release preparation and titrated upward as necessary, eventually converting to the extended-release preparation for compliance and full-day coverage. The major side effects in children include insomnia, possible exacerbation of tics, and the theoretical risk of seizures with the short-acting preparation. Bupropion should not be used in patients with bulimia. No blood monitoring is required.

Mirtazapine

Results of a recent controlled trial of mirtazapine (Remeron) showed little difference in response between mirtazapine and placebo in a controlled study of juveniles with depression. Anecdotal reports and clinical experience suggest that mirtazapine may be helpful in patients with ADHD who benefit from treatment with a stimulant but who suffer from insomnia and anorexia.

Nefazodone

Although open trials[233] and a small case series[234] of nefazodone (Serzone) showed promise, results of a 15-site double-blind, placebo-controlled trial only approached statistical significance over placebo in adolescents with depression.[235] At this time, given concerns over hepatotoxicity and the availability of many alternative medications with demonstrated efficacy, the role of nefazodone in the treatment of pediatric depression is limited.

Pharmacokinetics of Antidepressants in Children and Adolescents

Although the main pharmacodynamic effects of SSRIs are similar, the SSRIs are structurally dissimilar to one another and vary in their pharmacokinetics and drug interactions. The SSRIs inhibit specific hepatic isoenzymes and thereby increase the serum levels of other compounds. In the medical setting, treatment with antidepressants may produce clinically significant medication interactions. Parents and clinicians should be aware that SSRIs may interact with antibiotics, especially the macrolide derivatives that are currently being used on pediatric patients. Clinicians need access to updated databases on medication interactions and current references.[236]

Fluoxetine is a racemic mixture that is metabolized to its active metabolite, norfluoxetine. Both fluoxetine and norfluoxetine are substrates of CYP 2C9, 2C19, 3A4, and 2D6. Both fluoxetine and norfluoxetine are potent inhibitors of 2D6 and therefore may increase the levels of medications that are metabolized through 2D6 (e.g., certain antidepressants, antipsychotics, analgesics, calcium channel blockers, β-blockers, dextromethorphan, and ATMX). Wilens and co-workers[237] recently reported on the pharmacokinetics of fluoxetine and its major metabolite, norfluoxetine, in 10 children (6 to 12 years of age) and 11 adolescents (12 to 17 years of age). In this open-label study, patients received fluoxetine 20 mg per day. Mean steady states of fluoxetine and norfluoxetine were achieved, on average, within 4 weeks, although high between-patient variability was observed. Furthermore, on average, children accumulated higher amounts of fluoxetine (twofold) and norfluoxetine (1.7-fold) compared with adolescents. Accumulation of fluoxetine and norfluoxetine in adolescents was similar to the profile for adult patients. The clinical implications of this finding are that most children should be started on fluoxetine 10 mg per day.

Sertraline, which is produced as the S-enantiomer and metabolized to its active metabolite desmethylsertraline, is both a substrate of 2B6, 2C9, 2C19, 2D6, and 3A4. Both sertraline and desmethylsertraline are modest inhibitors of 2C9, 2C19, and 3A4. Case reports have shown that sertraline increases the concentration of phenytoin, pimozide, warfarin, cyclosporine, and diazepam. Sertraline is known to inhibit glucuronidation, and it has been reported to cause toxic levels of lamotrigine. Levels of sertraline may be reduced by adjunctive analgesic agents, such as carbamazepine and phenytoin.[236] Axelson and associates recently studied the pharmacokinetics of sertraline in adolescents.[238] They observed that the mean steady state half-life of sertraline 50 mg per day was significantly shorter than the single-dose half-life (15.3 ± 3.5 hours versus 26.7 ± 5.2 hours; $p < 0.001$) and the mean steady state half-life of 100 to 150 mg per day of sertraline (20.4 ± 3.4 hours). These authors suggested that adolescents may need doses greater than 50 mg per day to achieve a therapeutic response for

depression. Similarly, Axelson and associates studied the pharmacokinetics of sertraline in 29 children (6 to 12 years of age) and 32 adolescents (13 to 17 years of age). These investigators found that during treatment with sertraline 200 mg per day, the T_{max} (14.6 ± 16.1 vs. 10.8 ± 8 hours) and half-lives of sertraline (26.2 ± 8.4 versus 27.1 ± 8.2 hours) and its main metabolite desmethylsertraline (78.5 ± 50.6 versus 75.4 ± 37.1 hours) were similar in children and adolescents, respectively. These results also demonstrated that a single dose of sertraline 50 mg and a steady state dose of sertraline 200 mg per day led to a significantly increased C_{max} and an area under the curve (AUC) in children, compared with adolescents or adults. However, when these pharmacokinetic parameters were normalized for body weight, no significant differences were observed. These results suggest linear pharmacokinetics of sertraline in pediatric patients across the dose range of 50 to 200 mg per day, and the authors concluded that sertraline can be safely used within the adult dosage schedule.

Paroxetine is an S-enantiomer that is a substrate of 2D6 and, to a lesser degree, 3A4. Paroxetine has no significant metabolites, is a potent inhibitor of 2B6 and 2D6, and is a mild inhibitor of 1A2, 2C9, 2C19, and 3A4. Co-administration of paroxetine with substrates of 2D6 (e.g., antidepressants, antipsychotics, analgesics, calcium channel blockers, β-blockers, antiarrhythmics), or 2B6 (e.g., bupropion, nicotine, sertraline, diazepam, tamoxifen) is likely to increase levels of the substrate.[236] Findling and colleagues[239] studied the pharmacokinetics of paroxetine in 30 children and adolescents with MDD. The mean steady state half-life of paroxetine was 11.1 ± 5.2 hours, with tremendous interindividual variation. Urinary excretion of paroxetine correlated with cytochrome 2D6 activity. These authors concluded that paroxetine is metabolized more rapidly in pediatric patients than in adults.

Citalopram (CIT), a racemic mixture of R and S-citalopram (S-CIT), is demethylated via 2C19, 2D6, and 3A4. It is a mild inhibitor of 2D6, but in general it has few medication interactions. Reis and co-workers,[240] using data from two trials, studied the pharmacokinetics of CIT in 44 patients younger than 21 years of age who were treated naturalistically with a mean dose of CIT 30 mg per day. As in adults, large interindividual variability in levels of serum CIT and its main metabolite desmethylcitalopram (DCIT) and didesmethylcitalopram (DDCIT) were observed in these adolescents. The mean serum half-life of CIT was 36 hours. These authors found that the pharmacokinetics of CIT was influenced by gender, smoking status, the menstrual period, and treatment with oral contraceptives. The active enantiomer S-CIT has recently become available as Lexapro. Like CIT, it has few medication interactions.

Fluvoxamine (Luvox) is a substrate of 2D6 and 1A2, which has no significant metabolites. It is described as a pan-inhibitor because it is a potent inhibitor of 2B6, 2C9, and 3A4 and a mild inhibitor of 2D6. When adding any medication to fluvoxamine, clinicians should be cautious.[236]

The profiles of the pK for novel antidepressants have been reported as well. Bupropion (Wellbutrin or Zyban) is mainly metabolized by 2B6 to its main metabolite hydroxybupropion. Bupropion acts as a modest inhibitor of 2D6. Although smoking does not affect the pK profile, co-administration with paroxetine, sertraline, or other 2B6 inhibitors may cause interactions. Stewart and associates[241] examined the single-dose pK profile of bupropion SR (150 mg) in 75 adolescents (13 to 18 years of age). These investigators found no differences in the pK profile between smokers and nonsmokers; however, girls in this sample had an increased C_{max}, $t_{1/2}$, and AUC for both bupropion and hydroxybupropion.

Findling and associates[233] studied the pK profile of nefazodone (NEF) in 28 patients (N = 15 children, 7 to 12 years of age, and N = 13 adolescents, 13 to 16 years of age) treated for MDD. NEF is metabolized primarily by CYP 3A4 to at least three active metabolites: hydroxynefazodone (OH-NEF), triazoledione, and metachlorophenylpiperazine (mCPP). Formation of mCPP is dependent on CYP 2D6 activity. Although the pK profile showed significant variability, the C_{max} and AUC in children was observed to be greater than in adolescents and the serum half-life increased with increased dosage ($t_{1/2}$ 1.9 hours after first dose, 2.7 hours after 1 week, and 4.1 hours after 1 week on 100 mg twice per day). The pK profile for adolescents approximated that seen in adults. Substantial increases in concentration of mCPP were observed in the five patients (two children and three adolescents) considered poor metabolizers of CYP 2D6. A recent case series (two adults and one adolescent) described liver failure in three patients treated with NEF.[242] All patients developed jaundice and encephalopathy and showed prominent necrosis in the centrolobular area. One patient recovered without transplantation, one died after transplantation, and one underwent successful transplantation. In response to these cases, the FDA added a black box warning to NEF's labeling. The FDA warning reported liver failure that resulted in death or transplant in 1 per 250,000 to 300,000 patient years of NEF treatment (see www.fda.gov/medwatch/SAFETY/2002/ Serzone_deardoc.PDF). The FDA warning recommended not starting NEF in patients with active liver disease or with elevated baseline serum transaminases. The FDA further advised that patients should be educated about the signs of liver dysfunction, and NEF should be discontinued in patients who develop an elevated serum AST or ALT level. In May 2004 Bristol-Myers Squibb discontinued the sale of Serzone in the United States and Canada. Several generic formulations of NEF are still available.

Clinical Use of SSRIs

Given the likelihood of relatively similar efficacy, selection of an SSRI should take into consideration tolerability (e.g., side-effect profile), anticipated medication interactions, half-life (e.g., potential for bipolar switching), and adherence.[194] Whereas paroxetine, fluoxetine, citalopram, escitalopram, and sertraline may be associated with agitation and increased energy, fluvoxamine appears to be more sedating and can be useful in children with sleep difficulties associated with mood symptoms. SSRIs should be initiated at low doses (e.g., 5 to 10 mg fluoxetine, 12.5 to 25 mg sertraline, 5 to 10 mg citalopram, 2.5 to 5 mg escitalopram, 5 to 10 mg paroxetine, 12.5 to 25 mg fluvoxamine, and 18.75 to 37.5 mg venlafaxine) and titrated upward slowly.[222] Like fluoxetine, sertraline, paroxetine, and citalopram, escitalopram is now available as an elixir. Contrary to previous beliefs, adolescents typically develop depression before the onset of heavy tobacco use (which is associated with the

development of depressive symptoms).[243] Clinicians should consider directing adolescents with MDD and tobacco use to appropriate anti-smoking programs. Once an antidepressant response is obtained, patients and their families often benefit from encouraging adherence to prevent relapse; however, the ideal length of treatment in pediatric patients requires further study. After treatment is completed (typically 6 to 12 months after remission), the SSRIs should be slowly tapered, to prevent both a discontinuation syndrome and recurrence of symptoms. Patients and their families need education regarding the monitoring of future depressive episodes.

Treatment Nonresponse

Only approximately 60% of adolescents with depression will show an adequate clinical response to an initial treatment trial with an SSRI. The latest study of options after nonresponse to an SSRI, TORDIA,[231] evaluated the relative efficacy of four treatment strategies in adolescents who continued to have depression despite adequate initial treatment with an SSRI. This randomized controlled trial of 334 patients 12 to 18 years of age with a primary diagnosis of MDD that had not responded to a 2-month initial treatment with an SSRI was conducted at six U.S. academic and community clinics from 2000 to 2006. For adolescents with depression not responding to an adequate initial treatment with an SSRI, the combination of CBT and a switch to another antidepressant resulted in a higher rate of clinical response (54.8%; 95% confidence interval [CI], 47%-62%) than did a medication switch alone (40.5%; 95% CI, 33%-48%; p = .009). However, a switch to another SSRI was just as efficacious as a switch to venlafaxine (47.0%; 95% CI, 40%-55% *versus* 48.2%; 95% CI, 41%-56%; p = .83) and resulted in fewer adverse effects (increase in diastolic blood pressure and pulse, skin problems).

Side Effects and Complications

In general, SSRIs are well tolerated and have fewer side effects than TCAs, especially when taken in overdose. Common adverse effects of SSRIs include manic activation, agitation, gastrointestinal symptoms, irritability, insomnia, sexual dysfunction, and weight loss.[222,244] Whereas paroxetine, fluoxetine, citalopram, and sertraline may be associated with agitation and increased energy, fluvoxamine appears to generate sedation and is useful in children with sleep difficulties associated with mood symptoms. In approving fluoxetine for the treatment of juvenile depression and OCD, the FDA expressed concern that fluoxetine-treated patients may grow more slowly than patients treated with placebo (1.1 cm in height and 2 lb in weight) over a 19-week interval. Similarly, a small case series described slowing of growth during treatment with either fluoxetine (20 to 80 mg per day) or fluvoxamine (50 to 100 mg per day) in four Middle Eastern patients with TS or OCD.[245] Although these agents have been used for almost 15 years in juveniles without detection of significant effects on growth, clinicians should consider alternative treatments if a patient's height or weight inexplicably decelerates. Given the lack of CV effects with SSRIs, monitoring of vital signs and ECG does not appear necessary unless there is an additional medical concern.[5,246] Similarly, no specific blood monitoring appears necessary in children receiving SSRIs. Although it has not been well studied, Walkup summarized clinically relevant complications of SSRI pharmacotherapy in children and adolescents.[247] Activation, which is distinguished from a change in mood or impulse control, may be related to either akathisia, hyperactivity, or disinhibition; it usually responds to lowering of the dose. Signs of mania (which may include impulse dyscontrol, mood swings, grandiosity, hypersexuality, and aggression) may be observed and accompany bipolar switching. Treatment of mania relies on pharmacologic approaches. Celebration may occur in SSRI-treated anxious children who experience relief of their anxiety; they may seem impulsive or uninhibited. Developmental issues may be observed as anxiety or depression lifts, after which additional co-morbidities become evident (e.g., ADHD or Asperger's syndrome). Frontal lobe–type symptoms may appear and be manifested primarily by apathy. Gastrointestinal symptoms are very common, as noted previously. Adolescents prescribed SSRIs may experience sexual side effects, although reports of these side effects are minimal in controlled studies in this population.

Like adults, children may experience a discontinuation syndrome as they are tapered off SSRIs or if they miss their scheduled dose. Typically, this syndrome occurs among those taking SSRIs with shorter half-lives (e.g., paroxetine or venlafaxine), although it can occur with any antidepressant.[248] As in adults, the discontinuation syndrome is typically characterized by physical symptoms (e.g., nausea, gastrointestinal disturbance, diarrhea, dizziness, insomnia, lightheadedness, headache, shakiness, and sensations of a mild electrical shock), cognitive symptoms (e.g., confusion, poor memory, cloudiness, and forgetfulness), and emotional symptoms (e.g., increased crying, mood lability, and anxiety).[249] Patients and parents should be educated about the discontinuation syndrome, and steps should be taken to prevent its occurrence (including the use of SSRIs when necessary, encouraging adherence, tapering SSRIs gradually, and ensuring that the manufacturer of the medication stays the same throughout treatment if a patient is taking a generic preparation).[250] When patients experience a discontinuation syndrome, reintroducing the medication usually provides relief, although some patients may need to be switched to an SSRI with a longer half-life. A discontinuation syndrome has also been described as leading to a more complicated course of illness. In their review of the literature, Ali and associates[251] noted that antidepressant withdrawal in general, and SSRI withdrawal in particular, appears to increase the risk of mania in adults with BPD. The authors postulated either noradrenergic hyperactivity or cholinergic overdrive as the possible underlying pathophysiology.

Bipolar Disorder

Pediatric BPD is a relatively recent phenomenon in the modern child psychiatry landscape. NIMH recognized pediatric mania in 1995, 20 years after pediatric depression. There has been a growing awareness of the existence of pediatric BPD, a childhood symptom complex reminiscent of adult BPD.[252–254] The AACAP and the NIMH have convened round-table meetings, and the AACAP has issued practice parameters regarding the evaluation, diagnosis,

management, and research of pediatric BPD.[255–257] It is common for many children and adolescents with BPD to seek medical attention in emergency departments or develop severe, out-of-control symptoms during medical hospitalizations. Children may also be referred to PCPs for unremitting temper tantrums. Prepubertal mania is usually co-morbid with ADHD, and these patients typically present with extreme hyperactivity, impulsivity, and aggression.[258,259] Children with BPD commonly present with an extremely irritable or explosive mood associated with poor psychosocial function; it is often devastating to the child and the family. These children often overreact to minor environmental stressors (mood reactivity). Additional symptoms consistent with mania include grandiosity, unmodulated high energy, decreased need for sleep, over-talkativeness, increased goal-directed and pleasurable activity (e.g., social, work, school, and sexual), and poor judgment (e.g., seeking out reckless activities). Although the juvenile symptom complex of mania should be differentiated from ADHD, conduct disorder, depression, trauma, substance use and abuse, and psychotic disorders, these disorders commonly co-occur with childhood mania.[260] The clinical course of juvenile mania is most frequently chronic and mixed with co-occurring manic and depressive features.[251–264]

Pharmacotherapy

Until recently, lithium was the only FDA-approved drug for the treatment of BPD in children 12 years of age and older. In 2007 the FDA approved the use of risperidone (Risperdal) for acute treatment of manic or mixed episodes of bipolar I disorder in children 10 to 17 years of age. In 2008 the FDA approved aripiprazole (Abilify) for acute treatment of manic or mixed episodes associated with BPD (type I) in pediatric patients between the ages of 10 and 17.

Unfortunately, early-onset BPD appears less responsive to lithium.[265,266] Therefore children and adolescents with BPD are often treated with combinations of lithium, anticonvulsants, and atypical antipsychotic mood stabilizers.[267,268] If the patient does not respond to an adequate trial (in dose and time) of a single agent or cannot tolerate the medication, subsequent trials with alternative medication(s) are recommended. In manic or mixed presentations, with psychotic symptoms, additional antipsychotic treatment is recommended. In BPD with prominent symptoms of depression, combined treatment with a mood stabilizer and an antidepressant is indicated. Clinicians must be wary of the potential destabilizing effects of SSRIs in the treatment of bipolar depression in children and adolescents.[268] Recent data indicate that the management of BPD with or without co-morbid disorders (depression and ADHD) may require an aggressive treatment approach that combines several therapeutic agents.

Lithium

The use of lithium carbonate in BPD and treatment-resistant unipolar depression appears helpful; surprisingly, it has not been studied under controlled conditions. The usual starting dose of lithium ranges from 150 to 300 mg per day in divided doses, two or three times per day. Weller and co-workers[269] published dosage guidelines for lithium in children 6 to 12 years of age, suggesting the initial total daily doses (administered three times per day) of 600 mg per day for patients weighing less than 25 kg, 900 mg for patients weighing 25 to 40 kg, 1200 mg per day for patients weighing 40 to 50 kg, and 1500 mg per day for patients weighing 50 to 60 kg. There is no known therapeutic serum lithium level in children. Based on the adult literature, serum levels of 0.8 to 1.5 mEq/L for acute episodes and levels of 0.4 to 0.8 mEq/L for maintenance therapy are suggested. Although lithium is commonly used in pediatric patients with BPD, only one prospective well-controlled study has been conducted. In this small but seminal study, Geller and colleagues[270] found that treatment with lithium both improved global functioning and reduced frequency of positive urine drug screens among adolescents with BPD co-morbid with substance abuse.

Common short-term adverse effects of lithium include gastrointestinal symptoms (e.g., nausea, vomiting), renal symptoms (e.g., polyuria, polydipsia), and CNS symptoms (e.g., tremor, sleepiness, memory impairment).[271] Short-term adverse effects associated with the use of lithium are generally dose-related. The incidence of toxicity increases directly with increased serum levels, and symptoms respond favorably to dose reduction. It is important to monitor a child's hydration status because lithium induces mild dehydration that, when more severe, may lead to toxic accumulation of lithium. It is therefore prudent to consider withholding or reducing lithium doses in children who are dehydrated or who have experienced prolonged vomiting. The chronic administration of lithium may be associated with metabolic (e.g., substantial weight gain and decreased calcium metabolism), endocrine (e.g., decreased thyroid functioning), dermatologic (e.g., acne), cardiac, and renal dysfunction. Thus it is necessary that children be screened for renal function (e.g., blood urea nitrogen, creatinine), thyroid function (e.g., thyroid-stimulating hormone), ECG, and calcium level before lithium treatment is started and that these tests be repeated every 6 months. Female patients should undergo a pregnancy test and be educated about the dangers of lithium exposure during pregnancy. Particular caution should be exercised when lithium is used in patients with neurologic, renal, or CV disorders.

Alternative antimanic medications for children and adolescents include anticonvulsants.

Carbamazepine

Carbamazepine, approved for treatment of pediatric seizures (e.g., psychomotor, grand mal) and trigeminal neuralgia, is structurally related to the TCAs. Carbamazepine is not FDA-approved for the treatment of pediatric mania; however, anecdotal reports and some studies support its consideration.[272–274] Although carbamazepine may be useful, worsening behavior during treatment has been reported.[275]

Carbamazepine induces its own metabolism, which is usually complete after 3 to 5 weeks on the medication. Carbamazepine has many medication interactions,[236] induces the metabolism of substrates of 3A4 (e.g., haloperidol, phenytoin), and may reduce levels of valproic acid and increase lithium levels by reducing lithium clearance. Inhibitors of 3A4 (e.g., erythromycin) may increase levels of carbamazepine. The plasma half-life after chronic administration is between 13 and 17 hours. The therapeutic plasma concentration is variably reported as 4 to 12 µg/mL,

and recommended daily doses in children range from 10 to 20 mg/kg, administered twice per day. Because the relationship between the dose and the plasma level is variable and uncertain with marked interindividual variability, plasma level monitoring is recommended. Common short-term side effects include dizziness, drowsiness, nausea, vomiting, and blurred vision. Idiosyncratic reactions (e.g., bone marrow suppression, liver toxicity, and skin disorders [including Stevens–Johnson syndrome]), have been reported but are rare. However, given the seriousness of these reactions, careful monitoring of blood counts and liver and renal function is warranted initially and during treatment.

Oxcarbazepine

Oxcarbazepine (Trileptal) appears to have fewer reports of medication interactions and adverse effects (e.g., less effect on bone marrow and skin). However, minimal data are currently available regarding its efficacy in pediatric BPD. Its only RCT in manic or mixed BPD (type I) children (7 to 18 years of age) was negative.[276] Clinicians who prescribe it should monitor for hyponatremia and be aware that it can induce the metabolism of ethinyl estradiol.

Valproic Acid

Valproic acid (VPA) is an anticonvulsant that is FDA-approved for the acute and maintenance treatment of BPD in adults; by extension, it may be useful in the treatment of juvenile BPD. However, the evidence for VPA in childhood BPD has been mixed at best.

In an 18-month double-blind, placebo-controlled study of youths 5 to 17 years of age with bipolar I or II disorder initially treated with lithium and divalproex until in remission for 4 weeks, divalproex alone was equal to lithium alone in survival time until emerging symptoms of relapse or survival time until discontinuation for any reason.[277] In a prospective 6- to 8-week randomized, open trial, Kowatch and colleagues[274] compared the efficacy of lithium, carbamazepine, and VPA in 42 children and adolescents with BPD I or II. Using improvements in scores on CGI and Young Mania Rating Scale (> 50% change from baseline), these investigators observed response rates of 38% with carbamazepine, 38% with lithium, and 53% with VPA ($\chi 2$ = 0.85, p = 0.60). In the initial open phase of another trial, Wagner and co-workers[278] reported that 22 of 40 patients with BPD (55%) experienced more than 50% improvement in the Mania Rating Scale (YMRS) during open treatment with VPA in doses of 15 to 17 mg/kg per day. Finally, in the double-blind, placebo-controlled trial of divalproex ER in 150 pediatric patients (manic or mixed episode, 10 to 17 years of age), there was no differences in efficacy on primary or secondary measures or incidence of adverse events.[279]

VPA is primarily metabolized by the liver; it has a plasma half-life of 8 to 16 hours and a therapeutic plasma concentration of 50 to 100 µg/ml. Recommended initial daily doses are 15 mg/kg per day that are gradually increased to a maximum of 60 mg/kg per day, administered three times a day. Common short-term side effects include sedation, thinning of hair, anorexia, nausea, and vomiting. Idiosyncratic reactions (e.g., bone marrow suppression and liver toxicity) have been reported but appear to be rare. Asymptomatic elevations of serum glutamic oxaloacetic transaminase usually resolve spontaneously. Although fatalities resulting from hepatic dysfunction have been reported in children younger than 10 years of age with monotherapy, these have occurred primarily in children younger than 2. The risk of serious hepatic involvement is increased by concomitant use of other anti-seizure medications and may be dose-related. Careful monitoring of blood counts and liver and renal function are warranted initially and during treatment. Hyperammonemia has been reported, and depending on clinical impression, monitoring ammonia levels may be appropriate.

Atypical Antipsychotics

Increasingly, the atypical antipsychotic medications (including clozapine [Clozaril], olanzapine [Zyprexa], quetiapine [Seroquel], risperidone [Risperdal], ziprasidone [Geodon], and aripiprazole [Abilify]) are being used in the management of pediatric BPD. These medications differ from "typical" antipsychotics (e.g., chlorpromazine and haloperidol) in their receptor profile (D_2 blockade and the fact that they affect multiple other receptors, including serotonin), reduced likelihood of causing EPS, reduced likelihood of causing hyperprolactinemia (the exception is risperidone), and a greater benefit on the negative symptoms of psychosis and on cognition.[280] Whenever these medications are used, patients and families should be informed about the potential for side effects, including EPS, akathisia, neuroleptic malignant syndrome, and TD and dystonias. Although the risk of developing TD is lower with the atypical medications, the rate of occurrence is unknown. Patients treated with antipsychotic medications should be monitored regularly with the Abnormal Involuntary Movement Scale (AIMS) examination.

Risperidone

Risperidone is FDA-approved to treat pediatric mania.[281] Risperidone is usually initiated at 0.25 mg once or twice per day and titrated up to 3 to 4 mg per day in most pediatric patients, although it appears to retain its atypical properties in doses up to 6 mg per day. Its common adverse effects include weight gain, sedation, drooling, and elevation of prolactin levels. Although EPS is not common, clinicians should be aware of this possibility and recognize it when it occurs. Like adults, children and adolescents with EPS can be treated with oral or IM diphenhydramine or benztropine. Although pK studies in children are lacking, data in adults indicates that risperidone reaches peak concentrations within 1 hour, is metabolized through CYP 2D6, and has a half-life of 3 hours in extensive metabolizers and 17 hours in poor metabolizers.[282] There are case reports of hepatotoxicity, tachycardia, prolongation of the QTc interval, and stroke (in elderly patients).

Aripiprazole

Aripiprazole (Abilify) was FDA-approved for manic and mixed states in pediatric BPD I in 2008. Aripiprazole appears to have mixed agonist–antagonist properties and is described as a "dopamine/serotonin stabilizer." It has a long half-life and does not appear to cause significant interactions with other medications that are metabolized through the P450 system. It can cause akathisia. It is usually started at 2.5 to 5 mg per day and titrated to 10 to 15 mg per day (up to 30 mg/day in adult trials).

Olanzapine

Olanzapine is currently FDA-approved for acute and maintenance treatment of BPD in adults.[283] Frazier and co-workers[284] openly treated 23 children with BPD (5 to 14 years of age) with olanzapine for 8 weeks.[284] Of the 23 patients who completed this study, 61% responded (defined as more than 30% reduction in YMRS). These patients also experienced significant reductions in depressive symptomatology. The major side effects of olanzapine were sedation and weight gain (mean = 5 kg), although EPSs were not observed. In some patients the weight gain outweighed clinical benefits and necessitated switching to an alternative treatment, although in some patients the weight gain remained stable. In adults on atypical antipsychotics, hyperglycemia, new-onset diabetes, and diabetic ketoacidosis (50% occurred in those without weight gain) have been observed during treatment.[285,286] Olanzapine is available in injectable, tablet, and Zydis (melts on the tongue) forms. Olanzapine is typically initiated at 2.5 to 5 mg and can be titrated up to 20 mg. Olanzapine is metabolized, by way of glucuronidation (primary) and oxidation via CYP 1A2.[236] Grothe and colleagues[287] studied the pK of olanzapine in adolescents, observing a mean serum half-life of 37.2 ± 5.1 hours; boys and smokers metabolized it more rapidly.

Quetiapine

DelBello and associates[288] published results of an open trial that added quetiapine to VPA in the treatment of 30 adolescents with BPD. In this trial patients were treated openly with VPA (20 mg/kg) and then randomized to adjunct therapy with either placebo or quetiapine (titrated up to 450 mg per day). The group receiving the combination treatment showed significantly greater response rate (reductions in YMRS scores) compared with the VPA and placebo group. The patients receiving VPA and quetiapine experienced greater sedation and weight gain.

The pK of quetiapine has not been formally studied in children and adolescents. Data from adult studies indicate that quetiapine is readily absorbed from the gastrointestinal tract and reaches peak concentrations 1.5 hours after ingestion. It is metabolized primarily in the liver by CYP 3A4 and does not appear to be affected by gender, smoking, or race.[282] Occurrence of EPS appears low, but quetiapine can cause dizziness, sedation, and weight gain.

Ziprasidone

The atypical antipsychotic ziprasidone (Geodon) may also be used in the treatment of pediatric BPD. As of this writing, however, there is limited data regarding its efficacy for BPD in this population. Ziprasidone may increase QTc intervals, and thus before use obtaining a baseline ECG and family history of cardiac problems (especially early-onset arrhythmia) is wise. Although ziprasidone is primarily metabolized through aldehyde oxidase, it is also metabolized in part via CYP 3A4. Co-administration of ziprasidone with medications that may also lengthen the QTc interval (e.g., thioridazine, pimozide, droperidol, class IA and III antiarrhythmics) is not recommended. In children and adolescents, ziprasidone is initiated at 10 to 20 mg per day or twice per day and can be increased upward to 40 to 60 mg twice per day.

Additional treatments in pediatric BPD that are reasonable to consider but have little data to support their use include use of alternative anticonvulsants.

Alternative Anticonvulsants

Gabapentin (Neurontin) is approved as an adjunct therapy for seizures. It is not significantly metabolized in humans and has few medication interactions.[289] Trials with gabapentin for BPD in adults have been negative; however, it has reduced anxiety.

Lamotrigine (Lamictal) is an anticonvulsant that was recently approved in the maintenance treatment of BPD type I in adults. Lamotrigine's labeling contains a boxed warning that serious rashes, including Stevens–Johnson syndrome, occur in approximately 1% of patients younger than 16 years of age. The risk for rash seems to increase if lamotrigine is increased too quickly, the initial dose is greater than recommended, or it is administered with VPA. Mandoki[290] reported on a case series of 10 pediatric patients with BPD treated with VPA (500 to 1500 mg per day) without an adequate response. Lamotrigine (50 to 200 mg per day) was added to VPA, with significant improvement. The role of lamotrigine in treatment of pediatric BPD remains unclear.

Topiramate (Topamax) is an antiepileptic that has shown promise in treatment of BPD in adults.[291] Its only RCT in children with mania or mixed state bipolar I disorder (N=56; ages 6 to 17) was negative.[290] In trials with epilepsy, topiramate was associated with weight loss; however, it also can cause word-finding difficulties, oligohidrosis, and renal stones.[289] Topiramate has a half-life of approximately 24 hours, is excreted unchanged in the urine, and inhibits carbonic anhydrase as well as CYP 2C19.

Investigations into the phenomenology, diagnosis, and pharmacotherapy of pediatric BPD continue. Current guidelines support using pharmacotherapy in the context of an overall multimodal treatment plan.

Developmental Disorders

The term *developmental disorders* includes mental retardation (MR), pervasive developmental disorders (PDDs) (e.g., autism, Asperger syndrome), and specific developmental disorders previously called *learning disabilities* (e.g., nonverbal learning disability).[292] MR diagnosis requires impairment in intellectual function (e.g., IQ below 70) and deficits in at least two adaptive skill areas with onset before age 18. At any given time, approximately 1% to 3% of the population meet the diagnostic criteria for MR.[293,294] PDD symptoms develop before the age of 30 months and involve unusually restricted behaviors with impaired development of social skills (e.g., reciprocal interactions), communication skills (e.g., idiosyncratic language), and sensory–motor skills (e.g., hyporeactivity and hyperreactivity to sensory stimulation).[292] Children who have normal language and cognitive development but impaired social development (e.g., problems with social cues, few friends, oddities), may have Asperger syndrome.[295] Individuals with developmental disorders are at an increased risk of seizure disorders, hearing loss, and other medical co-morbidities.

Mental Retardation

In general, the treatment of specific developmental disorders is largely remedial and supportive. Although psychotropics can temporarily control behavioral and psychiatric complications in some children with developmental disorders, they have not been shown to affect the cardinal symptoms and the basic course of the underlying disorders. For example, in a multicenter double-blind, placebo-controlled trial of children with MR and disruptive behaviors, Aman and associates[296] demonstrated that treatment with risperidone (6 weeks of 0.02 to 0.06 mg/kg per day) led to reduced aggression and irritability. Common side effects included somnolence, headache, and weight gain (mean = 2.2 kg).

If the child with a developmental disorder also meets diagnostic criteria for ADHD or a mood disorder, the guidelines described for the treatment of these disorders are applicable. For example, stimulants appear generally well tolerated and effective in reducing symptoms of hyperactivity and impulsivity in patients with MR.[295,297]

Pervasive Developmental Disorders

Children with PDD often have aggressive, hyperactive, repetitive, and self-injurious behaviors that may respond to pharmacologic treatment. In October 2006 the FDA approved the use of risperidone for the symptomatic treatment of irritability (including aggression, deliberate self-injury, and temper tantrums) in children and adolescents with autism.[298] To date, four RCTs of risperidone in children with PDD have demonstrated moderate and clinically significant benefits in behavioral control, including disruptive and repetitive behaviors, hyperactivity, and self-injury.[299–303] Social and language impairments were only slightly modified by treatment, although results differed among studies. Open trials with a variety of atypical antipsychotics, including olanzapine[304] and ziprasidone,[305] have similarly shown promise in modulating maladaptive behaviors in patients with developmental delay.

A number of alternative pharmacologic agents, in addition to antipsychotics, are being employed for complications or co-morbidities of developmental disorders. Considering the relatively low toxicologic profile of these drugs compared with the antipsychotics, they are the preferred treatment for the management of these children. β-blockers (e.g., propranolol) may improve self-regulation in patients with developmental disorders and thus reduce agitation, aggression, and self-abusive behaviors.[306,307] Propranolol is usually given in divided doses throughout the day. Treatment is typically initiated at 10 mg twice per day and increased as clinically indicated. The dose range is 2 to 8 mg/kg per day. Short-term adverse effects of propranolol are usually not serious and generally abate when the drug is decreased or stopped. Nausea, vomiting, constipation, and mild diarrhea have been reported. Psychiatric side effects appear to be relatively infrequent but can occur; symptoms include vivid dreams, depression, and hallucinations. Propranolol's capacity to induce β-adrenergic blockade can cause bradycardia, hypotension, and an increase in airway resistance. Thus it is contraindicated in patients with asthma and certain cardiac conditions. Because abrupt cessation of this drug may be associated with rebound hypertension, a gradual taper is recommended. In a similar manner, clonidine, lofexidine and buspirone have been used to diminish aggression in patients with developmental disorders.[308–311]

For children with prominent obsessive behavior, rigidity, or compulsive rituals, recent studies indicate that the SSRIs may be helpful. In many cases, the full antidepressant dosage (discussed later) is necessary; however, children should be started with the lowest possible dose to prevent adverse effects such as disinhibition or agitation. Controlled trials in adults treated with fluoxetine[312] and fluvoxamine[313] have shown positive results. However, studies in children have been less robust. The long-acting benzodiazepines may also be useful as single or adjunctive agents in children with prominent anxiety symptoms, although a major adverse effect, disinhibition, may result in restlessness and more disturbed behavior.

Antidepressants and mood-stabilizers may be effective in controlling affective disorders, and stimulants may improve symptoms of ADHD when these disorders co-exist.

In response to an initial positive report, great interest and study has focused on secretin.[314,315] However, of the 10 controlled studies that have been conducted, 8 demonstrated no benefit of secretin over placebo, regardless of the form of secretin (biological versus synthetic),[316] following single-dose[317] or ongoing administration of secretin.[318] Despite mostly negative data for secretin, many parents elected to continue its use. At this time the role of secretin appears limited at best.

PSYCHOTIC DISORDERS

The term *psychosis* is generally used to describe the abnormal behaviors of children with grossly impaired reality testing.[319] The diagnosis of psychosis requires the presence of either delusions (false implausible beliefs) or hallucinations (false perceptions that may be visual, auditory, or tactile). Often, psychosis in children is seen with MDD, BPD, or severe dissociative states, such as PTSD. Psychotic disorders in children, as in adults, can be functional or organic. Functional psychotic syndromes include schizophrenia and related disorders and the psychotic forms of mood disorders. Organic psychosis can develop secondary to CNS lesions as a consequence of medical illness, trauma, or drug use. Children may manifest psychosis for a substantial amount of time without indicating its presence to parents or caregivers. Therefore all children with major mood disorders or those who have manifested abnormal or bizarre behaviors should be queried for the presence of psychosis.

Currently, the atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole), are first-line agents in the pharmacotherapy of psychosis in children and adolescents. In 2007 the FDA approved risperidone for treatment of schizophrenia in children 10 to 17 years of age.

Typically, atypical antipsychotics are initiated at a low dose and gradually titrated up to achieve efficacy. Risperidone is started at 0.25 mg twice a day and can be increased every day or two with close observation.[320] In patients treated over the long term with risperidone, clinicians should monitor weight, vital signs, and laboratory results (e.g., triglyceride, cholesterol, prolactin).[321,322] Olanzapine and quetiapine are generally more sedating and

are initiated at 2.5 to 5 mg per day and 25 to 50 mg per day, respectively.[323] Olanzapine has recently been investigated in two open studies in pediatric patients with schizophrenia.[324,325] Significant improvements were observed in children and adolescents; however, these patients experienced significant weight gain and sedation.

If trials with two or three atypical antipsychotics are ineffective, a trial with a typical agent (e.g., chlorpromazine, haloperidol) should be considered. The usual oral dosage of antipsychotics ranges between 3 and 6 mg/kg per day for the low-potency phenothiazines (e.g., chlorpromazine) and between 0.1 and 0.5 (up to 1) mg/kg per day for the high-potency antipsychotics (e.g., haloperidol). Antipsychotic medications have a relatively long half-life and therefore should not be administered more than twice daily.

Common short-term adverse effects of antipsychotics are drowsiness, increased appetite, and weight gain. Anticholinergic effects (e.g., dry mouth, nasal congestion, blurred vision) are more commonly seen with the low-potency phenothiazines. Short-term adverse effects of antipsychotics are generally managed with adjustments of the dose and the timing of administration. Excessive sedation can be avoided by using less sedating agents and prescribing most of the daily dose at nighttime. Drowsiness should not be confused with impaired cognition; it can usually be corrected by adjusting the dose and the timing of administration. In fact, there is no evidence that antipsychotics adversely affect cognition when used in low doses. Anticholinergic adverse effects can be minimized by choosing a medium- or high-potency compound.

Acute dystonia, akathisia (motor restlessness), parkinsonism (bradykinesia, tremor, and lack of facial expressions), and other EPSs are more commonly seen with the high-potency compounds (butyrophenones and thioxanthenes) and have been reported to occur in up to 75% of children receiving these agents. The extent to which antiparkinsonian agents (e.g., anticholinergic drugs, benztropine, trihexyphenidyl, antihistamines, the antiviral agent amantidine) should be used prophylactically when antipsychotics are introduced is controversial. Whenever possible, antiparkinsonian agents should be used only when EPS emerge. Akathisia may be particularly problematic in young patients because it is often underrecognized. When a child or adolescent starts on an antipsychotic and becomes acutely agitated with an associated inability to sit still and with aggressive outbursts, the possibility of akathisia should be considered. If this condition is suspected, it may be necessary to lower the dose of the antipsychotic. The centrally acting β-adrenergic antagonist propranolol often is very helpful in treating this adverse effect.

A benign withdrawal dyskinesia and a syndrome of deteriorating behavior have been associated with the abrupt cessation of these drugs. As in adults, the long-term administration of antipsychotic drugs may be associated with TD. Although children appear generally less vulnerable than adults to developing TD, there is an emerging consensus that this potentially worrisome adverse effect may affect children and adolescents in 10% to 15% of cases. Prevention (appropriate use for a clear indication, clear target symptoms, periodic drug discontinuation to assess the need for drug use) and early detection (with regular monitoring) are the only effective treatments for TD.

Little is known about the potentially lethal neuroleptic malignant syndrome in juveniles; however, preliminary evidence indicates that its presentation is similar to that in adults. This syndrome may be difficult to distinguish from primary CNS pathology; concurrent infection; or other, more benign side effects of antipsychotics that include EPS or anticholinergic toxicity. Treatment appears similar to those strategies used in adults.

In patients who do not respond to trials with either first-line atypical or typical antipsychotics or who experience significant dyskinesia from these medications, consideration should be given to a trial with clozapine (Clozaril).[326,327] In the United States and Europe, there has been considerable experience with clozapine in adolescents. Established dose parameters are not yet available; however, in one open study of clozapine for schizophrenic youths, doses from 125 to 825 mg per day (mean = 375 mg per day) for up to 6 weeks were necessary for effectiveness. Although remarkably effective in chronic treatment-resistant schizophrenia and affective psychosis, there is a dose-related risk of seizures and an increased risk of leukopenia and agranulocytosis in adolescents that is similar to the risk in adults; it requires close monitoring.

COMBINED AGENTS

Increasingly, multiple agents have been used in both clinical practice and research settings for the treatment of child and adolescent psychiatric disorders. This need has arisen out of an emerging awareness of the high rates of co-morbidity described in clinical and epidemiologic studies of juvenile psychiatric disorders. Previously, the law of parsimony dictated a single cause for each symptom complex; this led to the use of large doses of individual agents for a given disorder, often resulting in intolerable adverse effects. In contrast, the use of combined pharmacotherapy has permitted more targeted treatment and greater efficacy, often achieved with lower doses and fewer adverse effects.

Fluoxetine and MPH, for instance, have been described as useful in the management of children with depression and ADHD.[328] In addition, controlled investigations of single agents have produced inconclusive findings in many disorders. Enhanced response rates have been reported when traditional agents are combined. For example, improved anti-ADHD efficacy has been shown with the combination of stimulants and TCAs. Interest is growing in trials combining ATMX and stimulant pharmacotherapy for ADHD.

On the other hand, growing use of combined pharmacotherapy in children has drawn intense attention from the media and regulatory agencies.[329,330] On balance, rational use of combined psychotropics may produce significant benefits in the hands of experienced clinicians. It has become imperative for future research to provide clinicians with the evidence base for combined-agent pharmacotherapy.

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36 Behavioral Medicine

Brian A. Palmer, M.D., M.P.H.
Lisa Scharff, Ph.D.
Bruce J. Masek, Ph.D.

The field of behavioral medicine, now 30 years old, began when applied behavior analysis, behavior therapy, and psychophysiology emerged as clinical sciences. The field's inception drew inspiration from other sources, notably a vision of the limitations of the biomedical model, the value associated with the recognition that behavioral factors broaden our understanding of health and illness,[1] and dissatisfaction with the long-standing dominance of the psychoanalytic approach in psychosomatic medicine.[2]

Behavioral medicine was initially viewed in broad terms as an interdisciplinary field concerned with the development of knowledge in the behavioral sciences and techniques relevant to prevention, diagnosis, treatment, and rehabilitation of physical illness.[3] It grew rapidly in the 1980s. By the end of that decade, curricula in behavioral medicine were found in most medical schools and graduate programs in clinical psychology, and clinical units and research programs in behavioral medicine were operational in most major universities and medical centers. Even a few academic departments changed their names to incorporate *behavioral medicine* into their titles.[4] Thus, the stage was set in the 1990s for the pursuit of a scientific agenda that was ambitious and broad in scope to identify behavioral factors that influence the development and course of organic disease, to develop psychosocial interventions that reduce the effect of these behavioral factors, and to demonstrate that such psychosocial interventions improve clinical outcomes in organic disease through direct effects on the underlying pathology.[5]

Just how good is the clinical evidence from the past quarter century with respect to these propositions? Many believe that the evidence supports the notion that behavioral factors are involved in the development and course of most major diseases, and that psychosocial interventions effectively reduce the risk of illness, decrease morbidity and mortality, and improve health-related quality of life.[6–10] However, a minority views the same evidence as the product of seriously, if not fatally, flawed studies.[11–13] Both sides seem to agree that the mind can influence the body to the betterment or the detriment of one's health and that some of the evidence is worthy of further scrutiny in large-scale prospective, rigorously controlled clinical trials with hard biological end points.[14]

Currently, behavioral medicine still draws heavily on the theory and practice of applied behavioral analysis, behavioral therapy, and psychophysiology for interventions to modify the risk, course, and effect of organic disease. Stress, negative emotions, lifestyle, and quality of life among other factors are frequent targets for interventions. Clinical topics under the umbrella of behavioral medicine have expanded over the last 2 decades,[9] reflecting advances in biomedical science (e.g., organ transplantation), changing public health priorities (e.g., HIV/AIDS treatment and prevention), and innovative applications of existing technologies (e.g., aging). For those readers interested in a comprehensive review of the evolution of the field, a special issue of the *Journal of Consulting and Clinical Psychology*[15] is an excellent source.

The goals of this chapter are more modest. We present an overview of clinically important psychosocial factors that mediate both health and illness and discuss the most frequently employed interventions used in behavioral medicine to modify their impact. We conclude with an examination of behavioral medicine's role in the management of two very common clinical problems, irritable bowel syndrome and recurrent abdominal pain, to provide perspective on the practice of behavioral medicine in a hospital setting.

PSYCHOSOCIAL FACTORS AFFECTING HEALTH AND ILLNESS

Stress

Stress has been implicated directly or indirectly in the development and clinical course of a host of physical ailments, from the common cold[16] to coronary heart disease (CHD).[17] Stress is thought to play an important role in the development and maintenance of risk factors for organic disease, such as smoking, obesity, and physical inactivity.[18] The view that stress is ubiquitous and that it has harmful effects on the body's organ systems and defenses has infiltrated the public's consciousness. This view has been succinctly summed up as "a mania for pop psychosomatics, which writes off to stress everything from athlete's foot to cancer" (p. 739).[19]

From a clinical perspective the pathologic effects of stress are of concern. In susceptible individuals, chronic and persistent exposure to stressors, be they real (physical) or perceived (psychological), lead to a dampening of homeostatic mechanisms that restore internal stability and defend against disease.[20] As homeostatic mechanisms become less effective or break down completely under

the pressure of chronic stress, susceptible individuals are subject to exacerbations of existing illnesses or are predisposed to new diseases. The outcome of pathological stress depends on a variety of factors (including the type of stressor, the length of exposure, one's genetic predisposition, preexisting coping strategies, and the presence of social and environmental supports).[21] Behavioral medicine's answer to stress is a collection of techniques known as stress management. These techniques teach patients to lower levels of stress arousal, particularly in stressful social environments, and to enhance the relaxation response.

Negative Emotions

Interest in how emotional states affect health and illness is probably as old as medicine itself. Negative emotional states may be precursors to organic disease as suggested by recent studies of CHD[15] and essential hypertension.[22] Moreover, morbidity and a decreased quality of life are often seen in association with chronic pain disorders[23] and with cancer.[24]

Negative emotions (such as anger, sadness, and pessimism) are part of the human condition and are not necessarily harmful to health. The damaging effects are thought to occur when these emotions are expressed in their chronic forms: hostility, depression, and helplessness, respectively. Interventions used in behavioral medicine for negative emotional states have focused on the development of cognitive coping skills to replace the maladaptive thoughts, feelings, and behaviors that are the basis of negative emotional states.

The Relaxation Response

One strategy to counter the physiologic effects of stress is to employ the relaxation response. The relaxation response is induced by various forms of meditation, yoga, tai chi, breathing exercises, and guided imagery, to name a few,[25] and is associated with a number of physiologic changes (from decreased pulse and respiratory rate, to specific gene expression changes in short- and long-term practitioners).[26] Functional magnetic resonance imaging (fMRI) studies indicate that the practice of meditation induces the relaxation response and activates neural structures involved in attention and the control of the autonomic nervous system.[27] Instruction in the relaxation response combined with cognitive restructuring, exercise, and enhanced nutrition has been shown to reduce both physical and psychological symptoms in somatizing patients.[28]

Mindfulness meditation reduces anxiety and increases positive affect.[29–31] During an 8-week training program, mindfulness meditation was associated with an increase in antibody titers to flu vaccine and an increase in left frontal activation on electroencephalogram (EEG) as compared with wait-listed controls.[32]

RISK FACTORS

Nonadherence with Medical Therapy

Nonadherence with medical therapy occurs throughout the life span, and there is little doubt that low rates of adherence to established medical therapies contribute to increased morbidity, increased health care costs, and adverse consequences for public health.[33,34] A meta-analysis of 63 studies examining adherence and treatment outcome suggests that adherence is most strongly related to outcome in nonmedication regimens for treating chronic disease.[35] Many theories explain why some patients are nonadherent with diagnostic maneuvers and treatment. Belief in the efficacy of treatment, complexity of medical regimens, passive self-care decision-making, and problems with doctor–patient communication are some of the reasons put forth to explain why some patients fail to follow through with prescribed medical therapy.[36] Behavioral medicine interventions are based on the premise that nonadherence is a behavioral problem that is particularly suited to applied behavioral analysis methods that aim to modify overt behavior. The patient's beliefs about health and illness and the doctor–patient relationship are not considered relevant targets for intervention. The behavioral procedures of reinforcement and stimulus control have proven to be effective for the improvement of adherence from simple to complex medical regimens.[37] For example, in a study of refractory hypertension, one third of the sample achieved normalization of blood pressure simply through electronic monitoring.[38]

BEHAVIORAL MEDICINE INTERVENTIONS

Stress Management

The goal of stress management is to teach patients skills that relieve them from the harmful effects of stress. First, patients must learn to identify thought patterns and social situations that produce stress. Second, patients are taught relaxation techniques that cultivate low states of arousal. A host of relaxation techniques exist; none has been proven to be more therapeutic than any other for stress reduction. Some of the most commonly taught techniques are progressive muscle relaxation, deep breathing, imagery, and meditation. To become skilled in relaxation, patients must practice these techniques daily for 3 to 4 weeks. It is most helpful to provide patients with a CD version of the relaxation instructions that facilitates adherence with practice at home. Children as young as 7 years old can learn relaxation techniques.[39] The final step to prevention involves guiding patients in the use of relaxation techniques in their natural environment, replete with stressful stimuli.

Biofeedback is sometimes used to help patients learn about relaxation techniques. Immediate feedback about muscle tension, heart rate, surface skin temperature, and respiration can facilitate the learning process, particularly for patients who present with high levels of arousal, who harbor skepticism about the approach, or who doubt their ability to learn relaxation.

Cognitive Coping

Cognitive coping involves teaching a patient to identify negative thoughts and behaviors that increase their stress burden and the situations where stress occurs. Cognitive distortions (e.g., all-or-none thinking, overgeneralization, discounting the positives, jumping to conclusions, "should" statements, and personalization) are identified for and with the patient, and (negative) automatic thoughts and

core beliefs ("I am incompetent") are evaluated in light of evidence that supports and refutes them. Then, positive coping strategies (e.g., positive reappraisal, diverting attention, problem-solving, coping self-statements, disengagement, and relaxation techniques) are taught to replace negative patterns. Rehearsal of coping strategies during therapy sessions is critical for the successful application in the natural environment. Patients are encouraged to start using coping strategies at the first opportunity. Self-monitoring tools (such as diaries and checklists) are used first to assess maladaptive coping and then to monitor progress and to refine coping strategies as needed.

Behavioral Procedures

One of the most effective techniques to improve adherence is to provide feedback to patients on their adherence early in the course of therapy when they are most at risk for developing patterns of nonadherence. Objective measures of adherence (e.g., serum drug levels, urine metabolites, or physiological markers [e.g., blood glucose level or measures of pulmonary function]), when feasible, are the feedback methods of choice in this regard.[40] Positive and negative reinforcement are often employed to promote adherence with treatment regimens that extend over long periods. Positive reinforcement is the process by which rewards (e.g., parking vouchers, gift certificates, and negotiated privileges) are provided to the patient contingent on observed or objectively measured adherence at specified intervals. Negative reinforcement is the converse process by which patients lose the opportunity to earn money or privileges if they are nonadherent; they must remain adherent to avoid this possibility. Stimulus–control techniques include teaching patients to self-monitor adherence behaviors, to structure their medical therapy to have it occur while performing daily routines, and to enlist the social environment to generate external cues for adherence (e.g., a telephone call, e-mail, or postcard reminder).

Motivational Interviewing

Motivational interviewing is an empirically-supported intervention to improve outcome by strengthening patient commitment for behavior change.[41] The approach combines patient-directed and patient-centered methods to selectively reinforce the patient's self-motivational statements to take action.[42,43]

CLINICAL APPLICATIONS

Irritable Bowel Syndrome and Recurrent Abdominal Pain

A strong, documented relationship exists between stress and abdominal pain. Most people are familiar with the sensation of "butterflies" in the stomach when facing stress, and when bad news is delivered it can be referred to as "a kick in the stomach." Individuals with irritable bowel syndrome (IBS) or its childhood counterpart, recurrent abdominal pain, almost unanimously endorse stress as a trigger of their symptoms. Abundant and growing research evidence reveals that IBS and recurrent abdominal pain may be related to autonomic nervous system function and to an increased sensitivity to physiologic changes in the gut that are also highly responsive to stress.

Behavioral medicine treatments have been highly effective for IBS and recurrent abdominal pain[44,45]; they usually involve relaxation training to activate the parasympathetic nervous system and cognitive techniques to decrease the effects of stress on the body. Education is crucial to the process, because a patient needs to understand the rationale for treatment to be invested in it. Biofeedback training can also be a useful strategy; patients can receive immediate feedback and learn that they can have a significant amount of control over their own bodies. Finally, self-hypnosis has also been used successfully as a pain management strategy that can be integrated into a pain management program.

EDUCATION

Patients with IBS or recurrent abdominal pain frequently report that they have gotten the message from health care providers that their pain is "in their head." Often the explanation for pain provided by a family physician or gastroenterologist is designed to comfort a patient and to emphasize that no organic cause for the pain can be found; therefore, there is no disease process to worry about. What the patient often hears instead is a dismissal of the pain as not being real or as a statement that the doctor cannot be of help with their suffering. One of the significant contributions that behavioral medicine has made in the treatment of stress-related disorders is to focus on the importance of communicating with patients. Simply validating the pain, providing education about the physical effect of stress, and explaining that there are skills that can be learned to manage stress and pain can be extremely beneficial. A shift in perception from being a victim to having options (i.e., to take more control) can be an important first step in the management of chronic pain.

Of course, patients must believe in the efficacy of treatment and in their ability to do what it takes to be successful in the treatment (self-efficacy); one must be motivated to participate. Moreover, the extent to which individuals believe that what they do influences their health (internal locus of control) versus the extent to which they believe health care professionals or others influence their health (external locus of control) varies greatly. For a behavioral medicine intervention to work well, the individual needs to be invested in the work and involved in the treatment program.

RELAXATION TRAINING

Stress triggers of IBS or recurrent abdominal pain initiate activity in the sympathetic nervous system and affect multiple physiologic activities (including digestion, breathing, and heart rate). The cultivation of a state of low arousal by activating the parasympathetic nervous system is antithetical to this aroused state: one simply cannot be stressed and relaxed at the same time. Relaxation training is designed to teach parasympathetic arousal during times of stress, so symptoms of pain and resultant bowel function can be reduced or even eliminated. As reviewed earlier in this chapter, many types of relaxation training are available.

COGNITIVE COPING SKILLS

Cognitive treatments for IBS and recurrent abdominal pain tend to focus on the identification of stressful situations that may lead to symptoms, on examination of the thoughts or "internal dialogue" that takes place in these situations, and appreciation of how to change the stressful situation itself, the reaction to the situation, or both. Usually the focus is specifically aimed at stressful situations that can lead to episodes of pain. The symptoms themselves or worries about them can also be significant stressors. Individuals with diarrhea-predominant IBS, for example, often state that concerns about being far from a bathroom and worries about being able to access a bathroom when needed can trigger an episode of pain and diarrhea.

BIOFEEDBACK

Biofeedback can aid relaxation training and allow patients to gain insight into their own ability to control different aspects of their bodies. Many individuals who suffer from pain can become distanced from their bodies and lack insight as to what relaxation feels like. They can be taught, however, what relaxation looks like on a monitor, and learn through this method what they need to do in order to achieve that state.

Several types of biofeedback have been used with IBS patients. Thermal biofeedback is often used because it assesses a generalized relaxation response. A thermal sensor is applied to the finger, and relaxation techniques are employed to relax the muscles and activate the parasympathetic nervous system, thereby allowing an increase in blood flow to the hand with a resultant increase in temperature. Electromyographic biofeedback can also be used to teach relaxation of specific muscle groups. Another type of biofeedback that has been used specifically with IBS patients is bowel sound feedback, during which a stethoscope is used to teach patients to change their bowel sounds. No studies have investigated the efficacy of thermal or electromyographic biofeedback alone for IBS or recurrent abdominal pain, and most treatments incorporate elements of other behavioral medicine strategies. Evidence in support of bowel sound feedback as a treatment for IBS has been mixed.

Hypnosis

Hypnosis can be a very powerful and useful technique when put to use by a trained and experienced clinician. Because the use of hypnotic trance and suggestion tends to focus on changing perceptions and directed attention, it is particularly useful when working with patients who have chronic or episodic pain (Table 36–1).

After the induction is taught, specific images and suggestions can be used to induce a state of relaxation. Often "ego-strengthening" suggestions are used to help deepen the trance and allow the patient to focus. Several different types of images and metaphors can then be used to help the patient gain control of his or her symptoms. Images of flowing water in streams or waterfalls can be used as a metaphor for the gastrointestinal tract that is working smoothly, or suggestions of having possession of a switchboard that can be used to manipulate different parts of the body are often used to allow the patient to gain a sense of control over symptoms. As in relaxation training, an audiotape or CD can be made for the patient to practice at home.

TABLE 36–1 Review of Current Evidence from Controlled and Partially Controlled Trials for Medical Applications of Hypnosis[46]

Evidence of Efficacy (Supported by Multiple Randomized Clinical Trials)
Control of cancer pain
Control of labor and childbirth pain
Control of medical procedure–related pain and distress
Reduction of symptoms of irritable bowel syndrome
Improved postoperative outcome in wound healing, anxiety, and vomiting
Obesity (although effects are small)
Possible Evidence of Efficacy (Supported by Poorly Controlled Trials or Mixed Results)
Control of burn pain
Control of pain in terminally ill cancer patients
Reduction of symptoms of asthma
Smoking cessation
Reduction of symptoms of nonulcer dyspepsia
Reduction of symptoms of posttraumatic stress disorder
Reduction of symptoms of tinnitus
Reduction of symptoms of conversion disorder
No Evidence of Efficacy (Negative Controlled Trials)
Schizophrenia
Hay fever
Delayed-type hypersensitivity response

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Complementary Medicine and Natural Medications

37

Felicia A. Smith, M.D.
David Mischoulon, M.D., Ph.D.

Complementary and alternative medical (CAM) therapies constitute a diverse spectrum of practices and beliefs in current medical practice. The National Institutes of Health defines CAM as "healthcare practices outside the realm of conventional medicine, which are yet to be validated using scientific methods."[1] The term *natural medications* refers to medications derived from natural products that are not approved by the U.S. Food and Drug Administration (FDA) for their proposed indication.[2] Natural medications fall under the category of CAM and may include hormones, vitamins, plants, herbs, fatty acids, amino acid derivatives, and homeopathic preparations, among others. Although natural medications have been used for thousands of years, their use in the United States has increased dramatically over the past 10 to 15 years. In fact, a recent study found that in an American ambulatory adult population, 40% of patients routinely used one or more vitamin or mineral supplements.[3] Moreover, between 1990 and 1997, the prevalence of herbal remedy use increased by 380%, and high-dose vitamin use increased by 130%.[4] The consultation psychiatrist must therefore be informed about these medications to provide comprehensive patient care. This chapter provides an overview of the use of natural medications in psychiatry. Issues pertaining to general safety and effectiveness are discussed first, followed by a more specific look at some of the remedies used for mood disorders, anxiety and sleep disorders, menstrual disorders, and dementia. The final section is devoted to a description of two nonmedication alternative therapies: acupuncture and hypnosis.

EFFICACY AND SAFETY

Although there has been a recent increase in both government and industry sponsorship of clinical research involving natural medications, data regarding efficacy still lag behind. The true benefits of natural remedies are often unclear, and few systematic studies have addressed the question of effectiveness.[5] Because the FDA does not routinely regulate natural medications, issues of safety remain unresolved. One concern flows from the belief that if a remedy is "natural," it is therefore safe. Reports of toxicity may not reach the populations using the remedies, because they are often purchased over the counter. Moreover, data are limited regarding the safety and efficacy of combining natural medications, and about their use with more conventional medications.[5] This situation is very important to the consultation psychiatrist because of the prevalence of polypharmacy often seen in inpatient medical settings. It is also noteworthy that patients frequently do not disclose their use of CAM therapies to their physicians. In one study, fewer than 40% of CAM therapies used were disclosed to a physician,[4] thereby making it essential to ask patients specific questions about their use of prescribed and over-the-counter medications. Finally, significant variability exists between different preparations of natural medications. Preparations often vary in purity, quality, and potency, and efficacy and side effects may vary accordingly. As mentioned earlier, government- and industry-sponsored studies are increasingly being undertaken to further elucidate the potential uses, safety, and efficacy of these medications. The remainder of this chapter outlines what is currently known in this regard for a few such natural medications.

MOOD DISORDERS

Omega-3 fatty acids, St. John's wort (SJW), *S*-adenosylmethionine (SAMe), folic acid, vitamin B_{12}, and inositol have all been used for mood disorders. Here we describe the efficacy, possible mechanisms of action, dosing, adverse effects, and drug interactions of each of these medications. Because of the nature of consultation psychiatry, a particular emphasis is placed on the interface between their psychiatric and other medical uses, as well as on drug interactions.

Omega-3 fatty acids are polyunsaturated lipids derived from fish oil that have been shown to have benefits in a variety of health domains including rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, and systemic lupus erythematosus.[6] Cardioprotective effects have been demonstrated, as have several neuropsychiatric benefits. Eicosapentaenoic acid and docosahexaenoic acid are thought to be psychotropically active omega-3 fatty acids.[2] Lower rates of depression and bipolar disorder have been detected in countries where more fish is consumed, suggesting that omega-3 fatty acids may play a protective role in these disorders.[7] Omega-3 fatty acids also may have a role in the treatment of both bipolar disorder and unipolar depression. Close to 20, mostly positive, studies on patients with unipolar depression have been reported.[8] Though efficacy studies of bipolar illness have been more mixed,[9–12] most of the benefit in bipolar illness may be related to alleviating or preventing depression rather than mania.[13] In fact, there have been reports of cycling in bipolar patients who take omega-3 preparations without concomitant mood stabilizers,[14] so caution is warranted when treating bipolar patients. Mixed results have also been shown in the areas of postpartum depression[15–17] and schizophrenia.[18–21]

Although their mechanism of action is not completely clear, omega-3 fatty acids may function the way mood stabilizers do, by inhibiting G-protein signal transduction via reduced hydrolysis of phosphatidylinositol and other membrane phospholipids.[22] Other proposed mechanisms include neuronal membrane stabilization and antiinflammatory effects.[22] Commercially available preparations of omega-3 fatty acids vary in composition, and the optimal ratio of eicosapentaenoic acid to docosahexaenoic acid has yet to be determined. Psychotropically active dosages are generally thought to be in the range of 1 to 2 g/day, with the major side effect being dosage-related gastrointestinal (GI) distress.[8] There is a theoretical risk of increased bleeding, so concomitant use of high-dose nonsteroidal antiinflammatory drugs or anticoagulants is not recommended.[8] In sum, the use of omega-3 fatty acids is promising, particularly given the range of potential benefits and the relatively low toxicity seen thus far. However, larger studies are still needed.

St. John's wort (*Hypericum perforatum* L.) has been shown to be more effective than placebo in the treatment of mild to moderate depression.[14,23] Studies have suggested that SJW is as effective as low-dose tricyclic antidepressants (TCAs) (e.g., imipramine 75 mg, maprotiline 75 mg, or amitriptyline 75 mg).[2,14,23] Data comparing SJW and selective serotonin reuptake inhibitors (SSRIs) are more mixed, although in at least two cases SJW was shown to be as effective as sertraline and fluoxetine in the treatment of mild to moderate depression.[24,25] SJW has not shown a significant advantage over placebo in other studies[26–28]; however, some believe that a more severely depressed study population may have contributed to at least some of these outcomes.[2,5,14] Although hypericin is thought to be the main antidepressant ingredient in SJW, polycyclic phenols, pseudohypericin, and hyperforin are also thought to be active ingredients. Possible mechanisms of action include the inhibition of cytokines, a decrease in serotonin receptor density, a decrease in reuptake of neurotransmitters, and monoamine oxidase inhibitor (MAOI) activity.[2,5] Of note is that SJW should not be combined with SSRIs because of its MAOI activity and the possible development of serotonin syndrome, but no special diet is required for the patient on SJW.[14] The metabolism of SJW is not well understood, but it is thought to be hepatic. Suggested dosages range from 900 to 1800 mg three times per day depending on the preparation, and adverse effects include dry mouth, dizziness, constipation, and phototoxicity. A switch to mania in patients with bipolar disorder may also occur.[14,29] Finally, a number of drug–drug interactions with SJW are particularly noteworthy for the consultation psychiatrist. Because hyperforin induces cytochrome P450 (CYP) 3A4 expression, therapeutic activity of the following medications may be reduced: warfarin, cyclosporine, oral contraceptives, theophylline, digoxin, and indinavir.[2,5,14] Transplant rejections have been reported as a result of interactions between SJW and cyclosporine[14]; therefore, transplant recipients should not use SJW. Individuals with human immunodeficiency virus infection and on protease inhibitors should also avoid SJW because of drug interactions. In conclusion, SJW appears to be better than placebo and equivalent to low-dose TCAs for the treatment of mild depression. It may also perform comparably to SSRIs, but more data are needed. It may not be as effective for more severe forms of depression. Care should be taken because of the drug–drug interactions mentioned earlier.

In dosages of up to 1600 mg/day, SAMe has been shown to elevate mood in depressed patients. Meta-analyses and comprehensive reviews support antidepressant efficacy of SAMe when compared with placebo and TCAs.[30–32] However, many studies have used IM and IV preparations, as well as oral SAMe; early oral preparations of SAMe were unstable and rapid decomposition may have resulted in less robust efficacy findings.[31] Current oral preparations, although tosylated for improved shelf life, may nonetheless require high dosages for adequate bioavailability—in some instances, as much as 2000 to 3000 mg/day; the medication is relatively expensive, and the out-of-pocket cost may be prohibitive to some.[14,31,32]

S-adenosyl-methionine is the principal methyl donor in the one-carbon cycle, and SAMe levels depend on availability of the vitamins folate and B_{12}. SAMe donates methyl groups to hormones, neurotransmitters, nucleic acids, proteins, and phospholipids. Thus, SAMe has been proposed to work as an antidepressant by providing methyl groups in the reactions that result in the synthesis of acetylcholine, serotonin, and dopamine.[33] Potential adverse effects are relatively minor and include anxiety, agitation, a switch to mania, insomnia, dry mouth, bowel changes, and anorexia.[31–33] Sweating, dizziness, palpitations, and headaches have also been reported.[31–33] At least one case has been reported of suspected serotonin syndrome when SAMe was combined with clomipramine in an elderly woman.[34] No significant drug–drug interactions have been reported, and there is no apparent hepatotoxicity.[31–33] SAMe, therefore, is a natural medication that shows promise as an antidepressant. It appears to be relatively safe and is without significant interactions thus far, making it a particularly good candidate for augmentation therapy. One open study thus far has demonstrated benefit from open SAMe augmentation in SSRI partial responders.[35] Further study will help clarify issues of efficacy and safety.

Folate and B_{12}, vitamins obtained in the diet, play important roles in the synthesis of central nervous system (CNS) neurotransmitters (e.g., serotonin, dopamine, and norepinephrine). Sequelae of folate and vitamin B_{12} deficiencies include a variety of neuropsychiatric and general medical conditions (e.g., macrocytic anemia, neuropathy, cognitive dysfunction or dementia, and depression). Folate deficiency may result from inadequate dietary intake, malabsorption, inborn errors of metabolism, or an increased demand (e.g., as seen with pregnancy, infancy, bacterial overgrowth, and rapid cellular turnover).[33,36]

Certain drugs may also cause folate deficiency. These include anticonvulsants, oral contraceptives, sulfasalazine, methotrexate, triamterene, trimethoprim, pyrimethamine, and alcohol.[37] Vitamin B_{12} deficiency states may also result from inadequate dietary intake, malabsorption, impaired utilization, and interactions with other drugs. Included in such drugs are colchicine, H_2 blockers, metformin, nicotine, oral contraceptive pills, cholestyramine, K-Dur, and zidovudine.[37] Folate deficiency may also hinder antidepressant

response,[38] and folate supplementation may be a beneficial adjunct to SSRI-refractory depression.[39] Vitamin B_{12} deficiency, in turn, may cause an earlier age of onset of depression.[2] The recommended daily dosage of vitamin B_{12} is 6 µg, and that of folate is 400 µg. Because both vitamins are involved in the synthesis of CNS neurotransmitters, adequate levels provide optimal neurotransmitter synthesis that may aid in reversing depression. Finally, folate may mask vitamin B_{12} deficiency by correcting macrocytic anemia while neuropathy continues, so vitamin B_{12} levels should be routinely measured when high dosages of folate are given. Folate may also reduce the efficacy of phenytoin, methotrexate, and phenobarbital.[40] In summary, correction of folate and B_{12} deficiencies may improve depression or augment other antidepressant therapy. The recent FDA approval of 5-methyltetrahydrofolate (5-MTHF; Deplin) may present a desirable treatment option for depressed patients; 5-MTHF is thought to penetrate the blood–brain barrier more readily than other folate forms, and it may, in theory, deliver more of the active product to its site of action.[36] Psychiatrists should be mindful of potential deficiency states (as outlined here) and should check serum levels in patients at risk for deficiencies (such as elderly patients, the medically ill, or those who have not responded to antidepressant treatment).

Inositol, a natural isomer of glucose, is present in common foods. It has been found in small studies to be effective in the treatment of depression, panic disorder, obsessive–compulsive disorder, bulimia, binge-eating disorder, and possibly bipolar depression.[41–45] Effective dosages range from 12 to 18 g/day. Negative monotherapy trials with inositol have been run with patients with schizophrenia, dementia, attention deficit hyperactivity disorder, premenstrual dysphoric disorder, autism, and electroconvulsive therapy–induced cognitive impairment.[5,46] Augmentation studies of inositol with SSRIs in patients with depression and obsessive–compulsive disorder have been mostly negative.[47–49] One crossover comparison of inositol against fluvoxamine for panic disorder suggested similar efficacy for both agents.[43] Inositol is a polyol precursor in brain second-messenger systems that may reverse desensitization of serotonin receptors.[2,5] Mild adverse effects include GI upset, headache, dizziness, sedation, and insomnia. There is no apparent toxicity or known drug interactions at this time.[2,5] Treatment with inositol for the indications mentioned here currently appears safe and remains promising.

ANXIOLYTICS AND HYPNOTICS

Three natural agents are often used for their anxiolytic and hypnotic properties: valerian, melatonin, and kava. Valerian *(Valeriana officinalis)* is a sedating plant extract that has been used for over 2000 years. It is thought to promote natural sleep after several weeks of use by decreasing sleep latency and by improving overall sleep quality. The effects on slow-wave sleep increase with time. Valerian is thought to work by decreasing gamma-aminobutyric acid (GABA) breakdown.[2,5] Sedative effects are dosage related, with usual dosages in the range of 450 to 600 mg about 2 hours before bedtime. Dependence has not been an issue, nor has daytime drowsiness. Adverse effects, thought to be uncommon, include blurry vision, GI symptoms, headache, and dystonia. Because of potential hepatotoxicity, valerian should be avoided in patients with liver dysfunction. Major drug interactions have not been reported. Although valerian has been used as a hypnotic for many years (in pediatric and elderly populations as well as adults) with relatively few reported adverse effects, more trials are needed to further quantify efficacy and safety.

Melatonin is a hormone made in the pineal gland that has gained popularity for its use by travelers to avoid jet lag. It is derived from serotonin and is thought to play a role in the organization of circadian rhythms via interaction with the suprachiasmatic nucleus.[50] Melatonin generally facilitates falling asleep within 1 hour, no matter what time of day it is taken. Optimal dosages, although this is controversial, are thought to be in the range of 0.25 to 0.30 mg/day. Some preparations, however, contain as much as 5 mg of melatonin.[2,5] Daytime sleepiness and confusion have been noted with high dosages. Other reported adverse effects include decreased sex drive, retinal damage, hypothermia, and fertility problems. Moreover, melatonin is contraindicated in pregnancy and in immunocompromised patients.[2,5] There are few reports of drug–drug interactions. In conclusion, melatonin is a promising and relatively safe hypnotic, probably best used in people with insomnia secondary to circadian disturbances, and potentially useful in children with sleep difficulties. Caution should be taken in patients at risk, as noted.

Kava *(Piper methysticum)* is derived from a root originating in the Polynesian Islands. Although it is believed to have a mild anxiolytic effect, study results have been mixed. The mechanism of action is attributed to kavapyrones, which are central muscle relaxants involved in GABA receptor binding and norepinephrine uptake inhibition.[2,5] The suggested dosage is 60 to 120 mg/day, with GI upset, headaches, and dizziness being the major adverse effects. Toxic reactions, however, have been seen at high dosages or with prolonged use and include ataxia, hair loss, respiratory problems, yellowing of the skin, and vision problems. Even more worrisome are reports of severe, sometimes fatal, hepatotoxicity, including some requiring liver transplantation.[2,5] For this reason, the FDA has been investigating the safety of kava and has recommended that the duration of use not exceed 3 months. Although kava appears to be somewhat efficacious in the treatment of mild anxiety, current concerns about safety make cautious use essential. It should be used only under a physician's supervision and should be avoided by people who are taking other potentially hepatotoxic drugs or who have a history of recent alcohol abuse or liver disease of any sort.

PREMENSTRUAL AND MENOPAUSAL SYMPTOMS

Black cohosh *(Cimicifuga racemosa)* at a dosage of 40 mg/day has been shown to reduce physical and psychological menopausal symptoms.[51] Active ingredients are thought to be triterpenoids, isoflavones, and aglycones, which may participate in suppression of luteinizing hormone in the pituitary gland.[2,5] Mild side effects include headache, dizziness, GI upset, and weight gain. In the past few years, a few reports have emerged of possible liver toxicity,

convulsions, and cardiovascular problems, although some have argued that these toxicities could not be conclusively linked to black cohosh.[52] Black cohosh is not recommended for individuals who are pregnant or who have heart disease or hypertension. More data are needed to further specify beneficial effects as well as safety profiles.

COGNITION AND DEMENTIA

Ginkgo biloba comes from the seed of the ginkgo tree and has been a part of Chinese medicine for thousands of years. It has generally been used for the treatment of impaired cognition and affective symptoms in dementing illnesses; however, a possible new role has emerged in the management of antidepressant-induced sexual dysfunction.[53] Diminished memory and abstract thinking are target symptoms when used for individuals with dementia. Studies have shown modest but significant improvements, with a dosage of 120 mg/day, in both cognitive performance and social function.[54] Progression of disease may be delayed by 6 to 12 months. Further evidence suggests greater improvement for those with mild dementia and stabilization at most with more severe disease.[55] *Ginkgo biloba* has been proposed to enhance learning capacity, as evidenced by one study of healthy young volunteers who made significant improvements in speed of information processing, executive processing, and working memory when on the medication.[56] The body of evidence as a whole has been mixed,[57–59] however, and a recent systematic review suggests a lack of convincing evidence for acute or long-term benefits in young and healthy people.[60] The active components of ginkgo, flavonoids and terpene lactones, stimulate nerve cells that are still functional,[2,5] which seems to provide protection from pathologic effects such as hypoxia, ischemia, seizures, and peripheral damage. Because ginkgo has been shown to inhibit platelet-activating factor, it should be avoided in those at high risk of bleeding. Other side effects include headache, GI distress, seizures in epileptics, and dizziness. The suggested dosage of *Ginkgo biloba* is 120 to 240 mg/day with at least an 8-week course of treatment. However, full benefit may not be seen for a year. Comparisons between ginkgo and FDA-approved nootropics, based on a few meta-analyses[61] and one head-to-head study of ginkgo versus donepezil in patients with Alzheimer's disease,[62] suggest better tolerability for ginkgo, but somewhat more modest efficacy than cholinesterase inhibitors. In conclusion, *Ginkgo biloba* appears to be a safe and efficacious cognition-enhancing medication. It may also have a role in reducing antidepressant-induced sexual dysfunction, although this evidence is mixed and must be regarded as preliminary.[63] Further studies are needed to fully understand its complete and long-term effects.

Dehydroepiandrosterone (DHEA) is an androgenic hormone synthesized primarily in the adrenal glands, which is converted to testosterone and estrogen.[30] Although study results have been somewhat mixed, DHEA is thought to play a role in enhancing memory and in improving depressive symptoms.[30,64–66] Mechanisms of action may include modulation of *N*-methyl-D-aspartate receptors and $GABA_A$ receptor antagonism.[30] Synthetic DHEA is available in an oral formulation and as an intraoral spray, with dosages ranging from 5 to 100 mg/day. As in many other natural remedies, strength and purity are not regulated. In women, there is a risk for weight gain, hirsutism, menstrual irregularity, voice changes, and headache. Men may experience gynecomastia and prostatic hypertrophy, and the effects on hormone-sensitive tumors are not known.[30] Although early data are promising for DHEA, larger studies must be undertaken to clarify risks versus benefits before it may be safely recommended.

NONMEDICATION THERAPIES

Acupuncture has been used in Eastern countries for several millennia for the treatment of neuropsychiatric disorders, especially pain. Acupuncture is quite safe, with no major adverse events reported in a recent review of over 65,000 treatments.[67] Although some data support its use to treat a wide range of psychiatric disorders, including schizophrenia, bipolar disorder, substance abuse, and mood and anxiety disorders, the lack of an ideal placebo has been a major barrier in establishing its efficacy in Western studies. However, recent findings in the arena of functional neuroimaging may provide a deeper understanding of the role of acupuncture in mediating pain perception.[68] Further study will help elucidate potential neuropsychiatric benefits of this ancient Eastern treatment.

Hypnosis can be defined as "an event or ritual between a hypnotist and an hypnotic subject in which both agree to use suggestion to bring about a change in perception or behavior."[69] Hypnosis is thought to depend on the dissociative and imaginative abilities of the subject, on the motivation of the subject, and on the relationship between the hypnotist and the subject.[69] Mechanisms are unclear, but levels to which a patient can be hypnotized tend to fall on a bell-shaped curve. Although hypnosis may be used for a wide variety of medical and psychiatric conditions, the following disorders often respond better than others: anxiety, pain, asthma, phobias, nausea, vomiting, and bulimia.[69] Contraindications include unwillingness to be hypnotized, a history of paranoia, and an inexperienced hypnotist. Clinicians should exercise caution in patients with posttraumatic stress disorder or dissociative disorders, as hypnosis may precipitate intrusive (or false) memories in a patient who is not ready to confront them.[70] Because hypnosis may be employed at the bedside, it is particularly attractive to the consultation psychiatrist. Finally, hypnosis is a powerful tool when administered by properly trained individuals, and it may be used alone or as an adjunct in the treatment of a wide array of medical disorders.

CONCLUSION

The spectrum of CAM therapies is quite diverse in current medical practice and is gaining significant popularity in the United States. Historical lack of scientific research in this area has contributed to deficiencies in knowledge with respect to safety and efficacy of many of the natural remedies on the market today. A recent surge in funding by government and industry sources should help in this regard. Current knowledge about a few such therapies has been outlined in this chapter, including proposed treatments for mood disorders, anxiety and sleep disorders, menstrual disorders, and dementia. Many of these therapies may

prove to be a valuable addition to the armamentarium of treatments available to psychiatrists in the future. A particular emphasis was placed on potential adverse effects and drug–drug interactions, given the nature of consultation psychiatry. A general knowledge of these therapies and routine questioning about their use is an essential part of comprehensive care by the consultation psychiatrist.

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38 Difficult Patients

Daniel J. Zimmerman, M.D.
James E. Groves, M.D.

The medical equivalent of war is the care of the difficult patient. Doctors soldier steadily on through all kinds of clinical chores, arduous schedules, and "administrivia," but when they get to the types of patients variously called "obnoxious,"[1] "needy," "crocky,"[2] "malignant," and even "hateful,"[3] they fight the worst battles of their careers, become prone to clinical blunders, mess up their personal lives, violate boundaries, and get sued. The good news is that—almost without exception—the "difficult patient" situation makes the consulting psychiatrist more useful to treating physician and patient alike than in any other medical encounter. Harrowing though such situations may temporarily be, it is just this kind of consultation that earns the trust and respect of the physician consultee and generates more consultation requests later on. (And, really, there are few better ways for a psychiatrist starting out to build a practice than by becoming a specialist on care of the difficult patient.) Before turning to management strategies, it is worth reviewing the presentations of difficult patients.

TYPES OF DIFFICULT PATIENTS

Delirious patients may be assaultive. Guilty, bereaved spouses can be litigious. Temporal lobe epileptic patients are often clingy and viscous. Manic patients are emotional cyclones. Celebrities at times generate anxiety in their caregivers. Schizophrenics can be noncompliant. Anyone when ill can become angry, dependent, and hypochondriacal. Somehow none of these difficult situations necessarily produces "difficult patient" scenarios.

Difficult patients are almost always persons with personality disorders—with one exception: Only patients with addictions seem to contradict the difficult-patient-equals-personality-disorder rule (if one includes persons with eating disorders—thinness addicts). There has been a state-versus-trait debate about whether substances elicit a "true" or "underlying" personality *("in vino veritas")* as opposed to the idea of substances sickening or "poisoning" the true self (intoxication, dipsomania). Personality disorders lie closer to trait because they so seldom change much, and addictions and eating disorders lie closer to state because when they do change, the change can be rather dramatic. Every experienced physician can think of a patient with an addiction who was not typically difficult, and occasionally some "really bad actor" goes to Alcoholics Anonymous, gets sober, and a year or two later looks and acts like a real *mensch*. In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, (DSM-IV),[4] personality disorders are defined by clusters of traits, and addictions are states that the substance gives rise to. (For the purposes of management later on in this chapter, however, we will tend to think of excess alcohol as a personality disorder in a bottle.)

Not all patients with personality disorders are difficult patients. Looking at pure types through the lens of DSM-IV, those not necessarily belonging to the difficult patient paradigm are paranoid, schizoid, and schizotypal personality disorders (cluster A); likewise, avoidant, dependent, and obsessive–compulsive personality disorders (cluster C) do not necessarily belong to the difficult patient paradigm. It is not impossible to find the patient with schizotypal or paranoid personality who gets along well with the treating physician. Even the patient with dependent personality—if not angry but merely clinging—can be someone the physician enjoys working with. Although some of these may be difficult patients, it is really when we look into DSM-IV cluster B disorders that a pit of despair opens: antisocial, borderline, and narcissistic. (For the sake of this discussion, histrionic patients are grouped with borderline patients because, as difficult patients, they are almost indistinguishable.)

With these three diagnoses, there is almost a complete overlap between difficult patients and personality disorders. It is not Axis I or Axis III conditions that make for typically difficult patients, but the cluster B subset of Axis II disorders, the dramatic–emotional–erratic cluster. DSM-IV defines them as the following[4]:

- Antisocial personality disorder involves a pattern of disregard for, and violation of, the rights of others.
- Borderline personality disorder is characterized by a pattern of instability in interpersonal relationships, poor self-image, dysphoric affects, and marked impulsivity.
- Narcissistic personality disorder is embodied by a pattern of grandiosity, a need for admiration, and a lack of empathy.

The key word here is *pattern*. Personality traits lead to personality disorder "only when they are inflexible, maladaptive, and persisting and cause significant functional impairment or subjective distress."[4] These traits are enduring for most of the life span; they are pervasive (i.e., they color most of the patient's personal and social interactions). They deviate markedly from the expectations of the patient's culture. Finally, they do not result from another mental or physical disorder, such as depression or head trauma.

Antisocial and Narcissistic Personality Disorders

Patients with antisocial personality disorder display the defining trait of disregard for the rights of others. The disorder satisfies the general criteria for the other personality disorders and consistently manifests at least three of the following traits[4]: rule-breaking, lying, impulsivity or poor planning, belligerence, recklessness, irresponsibility or faithlessness, and a lack of conscience or empathy.

Narcissistic personality disorder[4] defines itself in the grandiosity and lack of empathy shown by at least five of the following traits: arrogance; a lust for power through beauty, love, brilliance, or money; convictions of "specialness"; a hunger for admiration; entitlement; exploitation and manipulativeness; stunted empathy (an inability to "feel into" the other person); envy; and displays of contemptuousness.

Antisocial personality disorder and narcissistic personality disorder are similar in terms of selfishness but different in terms of social destructiveness. One could think of the difference as that between criminality and shabby ethics. Whether these two entities differ more in degree or in kind is a question perhaps better left to religion or philosophy, yet in psychiatry one view has been that the personality disorders have similar ego defects (except in degree) and similar underlying psychic organizations[5–7] or even a common one called *borderline personality organization*.[8] If it is true that a change in social context (e.g., incarceration) brings out borderline personality in persons who otherwise look antisocial, as some have claimed,[9] there may be some utility to the notion of a core personality disorder called *borderline with several variant presentations*. At any rate, the management strategies discussed subsequently work for borderline and for other personality disorders alike, given a rigorous application and a sufficiently strong social structure.

The concept of an underlying or core borderline personality organization is a metaphor that has considerable utility in the discussion of the difficult patient. In the medical setting, antisocial and narcissistic patients are difficult only when they are acting like borderlines. The idea is that the underlying good–bad split or fragmented borderline personality organization is held together by the self-promoting program of the antisocial person and the grandiosity of the narcissist. Antisocial and narcissistic patients who believe their physicians' interests parallel their own are unctuous and undifficult ("prison sincerity"). When the psychopathy and grandiosity are punctured by illness or injury and thwarted by medical treatment, the underlying fragmented, rageful, splitting, attacking borderline comes out. In the discussion that follows, therefore, *borderline personality* is the referent paradigm of difficulty, to be discussed more at length and used interchangeably with *difficult patient*.

Borderline Personality Disorder

Borderline personality is so named[10] because it seemed to psychoanalysts to lie between the psychoses and the neuroses. Borderline patients are dreaded for their impulsivity, swings from love to hate, and maddening irrationality. They split the world into exaggerated dichotomies of good and evil. An interpersonal middle ground does not exist. These patients, by some combination of innate rage and inept parenting, cannot find a moderate position in any aspect of mental life.[11]

Borderline patients have a multifaceted personality disorder, "without a particular behavioral specialty."[12] Subtypes range from bordering on psychosis, in which the patient is chaotic or irrational, to bordering on neurosis, in which the patient desperately clings to others to feel real.[8,13] A few borderline patients cope with an inadequate sense of self by adapting like chameleons to the environment of the moment (the as-if personality).[14] The core borderline patient has the characteristics shown in Table 38–1, the current official diagnostic criteria.[4]

In the past, borderline personality was sometimes held to be a subset of biological depressive illness[15–17] or a variant of traditional diagnoses, such as hysteria, sociopathy, or alcoholism.[18,19] Because up to 90% of some samples of borderline patients have co-morbid conditions, some researchers questioned the construct validity of the borderline diagnosis, whereas others defended it[20–26]: As many as half of some borderline populations suffer a major depressive episode on Axis I; conversely, some 13% of Axis I alcoholics have co-morbid borderline personality. On Axis II, at least 20% of borderline patients receive an additional personality disorder diagnosis. Of these Axis I–plus–Axis II patients, some have remission of borderline symptoms

TABLE 38–1 DSM-IV Criteria for Borderline Personality Disorder

Borderline personality disorder is a pervasive pattern of instability of interpersonal relationships, self-image, and affects and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. Frantic efforts to avoid real or imagined abandonment; note: do not include suicidal or self-mutilating behavior covered in criterion 5
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
3. Identity disturbance: markedly and persistently unstable self-image or sense of self
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating); note: do not include suicidal or self-mutilating behavior covered in criterion 5
5. Recurrent suicidal behavior, gestures, or threats or self-mutilating behavior
6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7. Chronic feelings of emptiness
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

Adapted from American Psychiatric Association: *Diagnostic and statistical manual of mental disorders,* ed 4, Washington, DC, 1994, American Psychiatric Association.

when their affective disorder is treated or when active alcohol abuse stops, again confusing the validity of the diagnosis. (Because it is more closely related to management, differential diagnosis is discussed in a later section.)

Regardless of subtype or co-morbid diagnosis, however, borderline patients can abruptly flee treatment or develop psychotic transference and delusions about their caregivers.[27–29] Short, circumscribed episodes of delusional thinking in unstructured situations and when under stress are almost pathognomonic.[13,29–31] Borderlines display a signature trait, poor observing ego,[32] which is a dense denial of vital aspects of reality and irrationality to a degree that almost has to be seen to be believed. Although the relation of borderline personality to schizophrenia has long been debated,[14,33–35] it is likely that if there is a border with a biological illness, it is closer to affective illness[36–39] without being completely tangential to it.[40]

Heredity plays a crucial role in the cause of borderline personality. Innate intolerance to anxiety and a constitutional tendency toward rage are accepted even by psychoanalytic theorists regarding borderline personality.[41] The disorder resembles aspects of traits long thought to run in families, and evidence suggests that borderlines cluster in families with affective disorders—38% of borderline patients have first-degree relatives with some affective disorder[42]—and impulsivity and affective instability generally cluster in some families with borderline members even when depression does not.[43]

Theories of the nonbiological component also focus on the family of origin.[44,45] Psychoanalysts view borderline personality as arising from failure by the patient's mother to foster coherent differentiation between self and object in the first 18 months of life,[46,47] leading to the development of pathologic ego defenses (see Table 38–3). The patient does not learn to tolerate negative affects associated with separation[48,49]; this continues the child's clinging into adulthood, as if others were desperately needed parts of the self.[8,50,51] The borderline's adult relationships are called *transitional* after the transitional object.[52–54] The patient's mother (probably borderline herself[55]) apparently feared fusion with (and destruction of or by) the child. She could not let the child separate because of her own fears of being alone. On rapprochement, she tended to reject the child for "deserting" her.[52–58] She mostly saw the child as her own transitional object and—used as the imaginary playmate of the mother—the child never grew into an emotionally separate human being.

In borderline personality, the boundaries between the self and others are blurred, so that closeness seems to threaten fusion. Sexuality and dependency are confused with aggression. Needs are experienced as rage. Long-term relationships disintegrate because of an inability to find optimal interpersonal distance. Because of inadequate ego mechanisms of defense, there is little ability to master painful feelings or to channel needs or aggression into creative outlets. Ambivalence is poorly tolerated. Impulse control is dismal. The patient has a fragmented mental picture of the self and views others as all bad and simultaneously all potent, a chaotic mixture of shameful and grandiose images.[11]

In addition to the literature on inadequate parenting, there has been an avalanche of reports linking borderline personality with parental abuse, particularly sexual abuse.[59] The line of reasoning often put forth is that the child victim of sexual abuse (especially of chronic abuse[60]) used dissociation[61] as a defense against massive psychic trauma, and the dissociation became habitual, undermining ego integration. This association with sexual abuse is seen as variously explaining phenomena ranging from a propensity toward dissociative psychotic-like episodes, rage, sexual disorders, psychotic–erotic transferences in psychotherapy, and self-mutilation all the way to the co-morbidity of borderline personality with multiple personality and with eating disorders. The literature on abuse does have the important effect of spotlighting the relationship between borderline phenomena and dissociation, something the older literature underemphasized. Although the linkage to childhood sexual abuse is still being worked out, it is clear that a significant number of borderline patients, when asked to give a history of such abuse, do so (up to 33% of nonclinical populations and 57% of borderline psychiatric inpatients[59]); this has to be taken into account in management.[62]

Borderline personality is relatively rare; it occurs in perhaps 1% to 5% of the population.[63] Despite its small size, the borderline cohort stands out in the general hospital because of its florid presentation and poor prognosis[64,65] and because of the feelings of anger and helplessness stirred up in the caregivers.[66] These patients make themselves medical outcasts because they ruthlessly destroy the care they crave.

DIFFICULT BEHAVIOR AND THE CONSULTEE

The previous discussion about the DSM-IV diagnoses of difficult patients must be leavened with a simple fact: It is not the diagnosis of these patients that make them difficult for the consultee—it is their behavior. The relationship of the behavior to other aspects of mental life is schematized in Figure 38–1 and pharmacotherapy is presented in Figure 38–2.

Such patients have abnormally intense affects, poorer than average neutralizers of affect, or both. In any case, raw rage, naked dependency, and ontologic shame are present and are often found on the surface. The cognitive structures that ordinarily temper intense affects are distorted and primitive. The ego weakness of the patient is shown by the absence of higher-level defenses and by the primitive nature of the ones that are present.

Under pressure of intense affect (rage, terror, shame), the patient uses dissociation to a greater or lesser extent and enters the dream-like state that persons ordinarily enter only in extreme emergencies. In this dissociated state (which is probably present much of the time to some degree), the patient is distracted, numb, and difficult to reach. The pervasiveness of dissociation is one feature of borderline personality that is insufficiently discussed in the literature; however, it can contribute drastically to the pathologic cognitions of borderline patients and place a distorting lens of unreality between them and the real world.

Besides dissociation, the borderline patient uses denial of major aspects of reality to cope. This mythification of the external, threatening world is displayed in defenses called *primitive idealization*, *omnipotence*, and *devaluation*. As the

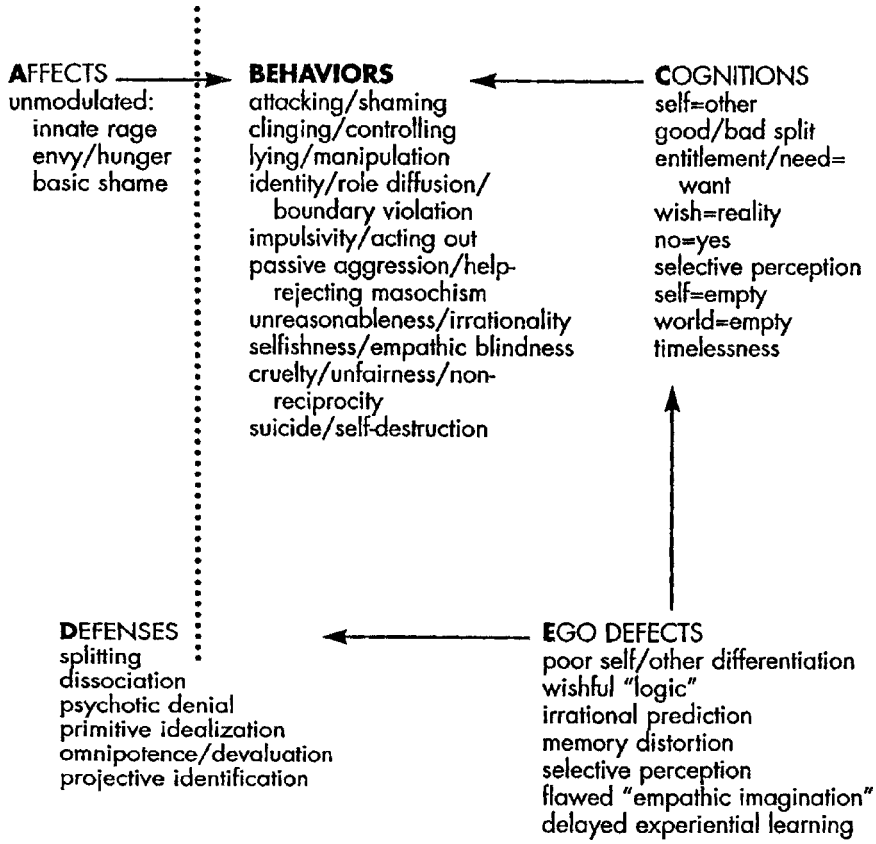

Figure 38–1. The difficult patient's types of problem behavior.

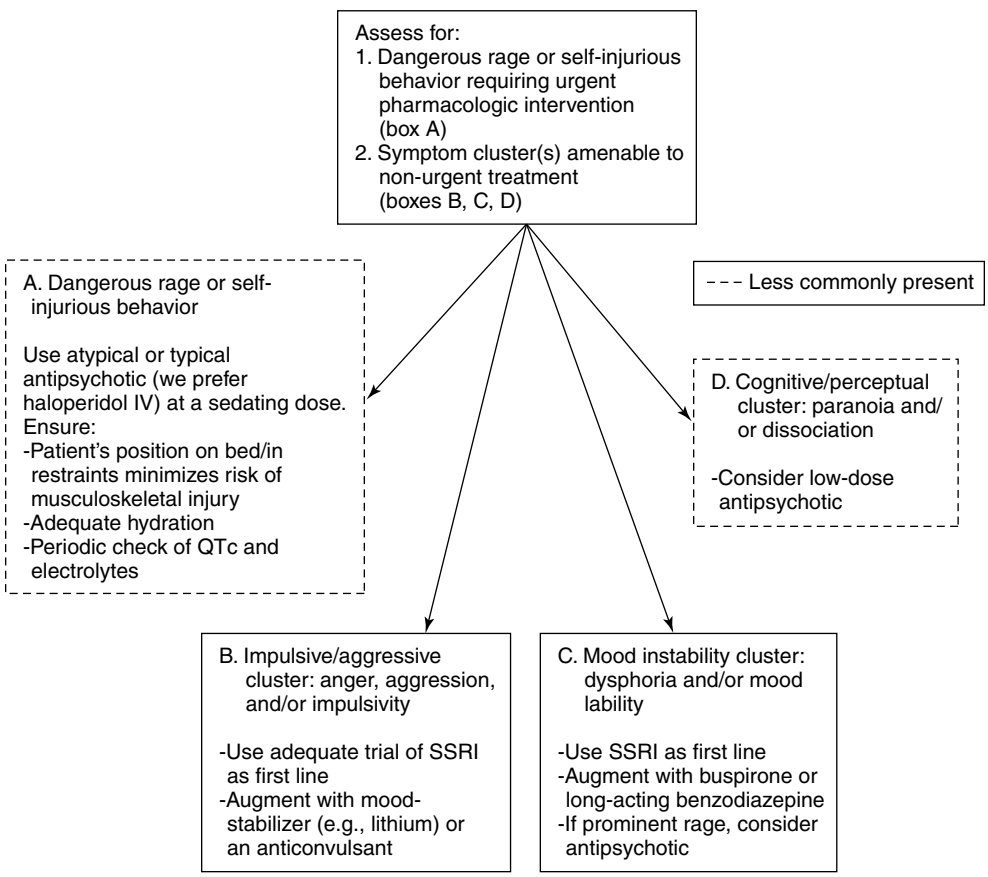

Figure 38–2. Psychopharmacologic treatment of the difficult patient.

names imply, these are metaphors for the dreamy, wishful, mythified world the difficult patient inhabits, a world of black and white and good and evil. These maladaptive defenses may be all too visible in the medical setting, but even more troubling are two others with which such patients unsuccessfully try to manage their extreme negative affects: splitting and projective identification.

Splitting is by definition a rigid separation of positive and negative thoughts or feelings. Normal persons are ambivalent and can experience two contradictory feeling states at one time; the borderline personality characteristically shifts back and forth, entirely unaware of one feeling state while in another. Sometimes one state is rigidly held while its opposite is projected onto the environment. The cause of splitting is unknown; it is said to protect the patient from the anxiety of reconciling contradictory extremes (at the expense of the already unstable personality). In social systems,[67–71] borderline patients can split the staff into warring "good" and "bad" factions that unwittingly act out the patient's internal world.

Projective identification[72–76] is said to consist of taking an unwanted aspect of the self, such as cruelty or envy, and wholly ascribing it to ("projecting it into") another. The patient then unconsciously pressures that person to own the projected attribute. Unaware that a self-fulfilling prophecy is being set up, the recipient complies with the projection and acts it out. These two mechanisms can complement each other, with projective identification being used to "confirm" one side of a polarized, split view of the world.[11]

Although the long-term psychotherapy of the borderline patient can involve therapeutic undoing of these defenses,[8,77] it is dangerous to confront such defenses in brief encounters in the medical setting. It is crucial, however, to be aware of their presence. For example, awareness of borderline splitting prepares the consultant to deal with the division of the medical staff into "good ones" and "bad ones." Recognition of the patient's primitive idealization, of a physician for instance, can help the consultant prepare for the furious devaluing that is to follow.

Helping the Consultee

The medical setting is a social system with its own history, boundaries, hierarchy, customs, and taboos. The introduction of a difficult patient into this culture sometimes places such stress on the system as to cause malfunctions in caregiving or outright extrusion of the patient, a situation that active psychiatric consultation can prevent.[78–80] Difficult patients are exquisitely vulnerable to caregivers' ordinary imperfections in communication and consistency, and they are often remarkably attuned to their caregivers' normal negative feelings of anxiety, shame, anger, and depression. Such patients are especially vulnerable to feelings of rejection by caregivers,[81] and their shaky defenses are even more compromised than usual by the stresses of illness and treatment.

After initial diagnosis and treatment of the patient, the consultant's next priority should be to gauge the amount of distress the staff is under. A psychologically naive medical staff can regress to a helpless or vengeful position in response to the patient's ingratitude, intractability, impulsivity, manipulativeness, dependency, entitlement, and rage. Regression in any social system can emerge as disagreement among staff; it can take the form of inappropriate confrontation of the patient, or it can manifest itself as a deterioration in the patient's behavior.[11] Regression seems to occur when there exists a large disparity between what is expected and what is found.[82] Troublesome dissonance of this sort between patient and staff generally occurs in any or all of three dimensions: perception of reality, values governing control and aggression, and rules about interpersonal closeness (Table 38–2).

The earliest clue to the nature of the dissonance lies in the consultation request.[83] Its tone, covert messages, intensity, timing, and route by which it reaches the consultant all can reflect the dissonance between patient and staff expectations. (In this sense, the consultation request resembles the chief complaint in the history, often the first, best clue to the problem.) Consultation is sought when the patient is out of touch with the staff's reality. Such dissonance can range

TABLE 38–2 Consultation Management of Staff and Difficult Patient Dissonance in the Medical Setting

TYPE OF DISSONANCE: CONSULTATION REQUEST	PATIENT'S PROBLEM BEHAVIORS	CONSULTANT'S WORK WITH THE CONSULTEE	CONSULTANT'S WORK WITH THE PATIENT
Dissonant reality: vague, confusing request for help; puzzled tone	Inappropriate to realities of illness or hospital; denial and demandingness	Explains patient's reality to staff; models "reality testing"	Diagnosis of any cognitive disorders; gives medication and reality-testing request
Aggressive dissonance: request to control or remove patient; fearful or angry tone	Menacing, self-destructive, or suicidal	Recommends social, chemical, or physical restraints necessary for safety	Evaluates potential violence; searches for source of patient's panic
Staff and patient dissonance regarding interpersonal distance: request consultant to take over care of patient; depressed, guilty tone to consultation request	Dependent	Gives permission to say "no" to patient's unrealistic, excessive demands	Clarifies for patient that some, but not all, needs can be realistically met
	Rejecting	Diminishes guilt and depression by stating impossibility of entirely satisfying patient	Allows patient some distance; repeatedly appeals to patient's "entitlement" and autonomous side
	Manipulative (dependent and rejecting)	Serves as forum for hatred toward patient; voices hateful feelings but behaves nonsadistically	Bargains; sets firm, noninterpretive limits on manipulation; clarifies patient's self-interest

from mild (when the patient is from a different culture) to severe (when the patient is psychotic). When the patient is docile, the request is matter-of-fact; when the patient manifests grotesquely sexual or aggressive behavior, the consultant might receive a shrill, disorganized call for help.

Consultation is sought when the patient's aggression violates staff expectations. The staff expects to be in control of the patient, who is expected to be grateful, compliant, and nondestructive. Dissonance in this dimension can range from mild, when the patient sulks, to severe, when the patient is violent or self-destructive. The tone of such a consultation request ranges from irritation to anger or outright fear, depending on the kind of aggression the patient displays.

Consultation is sought when the patient's need for closeness is different from what the staff deems appropriate. The staff expects the patient to be involved with the caregivers but to keep a certain distance. When the patient asks for repeated reassurances or when the patient makes inexhaustible or contradictory demands, a depressed, guilty request often ensues. Arrogant, peremptory consultation requests often herald a hostile, dependent, manipulative patient; depressed, tired requests can foretell an empty, clinging patient.

The primitive defenses[8,41,72–76,84] of the difficult patient can stimulate staff disagreement (Table 38–3). To cope with deep feelings of self-loathing, the patient might see the staff as loathsome—otherwise why would they care (projective identification)? Or the patient may see the staff as magically all good, to keep all the badness in the world away (primitive idealization). To make sense of a world in which people are both good and bad, such a patient might choose some people on the staff to be "all good" and some to be "all bad" (splitting). This "explains" for the patient "why" things always go wrong: The patient is caught between good and bad forces outside the self and therefore they are not the fault of the self. When the patient views the staff through the defense of splitting, the staff might eventually behave as if it were so. The patient will tell an "all good" staff member what terrible things an "all bad" staff member has done, said, or thought and then swear the "good" one to secrecy. As less and less communication takes place and as the patient escalates demands, the "good" staff and "bad" staff begin to disagree about the care of the patient because the borderline patient may be "good" with "good" staff and vice versa. The remedy for this depends on re-establishing open staff communication, even if it is hostile, to enable staff to get a well-rounded view of the patient. Firm, nonpunitive limit setting[67,69] (Table 38–4) is crucial for inpatient treatment because it must be made clear that the patient cannot destroy the caregiving system or be destroyed by it, no matter how intense the wishes or fears may be.

It is a natural human instinct to confront such patients angrily, but caregivers should exercise precautions during confrontations. Avoiding a confrontation of narcissistic entitlement is as important as it is difficult.[85] Such patients exude an offensive sense of deservedness that is always tempting for an overworked staff to confront angrily and suddenly. Often the difficult patient has only this sense of entitlement to keep a fragmented personality together during the stresses of hospitalization. Entitlement for the narcissist is what hope and faith are to normal persons. Preserving it requires a deliberate effort. Taken together, what Tables 38–2 to 38–4 show is that such behavior of the difficult patient (e.g., manipulativeness and entitled demanding)—obnoxious though they may be—sometimes function as defenses at a relatively high level for that patient. Stripping them away makes the patient fall back on even lower-level defenses, such as psychotic denial and dissociation, or—worse—to be defenseless, panic, or explode.

TABLE 38–3 Manifestations of Primitive Ego Defenses: The Difficult Patient in the Medical Setting

Splitting: Keeping completely apart two opposite ideas and their associated feelings. Staff are divided into "good ones" and "bad ones," reflecting the patient's incapacity to achieve ambivalence enough to see that caregivers have human limits, with "good" and "bad" qualities at the same time.
Projective identification: The tendency to see some staff as "bad" as the patient feels. This gets translated into behavior based on the following kind of "logic": "I'm bad and you take care of me, which means you're as rotten as I am, otherwise you wouldn't care for me." This perception is so powerfully held that the staff receiving it tend to act it out unconsciously.
Primitive denial: The alternating expungement from consciousness of first one and then another perception of opposite quality (in which it is called *splitting*) or a wish so powerful that it obliterates crucial aspects of reality contradicting that wish. For instance, fear might cause the patient to deny a serious condition and flee the hospital where it could be treated.
Primitive idealization: The tendency to see some staff as totally "good" to protect the patient from "bad" staff or from the patient's medical condition.
Omnipotence and devaluation: A shift (splitting) between the need to establish a relationship with a magical, powerful staff (primitive idealization) versus the conviction of omnipotence in the self that makes all others impotent by comparison (primitive idealization of the self). Omnipotent caregivers are supposed to deliver to the patient perfect care to protect against disease, and when this does not happen, the staff is seen as impotent and hateful. (Splitting makes the perception shift dramatically, whereas projective identification causes the staff to buy into the patient's primitive projections, making them come true).

Adapted from Groves JE: Management of the borderline patient on a medical or surgical ward: the psychiatric consultant's role, *Int J Psychiatry Med* 6:337–348, 1975.

TABLE 38–4 Rules for Confronting the Difficult Patient

Acknowledge the real stresses in the patient's situation.
Avoid breaking down needed defenses.
Avoid overstimulating the patient's wish for closeness.
Avoid overstimulating the patient's rage.
Avoid confronting narcissistic entitlement.

Adapted from Adler G, Buie DH: The misuses of confrontation with borderline patients, *Int J Psychoanal Psychother* 1:109–120, 1972.

Setting limits, avoiding confrontation, and avoiding overstimulation of the desire for closeness and rage are difficult to arrange in the fast-paced medical milieu.[85] Prevention of staff splitting is especially difficult because of the various subcultures in medicine. If, for instance, the patient chooses the nurses to be "all bad" and the physicians to be "all good," the nurses may displace anger to the physicians but be unable to express it directly because of role-induced sanctions, and the physicians may see the nurses as incompetent and unable to comprehend their treatment plan for the patient. Such situations are fertile ground for the splitter and require concerted effort toward open communication.

Pathologic dependency manifests in one of its extremes as manipulativeness: an intense, covert, contradictory, self-defeating attempt to get needs met.[3,84] It is the behavioral manifestation of a need by the patient to get close but at the same time maintain a safe distance from sources of emotional support. Some patients feel so empty that, paradoxically, getting their needs met threatens them with engulfment; they are so famished that closeness can actually make them feel merged with someone else and therefore not really alive. Such patients seem to have a deathly fear of what they most crave.

In limit-setting confrontations with manipulative, entitled patients, the consultant might have to model for the staff firmness, repetition, and an appeal to the patient's sense of entitlement (rather than an assault on it): "You deserve the best medical care we can give, and that's why we're recommending X, Y, and Z." The consultant has to keep uppermost in mind the appeal to the entitlement and not get drawn into logical or illogical arguments. Moreover, it is important to avoid interpreting the resistance to cooperation as a fear of dependency, a tactic that would at best leave the patient somewhat bewildered. Repetition is crucial. Encounters to engage compliance often have to be repeated two or three times at varying intervals before the patient agrees, for instance, to take medication.

Dependent, manipulative patients stir up sadism in the caregivers, which inhibits the setting of effective limits. The consultant supports the staff's self-esteem and performance by reinforcing strengths rather than by pointing out weaknesses, by teaching, by lending a conceptual framework to mitigate anxiety, by modeling interactions, and, most of all, by matter-of-factly stating that such patients stir up hatred even in the best of caregivers. Whenever the staff brings even a hint of negative reference to the patient, the consultant can say something like, "Yeah, these patients are manipulative and irritating as hell!" Or, "Everybody hates this kind of patient—I know I do." This personalization, juxtaposed with the consultant's own nonsadistic behavior toward the patient, legitimizes hostility toward the patient, but shares it among staff rather than inflicting it on the patient.

In general, the earlier in the hospitalization the consultant is called, the more overt is the reason for the consultation and the more effective will be the intervention because the difficult patient has had less time to project into the staff the intense, seemingly inborn shame such patients possess in great abundance. Late in the hospitalization, the consultant may be urgently called in to see the patient for vague reasons and arrive to find the situation in a shambles, the patient in restraints, the staff ashamed and in bitter conflict—and nobody either willing or able to say what has been going on.

Consultant's Role

The consultant's role in the management of the difficult patient consists of a specialized type of consultee-oriented approach in which countertransference hatred and fear are drawn away from the patient and strategically metabolized within the relationship between staff and consultant. The consultant should actively promote a behavioral management practicum[84] placed in the medical chart for reference and as a symbol of the psychiatrist's helping presence. This "recipe" discusses communicating clearly with the patient and among staff; understanding the patient's need for constant interaction with personnel; dealing with entitlement without confronting needed defenses; and setting firm limits on dependency, manipulativeness, rage, and self-destructive behavior.

Generally the consultant's approach should first lead directly to the consultee. The request should be elicited in person or at least on the phone because the written record never reveals all of the problems in the management of the difficult patient. Then the consultant goes to the head nurse to get a history of the patient's response to hospital routine. Next, the consultant reads the chart and compares medication orders with records of medication actually administered. The consultant will have generated some hypotheses and is now ready to test them in the examination of the patient. As the consultant proceeds through these steps, an orderly plan emerges (Table 38–5).

TABLE 38–5 Order of Priorities for the Difficult-Patient Consultation in the Medical Setting

1. Rapidly evaluate the most pressing psychiatric problems, beginning with physical or social restraints if the patient appears about to lose control of violent or self-destructive impulses.
2. Create a differential diagnosis of the difficult patient, with an explicit biopsychosocial formulation of the predominant conflicts and stressors.
3. Identify dissonance between staff and patient and formulate a plan of action to reduce it (see Table 38–2).
4. Provide treatment recommendations—psychological and pharmacologic (see Figure 38–2 and Table 38–2), short-term and long-term— taking into account the ongoing medical regimen and implicitly addressing dissonance between staff and patient while explicitly addressing the patient's conflicts.
5. Educate the consultee and staff to reduce dissonance and to lend a conceptual framework for dealing with future difficult patients.
6. Actively participate without grandstanding or actually taking over the total psychological care of the patient.
7. Follow up and be involved in disposition planning for the medical and psychiatric needs of the patient.

Adapted from personal communications with TP Hackett, AD Weisman, NH Cassem, AW Alonso, TD Stewart, K Nobel, JA Renner, OS Surman, and many others.

One helpful approach is the consultee-oriented model of consultation,[86] which involves thinking of the patient and staff as a single entity and dealing as much as possible with the strong, healthy part. The entity consists of two parts. One part, the difficult patient, has problems with object relations, pathologic behavior exacerbated under stress, and several self-defeating and infuriating defenses, especially splitting. To prevent being split, the consultant should try to deal mainly with the healthy part, the staff. Because the staff is often closely linked in an unwilling, hateful, and guilty alliance with the patient and its collective self-esteem is already damaged by encounters with the patient, the consultant should not damage it further by interpreting the staff's pathology.

The attempt to ally with staff rather than the patient is destined to encounter several kinds of resistance at the outset. First, the patient is eager to engage the consultant to find out whether the consultant is "all good" or "all bad." Second, the staff, needing distance from its sense of failure, wants the consultant to take over the care of the patient completely. Third, neither the staff nor the patient has the energy to understand what is going on; they are in pain and want relief now, preferably by removal of the patient.

The alliance with the staff depends to a large extent on previous experience with the consultant, how long it takes to answer the consultation request, and how much sense the advice makes. The alliance with the difficult patient is dramatically less important in terms of outcome than the alliance with the staff. Such patients are incapable of forming a real alliance, and their "alliances" are mostly primitive idealization. Ideally, the patient should be seen only briefly if there are enough data from other sources, and the staff is told that the consultant will work mainly with staff and see the patient infrequently.

Visiting the patient should be reserved in the early stages for the specific purpose of the consultant's alliance with the staff. Following the initial patient interview, the consultant goes to see the patient when a magical gesture of "taking over" is needed to comfort a desperate staff, when staff members feel that the consultant does not know how much they are suffering, and when the staff needs a specific model for carrying out recommendations on limit-setting or reality testing.

The consultation note, by its tone, specific information, and description of the patient in a way the staff can immediately recognize, remains in a medical record day and night as a tangible symbol of the consultant's helping presence. It outlines the request, history, mental status at the hour of the examination, and the psychiatric history. It is explicit about medications, and the potential for suicide and for violence. It includes specific, concrete management recommendations.

CASE 1

This was the conclusion of a consultation note for a difficult patient who had been spitting in her hyperalimentation line.

Impression: Ms. B is thought to have a chronic, severe personality disorder sometimes called borderline, meaning that she lies on the border of psychosis diagnostically and has only marginal social adjustment.

Recommendations: Continue haloperidol 2 to 10 mg IV twice a day as needed. Have brief, daily staff conferences to compare notes and reach a consensus about her surgical treatment plan. Try to have the same staff members work with Ms. B each day; bear in mind that she tends to panic at each change of shift. Set firm limits on her multiple and contradictory demands. She is quick to rage when her demands are not met and may threaten suicide. Do not imply that Ms. B does not deserve the things she demands, but rather say over and over again that you understand what she is asking, but because you feel she deserves the best possible care, you are going to continue to recommend the course dictated by your experience and judgment. If she continues spitting in her hyperalimentation line, assure her that physical restraint will ensue. (These limits do not mean that she should not be allowed to complain, but you need not tolerate more than twice as much as you would from the average patient.) Initiate suicide precautions (and search her luggage).

The consultant addresses dissonance arising from the patient's version of reality; tendency to act out; and demandingness, neediness, and rage. The consultant gives a mandate for open communication and daily staff conferences to prevent staff splitting and to provide a supportive environment. Firm limits, without challenging the patient's sense of entitlement, are set forth explicitly. The task now becomes one of seeing that recommendations are effected. There is nothing more frustrating than laboring to devise a treatment plan only to find that it is not carried out. When this happens, the consultant often finds that the source of resistance is still-unresolved dissonance between staff and patient (see Table 38–2).

Nowhere in the previous discussion is the unconscious motivation of the patient or of the staff brought to the attention of either. This is what is meant by *noninterpretive intervention*. Psychoanalytic interpretations foster a temporary regression and have no place in the consultation with the disruptive medical–surgical patient.[84,87] Instead, the consultant analyzes and reduces dissonance by speaking of its behavioral roots and consequences while resisting the temptation to illuminate interesting unconscious processes.

Medication

The psychopharmacologic management of difficult patients is quite complex and uncertain, again suggesting that borderline personality disorder (the referent paradigm of difficulty) is not simply a "border on" depressive disease. Based on the neuropsychiatric and psychopharmacologic literature, four clusters of personality disorder symptoms have been proposed as targets for pharmacotherapy.[88] The four clusters reflect difficulty with cognition or perceptual organization, impulsive and aggressive behavior, mood stability and dysphoria, and suppression of anxiety (see Figure 38–2). The personality disorder symptoms within each cluster might have a common neurobiological substrate that can serve as a rationale for treatment selection.

The impulsive–aggressive dimension and the mood-instability dimension are the two most relevant to cluster B personality disorders and, hence, the difficult patient.

Anger, aggression, and behavioral disinhibition constitute primary impairments in this domain, and they are thought to reflect dysfunction in the serotoninergic neurotransmitter system. Selective serotonin reuptake inhibitors (SSRIs) should be considered first-line agents for treating impulsivity and aggression in personality-disordered patients. However, if these patients do not respond well to adequate trials of SSRIs, augmentation with a mood stabilizer or an anticonvulsant can be considered, because there is empirical support for the use of divalproex sodium in this patient population.

The mood-instability dimension also appears to be most closely tied to the cluster B disorders and consists of mood dysregluation, depression, dysphoria, and emotional lability. These behaviors may have broad neurotransmitter underpinnings, possibly related to dysfunction in serotoninergic, cholinergic, or noradrenergic systems. SSRIs should be considered first-line agents for treating these symptoms. If augmentation is needed, buspirone or a long-acting benzodiazepine, such as clonazepam, can be considered. If rage is a prominent component of the mood dysregulation, antipsychotic agents should be considered.

When using the four-personality symptom clusters as a guide to pharmacotherapy for the difficult—personality-disordered—patient, the clinican should be mindful that the heterogeneity of DSM personality disorders results in patients having symptoms from several symptom clusters. For example, patients with borderline personality disorder tend to demonstrate behaviors from the impulsive–aggressive and mood-instability clusters, but some also exhibit symptoms within the cognitive–perceptual cluster. This reinforces the concept of selecting pharmacotherapy based on specific target symptoms rather than on a given personality disorder diagnosis. Experienced clinicians tend to use the symptom clusters as medication targets to avoid "chasing" single symptoms (to prevent situations in which a patient is prescribed four or more medications without a clear rationale). Clinical experience also suggests following guidelines (for dose and duration) for all medications to minimize treatment adjustments.

In terms of specific recommendations to the consultee, a trial of medication can be quite helpful in particular instances (see Figure 38–2). With patients exhibiting dangerous rage or other dangerous behavior, such as self-injury, antipsychotic medication titrated to a sedating dose may be life-saving.

Miscellaneous medications, ranging from methylphenidate to levodopa, have been reported to help difficult patients,[11] and there seem to exist single case reports touting almost any conceivable drug.[89] Given the present state of knowledge, it seems appropriate for the consultant to remember that mind and body are not separate, and that many seemingly insoluble problems respond to a search for, and aggressive treatment of, co-morbid psychiatric conditions, especially affective disorders and substance abuse. Common and uncommon medical conditions mimic personality disorders (just for illustration, three random instances in the literature are narcolepsy, Wolfram's syndrome, and Addison's disease[90–92]). Also, over the lifetime of any given patient, the relationship with a supportive physician is as healing as any drug.

PSYCHIATRIST'S WORK WITH THE PATIENT

Although design and promotion of the behavior management protocol and consultation with the staff are the initial work of the consultant, the psychiatrist performs the following tasks with the patient directly:

- The psychiatric mental status examination, differential diagnosis, and formulation (including the use of observations of transference and countertransference)
- Assessment of suicide potential
- Assessment of present need for control of violence (as opposed to making a prediction of dangerousness)
- Assessment of, and recommendations around, substance abuse and other "dysfunctional," addicted, or "co-dependent" patterns (e.g., inept parenting, eating disorders, spousal abuse, or obsessive–compulsive disorder)
- Rarely a highly focused, brief (one- or two-session) tactical psychotherapeutic intervention

Differential Diagnosis

If the consulting psychiatrist does not do it, there will not be a good mental status examination, psychiatric history, or biopsychosocial formulation in the medical record. However skilled or willing other specialists may be, only the psychiatrist has an understanding of the minute-to-minute fluctuations of transference and countertransference that occur early, even in a single interview. (Countertransference is so important as to be almost a diagnostic discriminator of borderline personality.[93]) Also, there is a kind of rigor and discipline that the experienced psychodiagnostician brings to these situations: No one else in the medical setting is, for instance, going to perform a Mini-Mental State Examination, ask about earliest memories, a history of sexual abuse, the content of dreams and fantasies, sexual worries, religious and spiritual concerns, disordered thoughts, and suicidal ideation—all in one interview—and then put them together into a differential diagnosis and formulation.

Differential diagnosis is crucial because co-morbidity is almost a hallmark of the difficult patient, and it is surprising (if not impossible) to encounter a cluster B patient who does not also have at least one of the following diagnoses: another personality disorder, substance-abuse disorders, affective disorders, anxiety disorders (especially panic and phobias), eating disorders, obsessive–compulsive disorder, posttraumatic stress disorder, adult attention-deficit/hyperactivity disorder, impulse-control disorder, or other disorders.

Suicide Assessment

The gravest predictors of a suicide attempt[94–99] by the difficult patient are the following:

- History of previous attempts, especially with high risk or a low chance of being rescued, and other violence
- Standard demographic predictors (advanced age, being single, and the like; see also Chapter 40 on suicide)
- Co-morbidity, especially with substance abuse and affective disorders
- Marginalized socioeconomic and cultural status

These predictors are the same whether the patient is in the medical setting or out of it, but there are other predictors specific to the medical setting: Recent worsening in the medical condition along with perceived rejection by caregivers[81] adds considerably to the risk of suicide. Suicide attempts in medical and surgical settings correlate not so much with depression in serious illness, such as cancer, but rather with anger over the loss of social supports. The large majority of suicide attempts occur in a clinical setting in which the patient's experience is of being abandoned: during failing treatment, at times of imminent discharge, in conjunction with disputes with the staff, or during staff holidays.

Some factors are poor predictors, notoriously the psychiatrist's countertransference.[99,100] Also, it is false to think that patients with antisocial personality or without clinical depression never kill themselves. Depression and the type of personality disorder are much less predictive of suicide than are punctured defenses and a "no-exit" situation, one the patient deems totally hopeless and inescapable. A good short mnemonic for immediate risk is the "3 H rule": hate, humiliation, and hopelessness. Strongly predictive are self-hate fused with hatred of another (often a spouse who has left), loss of face with extreme shame, and being trapped in a bad situation with no apparent prospect of escape.

Assessment of Potential for Violence

Problems arising when the patient has difficulty controlling aggression are helped when the consultant defines for the staff the range of responses, from supporting the sulking patient or even giving in to a mildly overcontrolling patient, to absolute limits on violence. The medical staff fear overreacting, and the consultant reduces anxiety by defining the management of varying degrees of aggression. Disruptions are mostly born of self-protective or fearful impulses in the confused or delirious patient. Rarely, however, a patient becomes dangerous. In those instances, the most common warning is fear; someone becomes scared of the patient. Staff almost never fear delirious behavior, controllable anger, or senile pique, but they do tend to become wary, then edgy, then frightened. This intuition in the caregivers is often the only warning the consultant gets before an explosion. Ominous signs in the patient are rapidly increasing demandingness; more frequent and intense anger, especially with abusive language; and mounting agitation and paranoia. The general feeling in the medical setting of an implacable crescendo of menace surrounding the patient is another ominous sign.

Before any decision about physical restraint of the patient is made, hospital security guards should be standing by on the ward. This is a first step in the decision-making process. Security can always be dismissed with thanks after standing by, but to delay summoning help until after such a decision is made risks panicking the patient, who may have an uncanny ability to sense an impending confrontation.

Such ideas refer to control of violent behavior in the immediate situation. Occasionally, however, the consultant is asked about the long-range "dangerousness" of the patient. This is an opinion that involves extrapolating from present behavior in a known, observed situation to a guess about the patient's interaction with a different milieu, one that might contain drugs, weapons, and situations beyond the psychiatrist's ken. Medicine is about healing, not social control. Dangerous persons (e.g., the man with schizophrenia and a gun, the person with an antisocial personality who commits rape) may in some sense be "difficult patients," but in these situations, they are not patients at all, but criminals.

Psychiatric opinions outside the medical purview violate an important boundary and feed the fallacy that all bad behavior is somehow psychiatric and that mentally ill persons have no personal responsibility for their behavior. What the psychiatrist can do, however, is document medical history from the consenting patient about drugs, access to weapons, felony convictions, and the like. Surprisingly often, such a patient discloses useful information in the context of a skillfully elicited childhood history of enuresis, fire-setting, and cruelty to animals. ("Were you ever accused of setting fires? Did anybody ever say you were mean to the neighbor's pets?") Such patients can be oddly eager to resurrect old denials and often are still indignant about them. They then sometimes go on to give themselves away and provide information needed to protect caregivers and other patients in the medical setting.

Substance Abuse

Substance abuse is the area in which the consultant can be most useful to patients with primitive personality problems. Substance abuse is such an issue for a significant proportion of difficult patients that excess alcohol can be thought of as a personality disorder in a bottle. More than half of some samples of borderline patients—two thirds in one study—abuse substances. Of these, perhaps up to a fourth have such a good response to abstinence that they no longer meet diagnostic criteria for the disorder.[22]

If one adds to the number of patients with substance abuse various other addictive, co-dependent, or dysfunctional problems (e.g., eating disorders, "sex and love addicts," or incest survivors), it is not implausible that almost any difficult patient would qualify for some sort of 12-step or "recovery" program. Such self-help groups have not excited much interest or research in psychiatry (and have even occasionally inspired disdain because of their focus on spirituality), but there are several conceptual reasons (based on Figure 38–1) why 12-step programs are ideal for difficult patients: Tenets of the "recovery" movement are essentially anti-psychological in their nature, and given the lack of observing ego of borderline patients, this is a benefit, not a deficit. Many borderline patients have such dramatic regressions when involved in psychological treatments that observers have suggested that much of their pathologic behavior is iatrogenic,[101,102] a reaction to too much empathy and psychoanalytic interpretation. Furthermore, such programs have two ingredients well known to help primitive character pathology: an emphasis on taking responsibility for oneself (as opposed to cultivating the victim role) and a highly structured series of steps and methods. Not least in importance, there are myriads of such groups meeting at almost any hour of the day or night in every location in the urban United States.

Not surprisingly, it requires great skill to persuade a difficult patient to identify with one of the 12-step programs. First, there is almost always dense denial of the abuse problem, along with a need to see the self as powerless and

victimized. Splitting patients and narcissists see themselves as "better than" persons in Alcoholics Anonymous, for example, and are so vulnerable to shame that they hesitate to take on another attribute they see as shameful. Also, the general culture outside such programs has little real information about what they can accomplish, so the patient is not only ashamed, but also usually ignorant of these resources.

There is an art to getting a difficult patient to consider that a problem with addiction, co-dependency, or the like may be the root of much of the suffering the patient endures. Practicing this art involves accumulating knowledge about such programs and having familiarity with some persons helped by them. It involves the ability to discern when the patient might be receptive, first to acknowledging an addictive problem and second to considering such a program. It involves knowing how to elicit information in a nonshaming way ("Do you find yourself drinking more than you really want to be drinking?"), presenting the condition as a disease and "not the person's fault," and introducing the ideas gradually in a nonthreatening way. ("Did your mom ever turn to Al-Anon for help with your father's drinking?" "Did you ever get help from the Adult Children of Alcoholics program or something like that?")

No difficult patient is ever educated easily, and it usually requires multiple inputs from numerous sources over many months even to begin to get some of these options accepted by the patient. The consulting psychiatrist is ideal to introduce such ideas and, given the relapse rate of difficult patients, might get another opportunity with the same patient in the future. The consultant can at least start the educational process without making the patient feel ashamed.

Brief Tactical Psychotherapy

Psychotherapy is a risky proposition, and the consultant is wise to resist the temptation to do much. Rarely, however, the crisis of an illness provides a unique chance for insight and growth for the patient with a primitive personality. This lucid interval is incidentally produced when an illness and treatment cut through the veils of dissociation surrounding such patients, their maladaptive projective defenses, and their habitual externalization of responsibility. In this context, sometimes the patient asks not only the superficial "why me," but also the deeper question, "Who am I that this is happening to?" In a certain sense, catastrophe throws the primitive individual into a developmental crisis in which there may be the potential for recouping a bit of the developmental lack of progress in the first 2 years of life—the maturation from the paranoid position to the depressive position—along with a capacity for grieving and the developing empathy for others that such maturational steps entail.

A study[103] of changes in pathologic narcissism in a cohort of subjects followed for several years found that a majority of them had improved significantly and that the improvement related to life achievements, new durable relationships, and disillusionment. These subjects displayed decreased grandiosity and deeper empathy for others as evidenced by better relationships. The disillusionment related to these improvements, moreover, had occurred at a critical juncture in the person's development and was of a certain type—challenging but not devastating. Rather than questioning the construct validity of narcissistic personality disorder (as was done in this study), the findings plausibly support the idea that certain painful, constructive real-life experiences help people change their primitive pathology. (That brief therapeutic interventions can further this process, even in primitive patients, is shown in some of the therapies detailed by Malan, Budman, Strupp, Bloom, Horowitz, and especially Winnicott.[104])

This is the rationale for a certain brief, tactical intervention by the psychiatric consultant who encounters the difficult patient during a medical or surgical crisis: how to keep the disillusionment from being completely devastating and help the patient make sense of it in terms of personal identity. (As Figure 38–1 shows, a vague sense of personal identity underlies much of the pathology of the difficult patient.) The patient is in a process of trying to adapt to the illness or injury, to work it through, to grieve losses, and to contain fears. In this context, the psychiatrist's aim is not merely to help further this grieving or adjusting process, but to accomplish a deeper, more lasting goal: using the illness or injury process as a template or map for other life changes, using the crisis of the moment to help the patient learn new ways of thinking about the self, and coping with rage, terror, and shame.

The tactical brief therapy of the difficult patient falls into two types of maneuvers: containment and intervention. Containment involves control of uncontrolled affect, distorted cognition, and destructive behavior. Intervention consists of correcting the misdirection of the patient's trajectory, previously determined by pathologic affect, distorted cognition, and self-defeating behavior. Containment and intervention roughly correspond to the two parts of traditional psychotherapy, the frame (scheduling, vacations, fee, phone calls, limits on acting out, confidentiality) and the content (symptoms, history, development, associations, discourse, dreams, fantasies, defenses, adaptation, transference, countertransference, and other nonframework components of therapy). This "moment" of brief tactical psychotherapy assumes the patient in the medical situation is temporarily contained and already in a dialogue with the psychiatrist about the illness or injury that brought the patient to this place at this time.

The therapist's first task—and therapist is what the consultant becomes at this moment—is to listen to see whether the patient is asking for intervention. The patient signals such readiness not only by addressing the impact of the illness or injury but also by mentioning the overall meaning of the patient's life, the patient's "story," the overarching narrative that helps any human being make sense of the world. If the tactical intervention is to be helpful, the patient must be the one to push for it. The therapist's experience at this point is of being passively drawn into the patient's turbulent material, yet actively steering the discussion away from affects too intense on the one side and cognitions that are psychotically distorted on the other.

So up to this point, the therapist's job has been careful listening and containment. If the patient is ready, the patient will introduce these two themes: the overall story of the patient's life and its meaning, and the meaning of the illness or injury that is serving as the focus of the tactical psychotherapeutic moment. The patient will tend to see the medical crisis as thematically pertinent to the meaningful life story—for instance, just another in a long series of

persecutions, a punishment for something bad the patient has done or is. The life story is generally a standard narrative of a search for perfect safety and love, a quest for power so the patient will never again be scared; there are seldom any major surprises at this point.

The therapist's first active step in the tactical intervention occurs now: labeling the life story; labeling the symbolic, adding metaphoric meaning of the illness or injury; and labeling the pain that is at the interface of the two. This is almost like offering a "title" for the story. ("All your life you've been a survivor; now you wonder if you can survive this terror.") The idea here is that, to survive, individuals have to construct a meaningful narrative of the crisis. Under pressure of converting experience into symbols and then into meaning, the primitive person may be forced to construct a more realistic life narrative (and hence a more coherent sense of personal identity).

If the patient continues to be receptive to tactical intervention, two things happen at this point: first, production of deeper material in symbolic form (mention of a fantasy or recurrent dream, some external, cultural symbol or icon, a movie or a television character) and, second, a rather pointed question for the therapist about what to do (an acceptance by the patient of the therapist as a relatively separate, helpful person). This turning point requires careful listening because the key organizing theme of the patient's life (as the patient sees it) is presented in this one moment of symbol formation along with the rather concrete question that follows directly after.

Here the therapist does not answer the patient's question about what to do with the illness assaulting the meaning in the patient's life. The therapist labels the assault, points out the crisis in meaning, and thematically throws the question back to the patient. ("In a way you're asking how to cope with this thing, but in a deeper way you're saying that you're Scarlett O'Hara, since you just mentioned her. How would Scarlett handle what you're going through?")

What the patient says next reveals whether the tactical linking of the two meanings and two stories seemed useful to the patient. If so, the patient produces more details of the life story, again asking the therapist what to do about the illness or injury. Again the therapist throws responsibility back to the patient, labeling meaningfulness issues and the importance of the illness or injury to it. ("You just mentioned losing your husband—like Scarlett O'Hara—and now you're asking how to cope with your boyfriend's reaction to your mastectomy. Scarlett fell back on Tara and her own resources. What resources do you have to draw on?")

This working-through cycle of question and deflection continues as long as the therapist has time and the patient has strength to bear the rage, terror, or shame of the moment. Usually the patient soon fatigues and moves the subject back to some specific entitled demand, such as getting more pain medication. This signals that the therapy part of the encounter is now over and that the consultant is once again back to management of the difficult patient.

Although the brief tactical psychotherapy just described is probably the most useful first-line approach, other psychotherapeutic methods have been designed for the treatment of borderline personality disorder and also can be applied to the difficult patient. Dialectical behavioral therapy (DBT),[105] transference focused psychotherapy (TFP),[106] mentalization-based therapy (MBT),[107] and schema focused therapy (SFT)[108] each have a somewhat different theoretical perspective; transference focused psychotherapy and mentalization-based therapy have shown efficacy in randomized, controlled trials for improving outcomes for those with borderline personality disorder. Although full implementation of these therapies is obviously not possible during a few consultation visits, familiarity with the theory and techniques they rely upon can enhance the consultant's ability to make sense of, and employ a therapeutic tool, in diverse situations. Table 38–6 summarizes these treatments and provides examples of how they can be adapted to encounters with the difficult patient.

TABLE 38–6 Psychotherapies for Borderline Personality Disorder and Their Relevance to the Difficult Patient

THERAPY	DEVELOPER	RELEVANT THEORY*	RELEVANT TECHNIQUES	EXAMPLE WITH THE DIFFICULT PATIENT
Dialectical behavioral therapy	Marsha Linehan	The patient is more emotionally vulnerable and reactive and is therefore ill-suited to a normal social environment	Acknowledge and validate the patient's difference while also encouraging change	Consultant: "This ward is a difficult place for you. Everyone's too busy to give you the help you need, and this illness is one of the most distressing things that's ever happened to you. Your rage and fear make sense. That being said, the doctors and nurses here really are trying their best. They're at least meeting you a third of the way. Do you think you could cut them a little more slack? Do you want me to communicate anything to them for you?"

Continued

TABLE 38–6 Psychotherapies for Borderline Personality Disorder and their Relevance to the Difficult Patient—*cont'd*

THERAPY	DEVELOPER	RELEVANT THEORY*	RELEVANT TECHNIQUES	EXAMPLE WITH THE DIFFICULT PATIENT
Transference focused psychotherapy	Otto Kernberg, John Clarkin	The patient is frozen in a state of immature emotional development where self is split into multiple negative and positive parts experienced successively in time, each infused with maladaptively powerful affects. Personality therefore lacks consistency and cohesion	Interpret the patient's successive self states to enhance the patient's awareness of the multiple roles she or he plays, which fosters a more integrated self	Consultant: "You say the doctors here are the best ever, but the nurses are all bitches. And at first you told me I understood you like no one else. But now that I'm trying to enforce the rules to protect your safety, you're ready to throw me on the trash heap. So it's almost like I experienced two different people: First you were so warm and tender and the next minute you were like a warrior ready to cleave me in two. Aside from letting you take off your heart monitor leads, which you know is too dangerous right now, how can we help you feel better heard and cared for?"
Mentalization-based therapy	Peter Fonagy, Anthony Bateman	The patient cannot make sense of the actions of self and others on the basis of intentional mental states, such as desires, feelings, and beliefs	Point out the patient's actions to help the patient draw a link between actions and what the patient is thinking and feeling; identify the patient's reactions to the therapist's words or actions and help them guess what you're feeling and thinking	Consultant: "Can you tell me what you were feeling and thinking while you were cutting yourself with that razor you brought in? Were you scared? Were you angry because we did something wrong?" Patient: "I told you to get the f*** out of here!!" Consultant: "I'm concerned about you and terrified when you scream like that. I know that scares other staff too. We'll need those restraints to keep you safe until we can understand you better and help you cope with this more safely."
Schema focused therapy	Jeffrey Young; influenced by the work of Aaron Beck	The patient's inner world is characterized by five modes, or aspects of self, that interact in destructive ways: the abandoned and abused child, the angry and impulsive child, the detached protector, the punitive parent, and the healthy adult	Develop the "healthy adult" by "limited reparenting," emotion-focused work (e.g., imagery and dialogues), cognitive restructuring and education, and breaking behavioral patterns	Patient: "I don't take my heart pills or my insulin usually for the simple reason that I'm a drop out and a druggie and what's the point of someone like me continuing to take up space on this earth." Consultant: (who has already established that the patient is not depressed but rather personality-disordered) "Multiple times already I've heard you be extremely hard on yourself. It would be useful to give that particular voice of yours a name. How about 'My Abusive Step-father'? When you hear yourself talking like that, try to remember that name. With outpatient therapy, you can learn how to tell that part of yourself to leave the rest of you alone and gradually he'll go away for good."

* With minor differences in emphasis all of these theories assume the same etiologic factors: innate temperamental difficulties, or an abusive or neglectful (or poorly matched in terms of temperament) relationship with a caregiver in early life.

Note: The patient = the borderline personality–disordered or difficult patient.

TERMINATION

Preparation of the difficult patient for discharge from the hospital is fraught with hazard. The patient not only might intensify disruptive behavior to prolong the hospital stay but also might simultaneously try to leave prematurely. The patient might secretly infect dressings or IV lines with saliva or feces and develop a fever while threatening to leave the hospital against medical advice. Or the patient might increase suicidal gestures, such as wrist slashing, to manipulate (get close to/stay distant from) the staff. Firm limits on sabotage and elopement should be discussed with the staff. Around termination, they should be more observant of the patient and more visible and firm. A specific discharge date should be firmly adhered to[109] despite a predictable worsening in the patient's psychological status.

After the patient has left, it is good for the consultant to touch base with the staff and the consultee once more to review the treatment and to share some of the consultant's own feelings. In this way, the consultant not only "terminates" with the staff but also paves the way for future work with the next difficult patient who comes to the general hospital.

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39 Emergency Psychiatry

Jennifer M. Park, M.D.
Abigail L. Donovan, M.D.
Lawrence Park, M.A., M.D.
Laura M. Prager, M.D.

Over the past 20 years, emergency psychiatry has developed into an independent subspecialty practice within psychiatry. Although formal board certification requirements are lacking, all accredited U.S. psychiatric residency–training programs follow minimum training guidelines for emergency psychiatry.[1] The emergence of emergency psychiatry as a specialized practice parallels the dramatic increase in patient volume in urgent and emergency care settings over the past decade. In 2001 there were more than 2 million visits to U.S. emergency departments (EDs) for mental health–related chief complaints, accounting for more than 6% of all ED visits and representing an increase in the percentage of all visits by 28% over the previous decade.[2] Among emergency mental health visits, substance-related disorders (30%), mood disorders (23%), anxiety disorders (21%), psychosis (10%), and suicide attempts (7%) are the most common.[2]

Psychiatric emergencies encompass a range of clinical presentations and diagnoses. Typically, such patients seek treatment in a state of crisis, unable to be contained by local support systems. Crises may be understood and addressed from a variety of perspectives, including medical, psychological, interpersonal, and social. Symptoms often consist of an overwhelming mental state that puts the patient and others in danger. Patients may have suicidal or homicidal ideation, overwhelming depression or anxiety, psychosis, mania, or acute cognitive or behavioral changes. More recently, emergency services have also been used for nonemergent conditions.[2] Increasing numbers of patients seek treatment at EDs for urgent conditions, routine conditions, or outpatient referrals because of lack of coverage for routine outpatient care, lack of community health care resources, or an inability to access health care. This has led to longer lengths of stay for some psychiatric patients in the ED, especially for those who demonstrate acute safety issues (suicidal or homicidal ideation) but lack insurance.[3]

The scope of emergency psychiatry includes core skills for psychiatric practice, as well as more specialized skill sets. In addition to the evaluation and treatment of severe psychiatric conditions, practitioners of emergency psychiatry are called on to evaluate and manage suicidal behavior, homicidal (or violent) behavior, agitation, delirium, and substance intoxication or withdrawal states. Because clinical practice lies at the interface of medicine and psychiatry, having knowledge concerning the assessment and treatment of medical conditions that involve psychiatric symptomatology is critical. Recently, emergency psychiatrists have also played important roles in an organized response to disasters.

The aim of this chapter is to provide a foundation for the clinical aspects of psychiatric emergency care. First, the general psychiatric emergency evaluation will be reviewed, with a particular focus on common initial symptoms. Then, special topics and the emergency treatment of children will be examined.

DEMOGRAPHICS

As of 1991, the United States had approximately 3000 dedicated psychiatric emergency services (PESs).[4] By 2007 a survey revealed that roughly 86% of general hospitals provided some type of emergency psychiatric care, with 45% having either a psychiatric emergency service or an in-house consultation service and 41% contracting with an outside source to provide emergency psychiatric care.[5] Among the patients treated at these specialized services, approximately 29% are diagnosed with psychosis, 25% with substance abuse, 23% with major depression, 13% with bipolar disorder, and 22% with personality disorders[6]; co-morbidity is common. Suicidal ideation is present among approximately one third to one half of the patients.[4]

Though some patients may self-refer to a PES while in crisis, patients may also be referred by family; friends; general practitioners; medical specialists; mental health treaters in the community; and employees of local, state, and public agencies. Since the occurrence of several school shootings by students, schools in the United States have become a major source of emergency referrals for violence and suicide assessments.[7] Police officers and representatives of the legal system are also a source of referrals, insofar as the PES serves as a conduit between the psychiatric system and the legal system.[8] The role of the PES is to help the police identify those patients with psychiatric illness and to re-route them to appropriate care, whereas those without acute psychiatric illness are returned to the legal system.

TYPES OF DELIVERY MODELS

Two general models are used to deliver emergency psychiatric services. In the first the PES exists as an independent service, co-located with a general emergency medical service or located separately in a stand-alone facility. In the second model, the PES functions as a consultation service that provides recommendations to primary emergency medical services. The model of services offered is determined by the volume of patients and the financial resources available.[9]

Delivery of emergency psychiatric care through an independent service offers several benefits. The first is safety: A PES physically separated from the chaos of a busy ED provides a secure environment for the assessment of patients (with limited access to sharp or dangerous objects, with quiet surroundings to decrease stimulation, and with the ability to observe and rapidly initiate psychiatric treatment). The unit may also have security staff who are trained to understand mental health issues and who can help maintain a safe environment. Many units also have specialized rooms for restraint and seclusion.[9] In addition, an independent PES is more likely to have individual rooms for private interviews, thus protecting the patient's privacy and dignity.

Another benefit of a dedicated psychiatric unit is the opportunity to staff the unit with specialized personnel who are trained in emergency psychiatric care.[4,9] An interdisciplinary staff of psychiatric residents and attending physicians, nurses, social workers, and case managers can enhance the care of patients with acute illness, for example, by coordinating medical care with colleagues in the ED. Psychiatric nurses also play an important role in the triage of mentally ill patients within the psychiatric unit and the ED. Their ability to manage the milieu in an emergency unit, provide individual support to patients, dispense psychiatric medications, and recognize situations that require immediate nursing and physician intervention is invaluable.

Some PESs also have access to "crisis beds" or facilities that are able to provide 24- to 72-hour observation. The ability to observe a patient whose mental state may change significantly after the initiation of antipsychotics or with a period of sobriety may decrease the need for inpatient hospitalization.[4,9,10]

A PES may also have a mobile crisis team, whose role is to evaluate patients in the community, defuse a crisis before a patient is treated at the ED, and decrease rates of hospitalization. As early as 1980, mobile initial response teams were described as a component of California community mental health centers and as an alternative to ED care.[11] One report from 1990 demonstrated similar hospitalization rates among hospital-based and mobile team emergency interventions,[12] whereas more recent reports have demonstrated decreased hospitalization rates associated with use of mobile teams.[13-15]

THE PSYCHIATRIC INTERVIEW

The psychiatric emergency evaluation is a concise, focused evaluation with the goals of diagnostic assessment, management of acute symptoms, and disposition to the appropriate level of care. Just as a visit to an ED for a medical complaint involves an initial triage (a brief evaluation of the severity of the problem), many emergency psychiatry models also depend on an initial assessment of the dangerousness of the psychiatric complaint itself, as well as in the context of co-morbid medical conditions. This initial, brief determination of acuity should screen for active medical issues that cause a change in mental status, as well as substance intoxication or withdrawal, suicidal or homicidal ideation, and other types of psychiatric symptomatology.

Many patients are willing to participate in a psychiatric interview, but some are not. Most states have enacted legislation that allows for holding individuals against their will if they are unable to care for themselves or if they present a danger to themselves or others. In the PES, if there is reason to believe that a person presents a substantial risk of physical harm to himself or herself or to other persons, or presents a very substantial risk of physical impairment or injury (because of an inability to care for oneself), the person may be held or sequestered in the PES or ED for further evaluation. The cornerstone of the initial psychiatric evaluation is a careful history that focuses on the temporal relationship among symptoms that have led to the emergency visit, on associated signs and symptoms, and on possible precipitants and causes. For patients with chronic mental health issues, it is also important to understand what triggered the emergency visit on that day in particular. In addition, a past history of medical illnesses, psychiatric illnesses, medication usage, allergies, adverse reactions to medications, patterns of substance use, a family history of psychiatric illness, and a psychosocial history serve as important aspects of the initial evaluation. Table 39–1 describes the components of the evaluation, and Table 39–2 describes the special features of a substance abuse evaluation.

TABLE 39–1 The Emergency Psychiatric Interview and Evaluation

- Chief complaint
- History of present illness, with a focus on symptoms and the context for these symptoms; include a safety evaluation, with assessment of suicidal and homicidal ideation, plan or intent, and any associated risk factors
- Past medical history, with a focus on current problems
- Past psychiatric history, particularly symptoms or events similar to the current presentation; include diagnoses, previous hospitalizations, and suicide attempts
- Allergies and adverse reactions to medications
- Current medications, including an assessment of compliance
- Social history, particularly how it contributes to the context for the emergency visit
- Substance use and abuse history
- Family history, including symptoms or diagnoses similar to the patient's presentation and a family history of suicide
- Mental status examination
- Review of medical symptoms, particularly any medical symptoms that may account for the patient's presentation
- Vital signs
- Physical examination, if indicated
- Laboratory studies and other tests, if indicated
- Assessment, including a summary statement, a statement about the patient's level of safety, and a rationale for disposition recommendations
- Axes I through V according to DSM-IV criteria
- Plan and disposition
- Documentation of any significant interventions (e.g., medication administration) and the outcome

TABLE 39–2 The Substance Abuse Interview

For each substance used, assess the following:
- Age of first use
- Amount and frequency of use
- Method of use (e.g., drinking, smoking, intranasal, IV)
- Time of last use and amount used
- Medical sequelae of use
- Social sequelae (relationship problems, school or work absences, legal problems)
- Longest period of sobriety
- Previous treatment (detoxification programs, outpatient programs, partial hospitalization)
- Method of maintaining sobriety
- Participation in self-help substance abuse programs (e.g., Alcoholics Anonymous, Narcotics Anonymous)
- Risk for withdrawal syndrome
- Patient's motivation to cut down or stop substance use
- Patient's need for assistance meeting goals to cut down or stop substance use

It is important to be aware of all potential information that may be included in an emergency psychiatric evaluation and then choose to elaborate on areas that are most relevant to the patient at hand. The interview should be a fact-gathering mission, and the elements of the history should both tell a story about the current symptoms and provide support for the disposition that the psychiatrist chooses. For example, though the developmental history may not be an important part of the evaluation for an otherwise healthy-appearing adult patient with depression, it may be very important in the assessment of a young patient with obvious cognitive deficits.

The emergency evaluation always includes an assessment of the patient's living situation and social supports, as well as a brief understanding of how he or she spends the day (e.g., at work, at school, or in a day program). This assessment defines the patient's baseline level of function. In addition, a review of the patient's health insurance is necessary because this often dictates the types of treatment programs that are available as disposition options.

Often, presentations to the PES are complicated, and patients may be unable, or unwilling, to provide an accurate history. For this reason an important feature of the evaluation is the collection of history from multiple sources (including family, friends, treaters, police, or emergency personnel who transported the patient). When several informants can be interviewed, data can be corroborated from the various sources, which can help the psychiatrist make informed disposition decisions.

THE MEDICAL EVALUATION

For any patient treated at an ED with an altered mental status (be it a change in cognition, emotional state, or behavior), it is crucial to rule out an underlying medical condition that causes or contributes to the problem. A change in mental state may indicate a primary psychiatric condition, a primary medical condition with psychiatric symptoms, delirium (an acute and reversible condition secondary to a medical illness), or dementia (a chronic condition associated with long-term, irreversible brain pathology). It is important to consider medical etiologies for any condition that appears psychiatric in nature because many psychiatric hospitals have limited resources to diagnose and treat medical conditions. The ED medical evaluation may be the most comprehensive that the patient receives. A missed medical diagnosis because of an assumed psychiatric diagnosis could result in dire consequences for the patient.

A medical work-up should be considered for any new onset of psychiatric symptomatology or any significant change or exacerbation of symptoms. This initial medical work-up is often referred to as *medical clearance*, a term that generally refers to a medical evaluation aimed at ruling out underlying medical conditions that cause or contribute to a psychiatric presentation. Although much attention has been paid to defining a standard for medical clearance, there is no clear consensus regarding the required elements of the medical evaluation.[16,17]

One retrospective study of 212 consecutive patients who underwent a psychiatric evaluation at an ED demonstrated that among patients with a known psychiatric history and no medical complaints (38%), screening laboratories and radiographic results yielded no additional information; those patients could have been referred for further psychiatric evaluation with the history, the physical examination, and stable vital signs alone. Among the patients deemed to require further medical evaluation (62%), all had either reported medical complaints or their medical histories suggested that further evaluation would be necessary before psychiatric referral.[18] Another study of the medical evaluation of ED patients with new-onset psychiatric symptoms demonstrated that two thirds had an organic cause for their psychiatric symptoms.[19] These studies suggest that careful screening is important among patients with new-onset symptoms, but additional medical tests may be of little benefit among patients with known psychiatric disorders and without physical complaints or active medical issues.

The medical evaluation should involve a thorough medical history, a general review of systems, and the assessment of vital signs, followed by a physical examination or laboratory tests (or both) as indicated. Practitioners should be vigilant of characteristics (e.g., homelessness or IV drug abuse), which may put a patient at risk for additional medical conditions. The medical tests to consider are listed in Table 39–3.

THE SAFETY EVALUATION

The safety evaluation is a mandatory component of every emergency evaluation and assesses the likelihood that an individual will attempt to harm himself or herself or someone else. Suicide is the eighth leading cause of death in the United States, and more than 90% of patients who commit suicide have at least one psychiatric diagnosis.[20] Patients 15 to 24 years of age and those over 60 are in the highest-risk groups for suicide.

The psychiatrist must ask about thoughts, plans, and intent of suicide and homicide. These questions should be followed up with more specific questions about access to the means for harm. If a patient has a plan or the intent to commit suicide, the lethality of the plan, as well as the patient's perception of the risk, must be assessed. A medically low-risk plan may still coincide with a strong intent to die if the patient believes that the lethality of the attempt is

TABLE 39–3 Tests to Consider in the Medical Evaluation of Patients with Psychiatric Symptoms

- Complete blood count ([CBC] to monitor for infection, blood loss)
- Electrolytes, blood urea nitrogen (BUN), creatinine (metabolic changes, hyponatremia or hypernatremia, abnormal kidney function, dehydration)
- Glucose (hypoglycemia or hyperglycemia)
- Liver function tests and ammonia (e.g., liver dysfunction due to hepatitis or alcohol abuse)
- Pregnancy test
- Serum toxicology screen (ingestion, intoxication, poisoning)
- Medication levels (ingestion of medications, e.g., lithium and tricyclic antidepressants)
- Urine toxicology screen (to identify or confirm substance abuse)
- Calcium, magnesium, and phosphorus (hypoparathyroidism or hyperparathyroidism, eating disorders, poor nutrition)
- Folate, thiamine (alcohol dependence, poor nutrition, depression)
- Vitamin B_{12} (megaloblastic anemia, dementia)
- Thyroid-stimulating hormone; this result may not be available immediately, but it may be available during an extended observation period (hypothyroidism or hyperthyroidism)

The following tests and imaging studies may also be considered in the medical work-up:

- Lumbar puncture (infection, hemorrhage)
- Electroencephalogram (seizure, changes due to ingestion of medications, dementia)
- Computed tomography (CT) (acute hemorrhage or trauma)
- Magnetic resonance imaging (MRI) (higher resolution than CT for potential brain masses or lesions, posterior fossa pathology, or when radiation exposure is contraindicated)

Adapted from Alpay M, Park L: Laboratory tests and diagnostic procedures. In Stern TA, Herman JB, editors: *Psychiatry update and board preparation,* New York, 2000, McGraw-Hill.

high. Similarly, the possibility that the patient could have been rescued if he or she had followed through on the plan should be evaluated; an impulsive ingestion of pills in front of a family member after an argument conveys less risk than a similar attempt in a remote location. If a patient has attempted suicide previously, details of that attempt may facilitate an understanding of the current risk. In addition, the clinician should assess other risk factors for suicide, which include the presence of a major mental illness, substance abuse, impulsivity, family history of suicide, recent loss (social, occupational, or financial), chronic illness, and access to lethal means.

The assessment of violence is similar to the assessment of suicide risk. Every patient should be asked about thoughts to harm others, as well as the patient's potential plans and intent. Observation of the patient's mental status, behavior, and impulsivity during the interview provides important information. Because previous behavior is the best predictor of future behavior, if there is any suspicion of impending violence, it is important to establish previous violent thoughts and behaviors, triggers leading to those events, and their relationship to substance abuse. Questions about legal issues related to violence are also appropriate. In addition, the target of violence should be assessed. Violence may lack a specific target or be directed toward a specific individual. If there is a likelihood of directed violence toward an identified person or persons, there will be a duty to warn the identified target.

The safety evaluation should include contact with others who know the patient. Although civil commitment laws differ from state to state, most states have provisions for the containment of a patient who is deemed at risk for harm to self or others; however, in many cases a patient with suicidal or homicidal ideation will choose voluntary hospitalization. In cases in which the patient has acknowledged suicidal or homicidal ideation, but it has resolved during the course of the emergency visit, care must be taken to create a clear plan for steps that the patient should take if the feelings or thoughts return. Most often, these involve contact with family members and treaters and a return to a psychiatric evaluation center or ED.

PSYCHIATRIC SYMPTOMS AND PRESENTATIONS

Diagnosis using *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria[21] can be difficult in the PES because patients are seen at a single point in time, often in the worst crisis of their lives. Although patients will not necessarily fit the criteria exactly, a search for the most common disorders (e.g., mood disorders, psychosis, anxiety disorders, substance abuse, and a change in mental status caused by a medical etiology [such as delirium]) will facilitate assessment. The following pages will outline some of the most common psychiatric presentations and patient characteristics in the ED.

The Depressed Patient

Depression is a common reason for seeking treatment at a PES. The severity of the depression may vary from mild to extremely severe; it may occur with or without psychosis or suicidal thinking. Anhedonia and other neurovegetative symptoms of depression are common complaints. Anxiety or anger attacks are often co-morbid with depression, and a history of mania must be assessed in every depressed patient to screen for bipolar disorder. Other medical conditions, especially hypothyroidism, must be considered. The severity of symptoms and the ability to participate in work and other routines may contribute to a diagnosis; however, the assessment of safety is essential in treatment planning.

The Anxious Patient

Although symptoms of anxiety may reflect a primary anxiety disorder, anxiety often heralds other disorders. Patients with psychosis may first describe anxiety about people who might try to harm them; patients with depression may have anxiety about financial or relationship difficulties. Psychomotor agitation, fidgeting, and pacing co-occur with anxiety but may also correlate with psychosis, alcohol withdrawal, or cocaine intoxication. Medical problems (e.g., hyperthyroidism, delirium) and medication side

effects (e.g., akathisia) may also be confused with anxiety. Chest pain and shortness of breath resulting from a panic attack are also common presentations to the ED that will require thorough medical evaluation in concert with a psychiatric evaluation.

The Psychotic Patient

Patients with psychosis suffer from disorganized thinking, hallucinations, delusions, or other forms of disordered thought (e.g., ideas of reference, thought broadcasting, or thought insertion). Patients with psychosis vary greatly in the severity of their symptoms; they may be affected by paranoia that has undermined their work or relationships or suffer from loose associations, delusions, or aggressive behavior. Because some patients have lost touch with reality and may be at risk for agitation or dangerousness, awareness for the safety of staff and other patients must be maintained. Among patients with new-onset psychosis, severe anxiety is common, and it may be difficult to differentiate from paranoia.

It is also important to rule out medical causes for symptoms, particularly among patients who lack a history of psychosis and whose age falls outside the usual range for the onset of psychosis (late teens to mid-20s). Auditory hallucinations are more common with psychiatric disorders, whereas visual hallucinations are more common in medical disorders, delirium, and substance abuse. Seizure disorders, delirium, metabolic changes, infections, ingestion, and withdrawal from alcohol or benzodiazepines should be considered in the differential for new-onset psychosis. Among the elderly with new-onset hallucinations, delirium and dementia should be strongly considered.

The Manic Patient

Manic patients can often be disruptive and provocative, with pressured speech, grandiosity, irritability, and flight of ideas. Such patients may be dressed or behave in an odd or seductive manner and may have impulsively traveled long distances. In mania with psychosis, paranoid thoughts and delusions or hallucinations often arise, leading to a lack of insight. It is important to assess for medical causes of mania, as well as for acute intoxication with cocaine or phencyclidine (PCP). Steroids can also contribute to manic symptoms, as can antidepressant medications.

The Patient with Intoxication or Withdrawal

Patients with substance intoxication or withdrawal often come to the attention of emergency personnel because of acute medical symptoms (e.g., unconsciousness, difficulty breathing, confusion). However, they may also come to the ED requesting referral for detoxification services or other substance abuse treatment. Substance abuse is frequently co-morbid with other psychiatric conditions. The following will outline the substances of abuse seen in the PES and key concepts in the assessment of substance abuse.

Alcohol

Alcohol intoxication can cause disorientation, ataxia, and slurring of speech; when high blood alcohol levels (BALs) are present, respiratory depression, coma, and death may follow. Chronic alcohol use leads to tolerance and a higher BAL without severe symptoms. For alcohol intoxication, treatment typically consists of observation, maintenance of the airway, and administration of IV fluids.

Alcohol withdrawal is medically dangerous and can be life-threatening. In its mildest form, alcohol withdrawal leads to irritability, tremor, autonomic instability (associated with an elevated blood pressure, pulse, and temperature), and sometimes seizures. Patients with a high tolerance for alcohol may be in alcohol withdrawal despite the presence of alcohol in their blood because of a relative withdrawal from the substance compared with their usual (intoxicated) state. Treatment of alcohol withdrawal generally involves use of oral or IV benzodiazepines (initially titrated to normalize vital signs and then tapered over several days), thiamine (to prevent Wernicke's encephalopathy), folic acid, and fluid repletion. A high-potency neuroleptic (e.g., haloperidol) can decrease psychomotor agitation associated with withdrawal. Prophylactic treatment with benzodiazepines and thiamine for patients at high risk of alcohol withdrawal is beneficial.

In more severe cases, alcohol withdrawal can lead to delirium tremens, which consists of a change in mental status, disorientation, visual hallucinations, and severe autonomic instability. Delirium tremens is a medical emergency with a mortality rate of 5% to 10%; it requires immediate medical care and treatment with IV benzodiazepines, thiamine, and fluids.[22]

Benzodiazepines and Barbiturates

Intoxication with benzodiazepines and barbiturates appears similar to intoxication with alcohol; it involves the presence of slurred speech, confusion, ataxia, and respiratory depression. Withdrawal is also dangerous and life-threatening; management is similar to that of alcohol withdrawal, including oral or IV benzodiazepines or barbiturates.

Opiates

Abused opiates seen in the PES include heroin, oxycodone, methadone, hydrocodone, and fentanyl. Intoxication can be identified by drowsiness and pupillary constriction; in addition, patients describe a sense of euphoria or calm. The greatest risk of opiate overdose is respiratory depression. Frequently, accidental overdoses occur when patients either miscalculate their dose after a period of abstinence (because of decreased tolerance) or when the drug is of a higher purity than expected. Opiate intoxication can be treated in the emergency setting with naloxone, an opioid antagonist, although drowsiness and respiratory depression may return as the naloxone wears off. In addition, the naloxone will cause an acute and uncomfortable withdrawal syndrome that often leads to agitation on awakening.

Opiate withdrawal is not life-threatening. Early symptoms include anxiety, yawning, diaphoresis, rhinorrhea, dilated pupils, abdominal and leg cramping, and chills. Elevated blood pressure, pulse, and temperature, as well as nausea and vomiting, will follow. A urine drug screen can usually confirm recent opiate use. In the emergency setting, symptomatic treatment consists of the use of clonidine for autonomic instability (monitor for hypotension), dicyclomine for abdominal cramps, and quinine sulfate for

leg cramps (limit to once per day on account of cardiovascular or renal toxicity). The patient can be referred to a licensed detoxification facility for methadone or buprenorphine detoxification.

Cocaine

Patients with cocaine abuse most often are treated at the ED suffering from medical symptoms (e.g., chest pain) or psychotic symptoms. The symptoms of cocaine intoxication include euphoria and grandiosity, irritability or agitation, lack of sleep, dilated pupils, and psychomotor restlessness (e.g., pacing, hand wringing, foot tapping, or choreiform-like movements). Patients may experience elevated blood pressure and temperature, tachycardia, palpitations, chest pain, and shortness of breath. Some patients experience hallucinations, paranoia, or agitation; antipsychotic medications are a useful treatment. With very high doses of cocaine, a patient can experience decreased responsiveness, seizures, and severe autonomic changes followed by coma and risk of cardiac arrest or ventricular fibrillation; treatment is supportive. Serum toxicology screens for cocaine, if available, may confirm very recent use of cocaine (within hours), whereas urine toxicology may confirm use up to 24 hours previously.

Although there is no clearly described withdrawal syndrome for cocaine, patients often experience a very strong urge to sleep once cocaine has left their system. They also describe feeling weak and tired, with cravings for days to weeks after use has ended.

Crystal Methamphetamine

Intoxication with crystal methamphetamine and other amphetamines may be recognized by mood lability or irritability, psychomotor agitation, confusion, and sweating. More severe cases may include paranoia, hallucinations, seizures, and fever. Treatment is supportive. Psychotic symptoms can be treated with antipsychotics.[23] Withdrawal from amphetamines leads to agitation, irritability, sleep disturbance, psychomotor agitation, and depressed mood.

Phencyclidine

Phencyclidine (PCP; also known as "angel dust") intoxication is usually heralded in the emergency setting by agitation, paranoia, hallucinations, and violent or bizarre behavior. Intoxication can cause nystagmus, ataxia, and slurred speech; at higher doses it may lead to seizures, hypertensive crisis, coma, and death. Treatment is supportive and should include management in a contained and quiet setting (because of the risk of violence). Antipsychotics, particularly high-potency neuroleptics (e.g., haloperidol), may be useful. PCP-induced psychosis can last from days to weeks; these patients may require hospitalization if symptoms do not improve within several hours.[23] There is no withdrawal syndrome from PCP.

Marijuana

Marijuana is a common drug of abuse among patients treated at the PES. Symptoms of intoxication include relaxed or elevated mood, alteration in the perception of time, tachycardia, and conjunctival injection.[23] Patients may report paranoia or hallucinations, although in these cases it is important to assess for other drugs of abuse and for underlying psychiatric disorders as well.

The Patient with a Change in Mental Status

When treating a patient who displays a significant change in mental state, the emergency psychiatrist must identify the underlying etiology. In general, changes in mental state represent delirium, dementia, or psychiatric conditions. Because psychiatric conditions are often a diagnosis of exclusion in the acute presentation, delirium and dementia must be ruled out. The Folstein Mini-Mental State Examination[24] can be useful to screen for cognitive changes. Dementia, a chronic and progressive condition characterized by memory and other cognitive impairments, is discussed elsewhere in this textbook (see Chapter 11).

Delirium, as defined by DSM-IV,[21] is a fluctuating state of consciousness and cognition that is caused by a variety of medical conditions. Delirium, also known as acute confusional state or encephalopathy, typically has an acute onset (over hours to days), has a fluctuating course, and is reversible. Disturbance in consciousness, reduced awareness of the environment, attentional difficulties, disorientation, and an inability to think or speak coherently are common symptoms of delirium. Psychomotor agitation is also common, though psychomotor retardation is possible. Symptoms typically associated with psychiatric diagnoses (e.g., auditory and visual hallucinations, acute changes in mood, psychotic or disorganized thoughts) may also be seen in delirious states. In general, it can be said that any medical condition has the potential to cause any type of alteration in mental state. Although certain underlying medical conditions are commonly associated with certain symptoms (e.g., anxiety or agitation with pheochromocytoma, mania with use of corticosteroids, and depression with interferon treatment), the underlying medical condition cannot be diagnosed by its presentation alone; all possible medical conditions must be considered.

Delirium may represent a serious or life-threatening condition. These conditions include Wernicke's encephalopathy, hypoxia, hypoglycemia, hypertensive encephalopathy, intracerebral hemorrhage, meningitis/encephalitis, poisoning (exogenous or iatrogenic), and seizures. Their assessment and treatment are outlined in Table 39–4. Other, less urgent conditions (including subdural hematoma, septicemia, subacute bacterial endocarditis, hepatic or renal failure, thyrotoxicosis or myxedema, delirium tremens, anticholinergic psychosis, and complex partial status epilepticus) may require acute interventions.[25] Once acute causes of delirium have been ruled out, other potential causes of delirium should be considered (see Chapter 10 for a more detailed discussion of delirium). When a medical diagnosis has been made, the primary objective is to address the underlying etiology. Nonetheless, symptomatic treatment of confusion or agitation associated with delirium should be administered.

If medical causes of delirium have been ruled out, a primary psychiatric diagnosis should be considered. A diagnosis of an Axis I primary mood or thought disorder often can be made on the basis of symptomatology. If the patient does not meet diagnostic criteria for an Axis I disorder, an Axis II personality disorder or personality traits should be considered. Agitation or threatening behavior may not be due to either an Axis I or an Axis II condition but may be

TABLE 39–4 Potentially Life-Threatening Causes of Delirium

CONDITION	DIAGNOSTICS	TREATMENT
Wernicke's encephalopathy	Clinical triad: change in mental status, gait instability, ophthalmoplegia	Thiamine 100 mg IM (may see improvement over the course of hours) status, gait instability, ophthalmoplegia
Hypoxia	Oxygen saturation/ABGs	Treat etiology
Hypoglycemia	Blood glucose	PO/IV administration of glucose, dextrose, sucrose, or fructose
Hypertensive encephalopathy	Blood pressure	Antihypertensive medication
Hyperthermia/hypothermia	Temperature	Cooling or warming interventions
Infectious process (e.g., sepsis, bacteremia, subacute bacterial endocarditis)	Infectious disease work-up	Treat infectious agent or site
Intracerebral hemorrhage	MRI/CT	Per hemorrhage type or location
Meningitis/encephalitis	LP, MRI	Antibiotic medication
Metabolic (e.g., chemical derangements, renal failure, hepatic failure, thyroid dysfunction)	Laboratory investigations	Per derangement
Poisoning/toxic reaction (e.g., environmental exposures, medications, alcohol, illicit substances)	Toxicology panel	Per toxin
Status epilepticus	EEG	Anticonvulsants and/or IV benzodiazepines

ABGs, Arterial blood gases; *CT,* computed tomography; *EEG,* electroencephalogram; *IM,* intramuscular; *IV,* intravenous; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging; *PO,* oral *(per os)*.

representative of longer-standing problems with behavior regulation and thus may not be amenable to acute psychiatric treatment.

The Agitated Patient

In the emergency setting, evaluation and treatment may be complicated by *agitation*, defined as the physical manifestation of internal distress. Agitation may be a sign of psychiatric distress or be related to an underlying medical etiology. Early signs include pacing, tapping of the fingers and feet, sighing, moaning, breathing heavily, fidgeting, staring intensely, and appearing distracted by internal stimuli. Physical signs (e.g., elevations in blood pressure, pulse, or respiratory rate) may be noted. Pressured or loud speech, invasion of others' personal space, clenching of the jaw, or tension of other muscles often indicates escalating agitation. Agitation can herald a psychiatric emergency; it jeopardizes the safety of the patient as well as others in the treatment environment, and it impedes optimal evaluation and treatment.

Agitation is best managed by attempting to prevent or treat it as early as possible. The agitated patient should be enlisted in this task (i.e., to monitor his or her own internal state, report increases in anxiety or distress, and consider effective means for the reduction of distress in order to avert any behavioral dyscontrol). Modulation of the environment (by decreasing interpersonal interactions and auditory or visual stimulation) is an important initial step in management. A safe environment (free from the risk of harm) should be created to reduce agitation for some patients. Staff or family members should be available to communicate with the patient. Offers of food and drink may also be helpful.

Rapid movements, yelling, slamming doors, and throwing objects are important signals that the patient is out of control. Threats or attempts to harm oneself or others signal that more must be done to keep the patient and the staff safe. If there is a risk of harm to the patient or others, a physically safe environment, without allowing the patient access to objects that could be used as weapons and using the least-restrictive means possible, should be arranged. Pharmacologic interventions to reduce agitation should also be considered. Further discussion of management of agitation, including medications and restraint and seclusion, is provided later in this chapter.

Drug or alcohol intoxication or withdrawal (including nicotine withdrawal), delirium, injury, pain, dementia, psychosis, mania, anxiety, and borderline and antisocial personality disorders are just a few of the diagnoses that lead to agitation in the PES.

MANAGEMENT OF ACUTE SYMPTOMS

The primary goal in the PES is to manage acute crises. The intervention chosen will depend on the patient's needs, the severity of illness, and the time and resources available. For some patients the intervention consists of the opportunity to speak to an understanding clinician, who can form an alliance, demonstrate empathy, and provide reassurance. Other patients require IM medication or restraint for agitation. Between those extremes are various therapeutic interventions designed to decrease the acuity of the patient's situation, provide education about mental illness and treatment, and help the patient and family members make informed decisions about treatment. The interventions provided in the PES can be broken down into four categories: the environmental intervention,

the psychological intervention, the medication intervention, and use of restraint and seclusion (the option of last resort).

Environmental Intervention

Although resources and space may be limited, the environmental intervention is of critical importance for a patient in crisis. The environment will determine if the patient will sit, stand, or lie on a stretcher; if he or she will wear street clothes or a hospital gown; and if the clinician will be alone with the patient or be accompanied by family members or other emergency staff. If possible, the interview should occur in a quiet, clean setting, where the patient and clinician can both sit comfortably and not be overheard by strangers in the ED. This, of course, depends on the patient's behavior; the presence of other staff or security in the ED is paramount for safety when working with a patient who appears agitated or impulsive. Attention to the patient's basic needs (e.g., offering a blanket in a cold room, being sure that the patient has access to a restroom, and offering the patient something to drink or eat) will assist in forming an alliance.

Psychological Intervention

Forming an alliance during a brief interview in an emergency setting can be a challenge. PESs are often busy, with long waits for evaluation and treatment; clinicians who work there are often pulled in different directions. A sympathetic comment after a patient has experienced an extended wait can facilitate an alliance.

The psychiatrist should allow the patient a few minutes at the beginning of the interview to describe the situation. Beginning the interview with several open-ended questions will help the patient feel heard, allow a brief assessment of the patient's mental status, and give the psychiatrist time to formulate a plan to guide the course of the interview. Because of time constraints, the PES evaluation often involves more closed-ended screening questions (to rule out major symptoms or diagnoses) than occur in other psychiatric arenas. Empathic comments demonstrate concern and allow the clinician to interject with appropriate questions to guide the interview.

In the PES the psychological intervention is often pragmatic. It may consist of formation of an empathic connection and education about psychiatric symptoms, treatments, or the mental health system. The clinician may help the patient gain insight into the problem at hand and brainstorm about alternative solutions. Some dependent patients will want help in making a decision about treatment, whereas the clinician may want to lead narcissistic patients to create solutions themselves. The psychiatrist may offer reassurance that a problem is not as overwhelming as it seems or that help is available. The simple act of validating a patient's feelings of being overwhelmed can often be a therapeutic intervention. The patient's and the family's unstated wishes or concerns should be identified and managed.

Questions or techniques that allow the patient to regress are rarely helpful in the PES; instead, the patient should be encouraged to identify coping skills that have been helpful at other times. Though the patient should be allowed to describe difficult feelings and release tension, there should be an expectation that the patient behave within the boundaries of what is safe and appropriate in that environment (e.g., it is not appropriate to punch walls to demonstrate anger). There will be times when a patient is too ill to participate within these boundaries, and accommodations can be made, but this circumstance usually indicates a need for referral to a higher level of care.

Another key to providing therapeutic care in the emergency setting is to understand potential countertransference reactions. Amid the stress of overcrowded and chaotic EDs and PESs, staff members at every level can become cynical and angry. Although these reactions are understandable, care must be taken to separate these frustrations from the health and welfare of patients. Acting on countertransference reactions can lead to unprofessional behavior and can compromise clinical care and safety. For many years at Massachusetts General Hospital, psychiatric residents have participated in a weekly supervision session that focuses on recognizing countertransference reactions and enhancing resilience after long nights in the PES.[26] Awareness of stress levels and scheduled breaks (to eat meals and relax during long shifts) are necessary to the provision of good care on an emergency service.

Intervention with Medication

Never underestimate the power of medication in a psychiatric emergency. For some patients, particularly those who are psychotic or acutely agitated, administering medication may be the primary intervention. Medication can decrease anxiety and paranoia, improve disorganization, and help a manic patient to sleep. Benzodiazepines decrease symptoms of alcohol withdrawal. Some patients who are initially overwhelmed are able to participate in the interview and psychological intervention only after medication has been administered. Medication should be considered early and often in the process of an evaluation. If the patient uses a medication at home on an as-needed basis for similar symptoms or has tried a medication before, the same medication can be offered to minimize potential side effects of new medications. If the patient has not tried medications, consideration of the symptoms, differential diagnosis, intended means of administration of the medication, and potential side effects will help narrow down the options.[27,28]

Potential medication regimens in the PES include benzodiazepines (particularly lorazepam [0.5 to 1 mg] PO or IM; a benzodiazepine should always be the first choice if alcohol withdrawal is suspected); atypical neuroleptics (e.g., risperidone [0.5 to 1 mg] in oral tablet, liquid, or rapidly dissolving form or olanzapine [2.5 to 5 mg] in oral tablet or rapidly dissolving form); and high-potency neuroleptics (e.g., haloperidol) combined with a benzodiazepine and an anticholinergic agent (diphenhydramine or benztropine) for more severe agitation. A commonly used combination that can be administered PO or IM is haloperidol 5 mg and lorazepam 2 mg, plus diphenhydramine 25 to 50 mg (for prophylaxis of dystonia). Newer parenteral formulations of atypical neuroleptics for the management of acute agitation are also available; options include olanzapine 10 mg IM, ziprasidone 10 to 20 mg IM, and aripiprazole 9.75 mg IM. Table 39–5 lists a range of medications that are used for adult patients in the PES.

TABLE 39–5 Medications Frequently Used in the Psychiatric Emergency Service for Adult Patients

MEDICATION	STARTING* DOSE	FORMULATION AVAILABLE
Benzodiazepines		
chlordiazepoxide (Librium)	25-50 mg	PO/IM/IV
clonazepam (Klonopin)	0.5 mg	PO
diazepam (Valium)	5-10 mg	PO/IM/IV (oral solution available)
lorazepam (Ativan)	0.5-1 mg	PO/IM/IV (oral solution available)
oxazepam (Serax)	15-30 mg	PO
Typical Antipsychotics		
chlorpromazine (Thorazine)	25-50 mg	PO/IM (oral solution available)
fluphenazine (Prolixin)	5-10 mg	PO/IM (oral solution available)
haloperidol (Haldol)	5-10 mg	PO/IM/IV (oral solution available)
perphenazine (Trilafon)	4-8 mg	PO (oral solution available)
Atypical Antipsychotics		
olanzapine (Zyprexa)	5-10 mg	PO/IM†
quetiapine (Seroquel)	25-50 mg	PO
risperidone (Risperdal)	1-2 mg	PO† (oral solution available)
ziprasidone (Geodon)	20 mg (10-20 mg IM)	PO/IM
Other Agents		
benztropine (Cogentin)	0.5-1 mg	PO/IM/IV
buspirone (BuSpar)	5-10 mg	PO
clonidine (Catapres)	0.1 mg	PO
diphenhydramine (Benadryl)	25-50 mg	PO/IM/IV (oral solution available)
gabapentin (Neurontin)	100-200 mg	PO
propranolol (Inderal)	20 mg	PO (oral solution available)
trazodone (Desyrel)	25-50 mg	PO

*Starting doses are for healthy adult patients. Consider lower doses in patients who are elderly or have a history of head injury or mental retardation.

†Also available in an orally disintegrating tablet.

IM, Intramuscular; *IV,* intravenous; *PO,* oral *(per os).*

Elderly patients, patients with mental retardation, and patients with a history of head injuries can be particularly sensitive to anticholinergic side effects or to paradoxical reactions of medications such as benzodiazepines. Smaller initial doses of medication should be used, with increases made slowly in these populations.

Restraint and Seclusion

In general, use of the least restrictive means of restraint is the standard of care in psychiatry. However, this principle must be balanced with the risk of imminent danger as determined by the clinical assessment.

Restraint and seclusion are treatments of last resort when the patient is at imminent risk of harming himself or herself or someone else. Unfortunately, controlled studies comparing the impact of methods of restraint and seclusion are lacking.[29] Recent efforts have focused most on methods for reducing the need for restraint and seclusion in psychiatric settings.

All staff involved in restraint and seclusion should be well trained in the techniques for the safe management of aggressive behavior. Such management begins with the use of verbal de-escalation techniques and environmental interventions (e.g., placing the patient in a private room to decrease outside stimulation). Medication should be offered early in the course of agitation and aggression. If these interventions are not successful, and the patient remains at risk for harm to self or others, seclusion (placing the patient in a locked room alone) becomes an alternative for management. For patients who remain aggressive or at serious risk for harm, physical restraint may be the last resort to maintain their safety and the safety of those around them. Generally, it is the physician who orders restraint or seclusion, but the entire team should be clear about the reason for the restraint and the procedures involved. Each member of the team should feel responsible for maintaining the safety of the patient and the other staff.

The patient in seclusion or restraint should also be monitored at all times. In most facilities there is a limit to the time that the patient may remain in restraint; however, attempts should always be made to remove the restraints as soon as possible. Almost every patient who requires restraint or seclusion can benefit from medication to decrease the symptoms that have led to agitation.

Treatment After the Acute Crisis

The availability of outpatient treatment varies greatly by location and accessible resources in the hospital or the community. Some PESs offer prescriptions for medications on discharge and even provide follow-up while patients are awaiting referral to outpatient facilities. Other programs treat only acute problems and do not prescribe but may have access to urgent appointments or an outpatient program with a short wait list. Either way, after the management of the acute problem, treatment planning is part of every disposition.

The emergency psychiatrist must have a thorough knowledge of the local mental health resources. Inpatient units, crisis stabilization units, residential treatment services, partial hospitalization programs, detoxification units, and outpatient programs serve as alternative levels of care after the PES evaluation. Admission criteria vary, and many programs depend on prior approval by insurance companies. The acuity of the patient's symptoms, the insurance coverage, and the psychosocial support system must all be weighed to determine the appropriate level of care. Decisions made with the patient, the family, and other treaters should be coordinated.

SPECIAL POPULATIONS

The Personality-Disordered Patient

Patients with borderline or antisocial personalities usually require a significant amount of time from PES staff to coordinate their care. Such patients may request special services or favors that are outside of the normal routine of the unit. They may file complaints or even threaten to harm or kill themselves or others if the clinician is unwilling to provide the treatment that the patient prefers. These threats often are statements of desperation, though each statement must be evaluated with the patient's history and current situation in mind.

Problems often occur because of splits between staff members who disagree about how the patient should be managed. The most important aspect of the treatment of these patients is for the PES team to provide clear boundaries regarding the scope of care available, the role of individual staff members, and the goal of the emergency intervention. Outside contacts who know the patient may be able to provide insight for the purposes of the safety assessment.

The Grieving Patient

Management of acute grief (e.g., after a traumatic event or a death within the ED, the loss of a relationship, or the anniversary of a loss) is a common reason for referral to the PES. Grief is the normal response to loss and can manifest in many ways, including feelings of shock, sadness, anxiety, anger, and guilt.[30] The most common symptoms are outlined in Table 39–6, and any of these may be exhibited during the emergency evaluation. Brief periods of hearing the voice of a deceased spouse or feeling unable to participate in the routines of daily life are normal; they allow the patient time to come to terms with the loss. However, extended periods of depressed mood, anhedonia, and other neurovegetative symptoms may indicate an episode of major depression and require more immediate treatment.

The role of the psychiatrist in working with a grieving patient is to provide a supportive environment. Some patients will want to sit quietly, others will want to talk, and others will cry. If the situation is ongoing (e.g., a family member's injury is being treated in the ED), accurate information should be provided and false hope should not be given. Clinicians should help patients recognize how they have handled losses in the past and support similar coping skills.

TABLE 39–6 Symptoms of Grief

Somatic distress
- Throat tightness
- Shortness of breath and sighing
- Muscular weakness
- Loss of appetite and abdominal discomfort or emptiness

Preoccupation with the image of the deceased
- Visualizing the deceased or hearing the voice of the deceased
- Imagining conversations with the deceased

Guilt about things done or not done

Hostility toward others

Changes in behavior
- Pacing or moving aimlessly
- Difficulty initiating the normal routine

Adapted from Lindemann E: Symptomatology and management of acute grief, *Am J Psychiatry* 151(6 suppl):155–160, 1994.

Victims of Domestic Violence and Trauma

Domestic violence (i.e., an individual's use of force to inflict emotional or physical injury on another person with whom the individual has a relationship) affects spouses, partners, children, grandparents, and siblings of all races and genders. Between 2 and 4 million women are abused each year in the United States, and domestic violence has become the leading cause of injury among women between 15 and 44 years of age.[31] Men can also be victims of domestic violence.

Patients in the PES should be asked whether they have been a victim of violence or trauma, whether this contributes to their presenting symptoms, and whether they are safe in their current living environment. Symptoms of posttraumatic stress disorder should be screened for and included in treatment planning. Patients need not be asked to describe explicit details about past traumas. Instead, the patient can be helped to understand that the process of working through trauma should occur with a therapist who can provide long-term support, and then the clinician can provide an appropriate referral.

The Homeless Patient

It is estimated that approximately 20%[6] to 30%[32] of the patients who are treated at PESs are homeless,[6] and this characteristic adds complexity to the psychiatric evaluation. When a patient has insomnia or the fear of being harmed by others, it may be difficult to determine whether the symptoms are due to a psychiatric disturbance or the inherent risks of homelessness. Homeless patients are at greater risk for substance abuse, tuberculosis, skin conditions, and other serious chronic medical conditions (e.g., diabetes, acquired immunodeficiency syndrome [AIDS], and cancer); it is especially important to provide good medical screening during the assessment. The clinician must also account for the patient's housing situation and access to meals and medical care in the course of disposition planning. A treatment plan adapted to these realities is much more likely to succeed[33]; however, despite careful disposition planning, homeless patients are more likely than other patients to have repeat visits to the PES.[32]

EMERGENCY ASSESSMENT OF CHILDREN

Demographics

There are very few studies of emergency psychiatric presentations among children. It is estimated that there are about 434,000 annual pediatric visits for mental health conditions in the United States, which constitutes about 1.6% of ED visits in this age group (younger than age 19). Adolescents between 13 and 17 years of age account for more than two

thirds of the visits, and suicide attempts account for 13% of the visits. The most common diagnoses include substance-related disorders (24%), anxiety disorders (16%), attention-deficit and disruptive disorders (11%), and psychosis (10%). Nineteen percent of ED mental health visits result in inpatient admission, compared with only 9% of non–mental health visits in the same age group.[34] A study that analyzed data about young people (ages 7 to 24 years) treated at EDs for deliberate self-harm reported an annual rate of 225 per 100,000.[35] Among those patients, 56% were diagnosed with a mental disorder (including 15% with depression and 7% with substance use disorders), and 56% were referred for inpatient admission. Frequent precipitants for ED visits include family crises (e.g., death, divorce, financial stress, domestic abuse), disturbed or truncated peer relationships, and recent change of school.[36-38]

Basic Principles

Few child psychiatric emergencies are life-threatening; all result from the complex interaction of psychosocial, biological, and systems issues.

The primary goal is the safety of the child, and this principle must guide all subsequent plans for treatment or disposition. The clinician must always consider the possibility of abuse or neglect as the precipitant for the visit to the ED.

The evaluation itself is based on a developmental approach. The clinician must choose age-appropriate techniques with which to conduct the examination, and the assessment must be based on a solid understanding of normative behavior within each developmental stage.

The emergency psychiatric assessment of a child is often more complicated and time-consuming than the evaluation of an adult. The clinician must be familiar with resources for children and families within the community mental health system. Thorough evaluation often requires phone calls to outside providers (including pediatricians, school administrators, guidance counselors, and outpatient mental health professionals).

The Evaluation

The initial step in the assessment of a child in the PES is identification of the child's legal guardian(s). In routine cases the legal guardians are the biological parents who accompany the child to the hospital. In complex cases the child's legal guardian may be court-ordered to be only one parent, another relative, a foster parent, or a representative of the state agency responsible for the care and protection of children. Custody can be split into several parts, and one guardian can have legal (or decision-making) custody while another guardian retains physical custody. Sometimes a child remains in the home of the biological parent, but a state agency assumes responsibility for decisions regarding medical care. The clinician should never assume that the adult who accompanies the child is the legal guardian or that a friend or neighbor can offer consent for the assessment. Except in very rare, extenuating circumstances, the legal guardian must come to the assessment center and participate in the evaluation because that person will be a key factor in disposition.

The clinician who evaluates children in an ED should base the method of assessment on the age of the child, although the interview may also include many standard elements of the psychiatric history as listed in Table 39–1. The *style* and *process* of the interview and mental status examination depend on the age of the child.

Preschoolers (1 to 5 years), many of whom may be preverbal, are unable to provide a coherent narrative of the events leading up to the ED visit. The clinician must interview the parent or guardian to obtain the details of the history but should also pay careful and close attention to the interaction between the child and the caregiver as well as to the child's hygiene. Mental status assessment should focus on the child's behavior, level of agitation, mood, affect, and ability to take direction and accept reassurance from the caregiver. Common precipitants for ED visits in this age group include impulsive or dangerous behaviors (e.g., running away from home or from a caregiver in a public place, fire setting, or hitting a younger sibling).

Latency-age children (5 to 11 years) can often provide a clear description of the event that brought them to the ED but usually lack the ability to place the specific event within a larger context. It is often helpful for the clinician to interview the parent or caregiver before meeting with the child. Assessment of the mental status includes observations of the child's interaction with the caregiver; attention to speech and language; and direct questions about mood, affect, and risk for self-injurious behavior. Children who are younger than 6 years of age might retain their magical thinking and thus not yet be able to distinguish fantasy from reality.

Adolescents (12 to 18 years) should ideally be interviewed before the clinician speaks with caregivers or other concerned adults. This approach reinforces and supports the adolescent's desire for autonomy and control. Mental status assessment involves assessment of mood, affect, thought process and content, cognition, insight, and judgment, as well as suicidal and homicidal ideation.

Finally, the evaluation must include an assessment of the social situation. Being familiar with the local communities and school systems around the hospital will help the clinician better understand the social context of the PES visit. An inner-city school with few resources is very different from a wealthy suburban school with counselors and school nurses who can identify new problems and monitor medications; knowing these details will help the clinician make appropriate decisions about the treatment plan. It is also important to know the types of treatments that the child has accessed before. A child whose severe depression has failed to improve after several medication trials and participation in months of residential treatment programs is very different from one who seeks treatment for the first time with anxiety symptoms. The previous treatment history will inform the disposition decision.

As with adult patients, the options available for disposition vary widely by location and accessible resources through the hospital and community programs. The clinician must have an accurate working knowledge of the available resources and how to access them in order to facilitate appropriate disposition planning for the child in crisis.

Management

The agitated or aggressive child requires rapid diagnostic assessment and management. The differential diagnosis should focus first on organic (medical) causes of the behavior (including elevated lead levels [particularly for children under 5 years]), seizure disorders, metabolic abnormalities, medication (prescription or over-the-counter) ingestion or overdose, withdrawal from medication or recreational drugs, hypoxia, infection, and intoxication.

If an organic etiology is suspected, vital signs and laboratory studies should be obtained immediately. Laboratory studies might include a complete blood count (CBC); serum electrolytes (including blood glucose); serum and urine toxic screens;[39] and, in young women, a pregnancy test. It is usually helpful to control the environment and decrease stimulation by placing the child in a private room, sometimes with one family member who can be soothing and reassuring. With very young children, it can be helpful to offer food and drink.

Sometimes it is necessary to administer medication to control agitated or acutely intoxicated children, particularly if they are in danger of harming themselves or others. It is best to ask the parent or guardian which medications the child usually takes and administer either an additional dose of a standing medication or an existing as-needed medication. Administration of an oral medication is always preferable to an IM injection, but it is not always possible if the child is unable to respond to verbal direction or limit setting.

The choice of medication and route of administration depend on the severity of the agitation and the age of the child. Medications to consider include diphenhydramine (1.25 mg/kg per dose PO or IM if the child has no history of paradoxical excitation); clonidine (at a dose of 0.05 to 0.1 mg PO); an atypical neuroleptic (e.g., risperidone [0.5 to 1 mg] in oral tablet, liquid, or rapidly dissolving form or olanzapine [2.5 to 5 mg] in oral tablet or rapidly dissolving form or IM preparation); benzodiazepines (particularly lorazepam [0.5 to 1 mg] PO or IM can be helpful but can also cause paradoxical excitation and disinhibition); and for an older, acutely agitated adolescent, it is appropriate to use a high-potency neuroleptic (e.g., haloperidol) combined with a benzodiazepine and an anticholinergic agent (diphenhydramine or benztropine).

Physical restraints (e.g., locked leather restraints) are sometimes necessary and should be placed only by trained security personnel according to guidelines established by the appropriate state Department of Mental Health. Family members should leave the room during any form of restraint and be debriefed later about the course of events and reasons for particular interventions.

LEGAL RESPONSIBILITIES OF THE EMERGENCY PSYCHIATRIST

The emergency psychiatrist is responsible for knowing the legal regulations and local standards of care related to capacity evaluations, confidentiality, release of information, commitment standards, and mandatory reporting for patients with psychiatric symptoms who are treated at the PES. Although specific standards may differ, the following features may assist with understanding these general responsibilities. In all cases it is important to document carefully all steps involved in the decision-making process and to consult with a forensic psychiatrist or legal counsel trained in mental health law in difficult cases.

Capacity Evaluation

The capacity evaluation is often requested by other medical providers to determine whether a patient has the ability to make an informed decision about a particular medical procedure or treatment course. The determination of capacity is not based on legally determined criteria but rather on widely accepted clinical standards. In addition, a capacity evaluation applies to a single decision at a single moment in time; when in question, the patient's ability to make global medical decisions is determined through a court-based competency hearing and is outside the purview of the hospital psychiatrist. A patient is presumed to have capacity to make medical decisions until proven otherwise. The key components of this evaluation include the assessment of whether the patient can express a choice that is stable over time, understand the relevant information, appreciate the consequences of the decision, and manipulate all of the data in a logical fashion. In addition, capacity exists on a sliding scale that incorporates a risk:benefit analysis of the particular treatment in question; a patient may have capacity to decline a treatment with low benefit and high risks and at the same time not have the capacity to decline a treatment with high benefit and low risks. In many cases the psychiatrist will find that the patient's ability to make a clear and rational decision depends on an opportunity to learn more about the specific medical procedure. If the psychiatrist can coordinate further communication between the medical or surgical team and the patient, the capacity evaluation may become unnecessary.

Confidentiality and Release of Information

The care of psychiatric patients requires a strong commitment to confidentiality; in the emergency setting, all attempts are made to gain permission for any collateral contact regarding the patient's condition. However, for patients who present a risk of harm to themselves or others, it is sometimes necessary to consult with treaters or family members without the patient's consent. It is important to document clearly why the contact was made and to use the contact to gain information that will assist in the safety assessment. Although it is reasonable for the clinician to receive information necessary to maintain the safety of the patient, the clinician should limit the confidential information provided to the other party.

Another situation in which a breach in confidentiality may be justified is when a clinician learns that a patient is at imminent risk to harm another individual. The standards for the clinician's duty to protect the potential victim are different in every state, but most are based on the original Tarasoff case in California in 1976.[40]

Civil Commitment

Civil commitment refers to the state's ability to hospitalize an individual involuntarily because of risk of harm due to mental illness.[40] The commitment regulations and

processes vary by state. Most regulations incorporate risk of harm to self, risk of harm to others, and inability to care for self, all owing to psychiatric pathology, as the basis for civil commitment. The safety evaluation described in this chapter provides the clinician with a basic outline of an assessment to determine risk and is an important component of the assessment that may lead to civil commitment.

Mandatory Reporting

Most states have regulations regarding mandatory reporting for suspected child abuse,[41] elder abuse,[42] and abuse of individuals with mental retardation. In most cases mandatory reporters are obligated to report situations in which they suspect abuse, whether or not they have clear evidence; they are protected against claims of a breach of confidentiality under these conditions.[40] Mental health clinicians should be aware of whether they are considered mandatory reporters in their state and how to contact the appropriate agencies.

ROLE OF THE PSYCHIATRIST IN DISASTER PREPARATION

In the face of recent catastrophic events such as terrorist attacks and large-scale natural disasters, efforts have been undertaken to prepare medical teams to manage disasters. The role of psychiatry in this response is often overlooked until the actual event occurs. In the midst of a disaster response, the psychiatrist's ability to tolerate extreme affect becomes immediately useful. The psychiatrist can offer aid in at least four different arenas: organizational aid and planning for disaster response; treatment of psychological reactions to stress (using pharmacologic, psychotherapeutic, and interpersonal interventions), acutely and over the long term; provision of support to family members and friends of victims of the disaster; and support of medical staff who participate in disaster response (including emergency personnel, hospital staff, administrative staff, and other support personnel).[43,44]

Emergency psychiatrists are particularly well adapted to assist with disaster response. They are familiar with the medical and psychological effects of trauma, adept at working with grieving family members, and familiar with the resources in the community that can assist with long-term treatment. Disaster psychiatry is a growing field, and emergency psychiatrists will likely play an important role in the future of disaster-response planning.

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Care of the Suicidal Patient

Rebecca W. Brendel, M.D., J.D.
Marlynn Wei, M.D., J.D.
Isabel T. Lagomasino, M.D., M.S.H.S.
Roy H. Perlis, M.D.
Theodore A. Stern, M.D.

Suicide, or intentional self-harm with the intent of causing death, is the eleventh leading cause of death in the United States, accounting for more than 30,000 deaths each year.[1] Nonlethal self-inflicted injuries are even more prevalent, accounting for nearly 600,000 emergency department (ED) visits per year[2] and reflecting the high ratio of suicide attempts to completed suicides. Psychiatric disorders, as the most powerful risk factor for both completed and attempted suicide, are associated with more than 90% of completed suicides[3,4] and with the majority of attempted suicides.[5–7] In addition, medical illness, especially chronic illness, is also associated with an increased risk of suicide.

Psychosomatic medicine psychiatrists must be familiar with the evaluation and treatment of patients who contemplate, threaten, or attempt suicide not only because of the risk of suicide associated with psychiatric and medical illness, but also because they are likely to be asked to evaluate patients who are medically or surgically hospitalized following a suicide attempt. Although guided by knowledge of epidemiological risk factors for suicide (Table 40–1), the clinician must rely on a detailed examination and on clinical judgment in the evaluation of current suicide risk.

EPIDEMIOLOGY AND RISK FACTORS

Epidemiology

Suicide accounts for 1.3% of the total number of deaths in the United States each year.[1,8] For every person who completes suicide, approximately 8 to 10 people attempt suicide.[9,10] Although no nationwide data on annual attempted suicides are available, research indicates that for every completed suicide, approximately 8 to 25 attempts are made[11–13]; that is, some individuals make more than one unsuccessful attempt. Each year, EDs treat nearly 600,000 self-inflicted injuries or suicide attempters.[2,14,15] These visits represent approximately 0.5% of all annual ED visits.[2,14]

Use of firearms is the most common method of committing suicide for both men and women in the United States, accounting for between 50% and 60% of annual suicides.[12,13] Suffocation, including hanging, is the second most common cause of suicide overall in the United States, and the second most common cause in men, accounting for approximately 6500 suicide deaths per year.[15,16] Poisoning, including drug ingestion, is the third most common cause of completed suicide in the United States and the second most common cause in women, accounting for approximately 5500 deaths per year.[15,16] Historically, drug ingestion has accounted for the majority of unsuccessful suicide attempts.[17,18]

Suicide rates differ by age, gender, and race. Rates generally increase with age; people older than 65 years are 1.5 times more likely to commit suicide than are younger individuals, whereas white men over age 85 years have an even higher rate of suicide.[14,19,20] The number of suicides in the elderly is disproportionately high; the elderly appear to make more serious attempts on their lives and are less apt to survive when medical complications from an attempt ensue—one out of four attempts in this group results in a completed suicide.[19–21] Although the elderly have the highest suicide rates, suicide in young adults (between the ages of 15 and 24) rose threefold between 1950 and 1990, becoming the third leading cause of death following unintentional injuries and homicide.[12,22,23] From 1990 to 2003, the suicide rate declined in the 10- to 24-year-old age group.[23,24] However, in 2004, for the first time in a decade and a half, the suicide rate in this age group increased by 8%.[24] In addition, hanging/suffocation became the most common method of suicide among girls in this age group.[24] Whether this rise in suicide in young people is a sporadic event or evidence of a trend remains to be seen as data for subsequent years become available.

Men are more likely to complete suicide than are women, although women are more likely to attempt suicide than are men. Four times more men than women complete suicide,[8,25] although women are three to four times more likely than men to attempt suicide.[25,26] The reasons for these disparities have not been established clearly. Whites and Native Americans attempt and commit suicide more than nonwhites.[5,12,25] African Americans and Hispanics have approximately half the suicide rate of whites.[25,27,28]

Psychiatric Risk Factors

Psychiatric illness is the most powerful risk factor for both completed and attempted suicide. Psychiatric disorders are associated with more than 90% of completed suicides[3,4,25,29] and with the vast majority of attempted suicides.[5–7] Mood disorders, including major depressive disorder (MDD) and bipolar disorder, are responsible for approximately 50% of

TABLE 40–1 Risk Factors for Suicide

Psychiatric illness
- Major depression
- Bipolar disorder
- Alcoholism and drug dependence
- Schizophrenia
- Character disorders
- Organic brain syndrome
- Panic disorder

Race
Marital status (widowed, divorced, or separated)
Living alone
Recent personal loss
Unemployment
Financial/legal difficulties
Co-morbid medical illness (having chronic illness, pain, or terminal illness)
History of suicide attempts or threats
Male gender
Advancing age
Family history of suicide
Recent hospital discharge
Firearms in the household
Hopelessness

completed suicides, alcohol and drug abuse for 25%, psychosis for 10%, and personality disorders for 5% (Table 40–2).[30,31]

Up to 15% of patients with MDD or bipolar disorder complete suicide, almost always during depressive episodes[32]; this represents a suicide risk 30 times greater than that of the general population.[33,34] True lifetime risk may be somewhat lower, because these estimates (and those for the other diagnoses discussed later) typically are derived from hospitalized patient samples.[30] The risk appears to be greater early in the course of a lifetime disorder, early on in a depressive episode,[11,35] in the first week following psychiatric hospitalization,[36] in the first month following hospital discharge,[36] and in the early stages of recovery.[36] The risk may[37] or may not[38] be elevated by co-morbid psychosis. A 10-year follow-up study of almost 1000 patients found that those who committed suicide within the first year of follow-up were more likely to be suffering from global insomnia, severe anhedonia, impaired concentration, psychomotor agitation, alcohol abuse, anxiety, and panic attacks, whereas those who committed suicide after the first year of follow-up were more likely to be suffering from suicidal ideation, severe hopelessness, and a history of suicide attempts.[37] A study of 667 patients with MDD found that patients who reported prior suicide attempts had more current general medical conditions, more current alcohol or other substance abuse, more work hours missed in the past week than nonattempters, and also reported more current suicidal ideation.[39]

TABLE 40–2 Percentage of Suicides with a Given Psychiatric Disorder

CONDITION	PERCENTAGE OF SUICIDES
Affective illness	50
Drug or alcohol abuse	25
Schizophrenia	10
Character disorders	5
Secondary depression	5
Organic brain syndromes	2
None apparent	2

Approximately 15% to 25% of patients with alcohol or drug dependence complete suicide,[35,40] of which up to 84% suffer from both alcohol and drug dependence.[40] The suicide risk appears to be greatest approximately 9 years after the commencement of alcohol and drug addiction.[3,41] The majority of patients with alcohol dependence who commit suicide suffer from co-morbid depressive disorders,[35,42,43] and as many as one third have experienced the recent loss of a close relationship through separation or death.[44]

Nearly 20% of people who complete suicide are legally intoxicated at the time of their death.[45] Alcohol and drug abuse are associated with more pervasive suicidal ideation, more serious suicidal intent, more lethal suicide attempts, and a greater number of suicide attempts.[46] Use of alcohol and drugs may impair judgment and foster impulsivity.[36,47]

Approximately 10% of patients with schizophrenia complete suicide, mostly during periods of improvement after relapse or during periods of depression.[43,48,49] The risk for suicide appears to be greater among young men who are newly diagnosed,[49–51] who have a chronic course and numerous exacerbations, who are discharged from hospitals with significant psychopathology and functional impairment, and who have a realistic awareness and fear of further mental decline.[49,51] The risk may also be increased with akathisia and with abrupt discontinuation of neuroleptics.[35] Patients who experience hallucinations (that instruct them to harm themselves) in association with schizophrenia, mania, or depression with psychotic features are probably at greater risk for self-harm, and they should be protected.[52]

Between 4% and 10% of patients with borderline personality disorder and 5% of patients with antisocial personality disorder commit suicide.[53] The risk appears to be greater for those with co-morbid unipolar depression or alcohol abuse.[54,55] Patients with personality disorders often make impulsive suicidal gestures or attempts; these attempts may become more lethal if they are not taken seriously. Even manipulative gestures can turn fatal.[52] A prospective cohort study of 7968 patients examined suicide rates up to 4 years after a deliberate self-harm episode and found an approximately 30-fold increase in risk of suicide compared to the general population.[56]

As many as 15% to 20% of patients with anxiety disorders complete suicide,[57] and up to 20% of patients with panic disorder attempt suicide.[58] Although the risk of suicide in patients with anxiety and panic disorders may be elevated secondary to co-morbid conditions (e.g., MDD and alcohol or drug abuse), the suicide risk remains almost as high as that of major depression, even after co-existing conditions are taken into account.[59] The risk for suicide attempts may be elevated for women with an early onset and with co-morbid alcohol or drug abuse.[58] Patients with obsessive–compulsive disorder (OCD) have also been found to be at high risk for suicidal behavior, with a history of suicide attempt reported in 27% of subjects in one study.[60]

The first prospective study of body dysmorphic disorder (BDD) found that patients with BDD have rates of suicidal ideation that are approximately 10 to 25 times higher than those in the general population and that their suicide attempt rate was 3 to 12 times higher. The completed suicide rate of patients with BDD is still being studied.[61]

One study of 754 inpatients and 1100 patients assessed following discharge from a psychiatric inpatient unit found that nearly a quarter of the inpatient suicides occurred within the first 7 days of admission—the majority died by hanging. Postdischarge suicide was most frequent in the first 2 weeks after leaving the hospital, with the highest number of deaths occurring on the first day following discharge.[62]

Medical Risk Factors

Medical illness, especially of a severe or chronic nature, is associated with an increased risk of suicide and is thus considered a risk factor for completed suicide (even though there is most likely a multifactorial relationship between medical illness and suicide).[16,63,64] Medical disorders are associated with as many as 35% to 40% of suicides[65] and with as many as 70% of suicides in those older than 60 years.[66] Acquired immunodeficiency syndrome (AIDS), cancer, head trauma, epilepsy, multiple sclerosis, Huntington's chorea, organic brain syndromes, spinal cord injuries, hypertension, cardiopulmonary disease, peptic ulcer disease, chronic renal failure, Cushing's disease, rheumatoid arthritis, and porphyria have each been reported to increase the risk of suicide. Notably, however, few investigations concerning the increased risk for suicide in these populations have controlled for the effects of age, gender, race, psychiatric disorders, other medical disorders, or use of medications. Studies of patients who commit suicide on general hospital medical or surgical units have also not been well-studied. A recent review of these rare cases suggests that agitation and a readily available lethal means of suicide are potent risk factors (as are past psychiatric illness, substance abuse, suicidal ideation, and depression).[67]

Patients with AIDS appear to have a suicide risk that is greater than that of the general population, and estimates of the increased risk range from 7 to 66 times greater than the general population.[30,68,69] It is generally accepted that the risk of suicide in human immunodeficiency virus (HIV) infection is increased approximately sevenfold.[16,68] Testing for antibodies associated with HIV-infection has resulted in an immediate and substantial decrease in suicidal ideation in those who turned out to be seronegative; no increase in suicidal ideation was detected in those who were seropositive.[70] Sexual orientation among men, in and of itself, has not been identified as an independent risk factor for completed suicide.[12,71]

Cancer patients have a suicide rate that is almost twice as great as that found in the general population and the risk appears to be higher in the first 5 years after diagnosis.[68,72,73] A large retrospective cohort study of patients diagnosed with cancer in the United States from 1973 to 2002 found that suicide rates varied among patients with cancers of different anatomic sites, with the highest risks observed in the following order: the lung and bronchus, stomach, oral cavity and pharynx, and larynx.[73] Head and neck malignancies have been associated with a risk of suicide 11 times greater than that of the general population (possibly due to increased rates of tobacco and alcohol use and the resultant facial disfigurement and loss of voice).[68] In men, gastrointestinal cancers are associated with a greater risk of suicide.[61] Other factors that may place cancer patients at greater risk include poor prognosis, poor pain control, fatigue, depression, hopelessness, delirium, disinhibition, prior suicide attempts, recent losses, and a paucity of social supports.[74,75]

Like cancer patients, individuals with head trauma, multiple sclerosis, and peptic ulcer disease have approximately twice the risk of suicide as those in the general population.[68,76,77] In patients with head injuries, the risk appears to be greater in those who suffer severe injuries and in those who develop dementia, psychosis, character changes, or epilepsy.[76–78] In patients with multiple sclerosis, the risk may be higher for those diagnosed before age 40 years and within the first 5 years after a diagnosis has been made.[79] In patients with peptic ulcer disease, the increased risk is thought to be due to co-morbid psychiatric and substance use (especially alcohol) disorders.[68,78]

Between the increased risk of suicide of approximately twofold for cancer, head trauma, multiple sclerosis, and peptic ulcer disease, and the increased risk in HIV-infected/AIDS patients (estimated to be at least nearly sevenfold), there are a number of medical illnesses associated with intermediate increases in suicide risk. These illnesses and conditions include epilepsy, systemic lupus erythematosus, spinal cord injuries, Huntington's disease, organic brain syndromes, and chronic renal disease. Patients with end-stage renal failure treated with hemodialysis may have the highest risk of all subgroups.[68,80] As many as 5% of patients with chronic renal failure on hemodialysis die from suicide; those who travel to medical centers for dialysis have a higher suicide rate than those who are dialyzed at home.[10] The risk for suicide among these patients may be as high as 400 times that of the general population.[81]

Patients with epilepsy are five times more likely than those in the general population to complete or to attempt suicide.[68,82–84] Sufferers of temporal lobe epilepsy, with concomitant psychosis or personality changes, may also be at greater risk.[68,82,83,85]

Delirious and confused patients may suffer from agitation and destructive impulses and be unable to protect themselves from harm.[74] In victims of spinal cord injury, the risk is actually greater for those with less severe injuries.[86,87]

Hypertensive patients[78] and those with cardiopulmonary disease[52] may also have a higher risk for suicide than those in the general population. Although previous reports suggested that β-blockers could contribute to increased risk by promoting depression,[78] recent studies suggest that β-blockers do not increase the risk of developing depression.[88] Patients with diabetes have more hopelessness and thoughts of suicide than internal medicine outpatients, although fatal and nonfatal suicidal behavior has not been well-studied in this population.[89] Finally, an association between suicide and very low cholesterol levels has been reported, but the connection is still under investigation.[16,30]

Suicidal ideation in pregnancy has been associated with unplanned pregnancy, current major depression, and a co-morbid anxiety disorder.[90] Completed suicide and suicide attempts are less frequent during pregnancy and the postpartum period than they are in the general population of women. However, suicides account for almost 20% of postpartum deaths.[91]

Surgical procedures have also been associated with a higher risk of suicide. Six epidemiological studies have concluded that the suicide rate in women who received cosmetic breast implants was approximately twice the expected rate based on estimates in the general population.[92–97]

Bariatric surgery is associated with an increased risk of death from non–disease related causes, including suicide, compared to other severely obese individuals. More research is necessary to determine whether these high rates of suicide are due to preexisting psychiatric illness in cohorts of surgery patients or to the postsurgical complications of the surgery or its impact on quality of life.[98]

Suicide has been distinguished from life-ending acts and end-of life decisions in the literature, based on patients with chronic kidney disease and dialysis.[99] Discussion of physician-assisted suicide is addressed in the end-of-life chapter (Chapter 41). Among patients with advanced AIDS, the desire for hastened death has been found to be 4.6% to 8.3%, significantly lower than the rate found in studies of patients with advanced or terminal cancer.[100]

Familial and Genetic Risk Factors

A family history of suicide, a family history of psychiatric illness, and a tumultuous early family environment have each been found to have an important impact on the risk for suicide.[12,65] As many as 7% to 14% of persons who attempt suicide have a family history of suicide.[101] A family history of suicide confers approximately a twofold increase in the risk for suicide after family psychiatric history is controlled for.[102] This increased suicide risk may be mediated through a shared genetic predisposition for suicide, psychiatric disorders, or impulsive behavior,[35,50,103] or through a shared family environment in which modeling and imitation are prominent.[104]

Genetic factors are supported by evidence that monozygotic twins have a higher concordance rate for suicide and suicide attempts than do dizygotic twins, and by evidence that biological parents of adoptees who commit suicide have a higher rate of suicide than do biological parents of nonsuicidal adoptees.[30,103,105] However, little is known about the specific genetic factors that confer this risk.[30] Studies have largely focused on serotonin neurotransmission, including genetic mutations in the rate-limiting enzyme in serotonin synthesis, L-tryptophan hydroxylase, serotonin receptors, and the serotonin transporter; however, this investigation is still preliminary.[102,106–108] Overall, it is estimated that one third to one half the risk of suicide is genetically mediated.[102]

Numerous familial environmental factors may also contribute to suicide risk. A tumultuous early family environment (including early parental death, parental separation, frequent moves, and emotional, physical, or sexual abuse) increases the risk for suicide.[109] A child's risk of future suicide attempts or completion may also be increased through modelling of suicidal behavior in important family members.[30]

Social Risk Factors

Widowed, divorced, or separated adults are at greater risk for suicide than are single adults, who are at greater risk than married adults.[110,111] Married adults with young children appear to carry the lowest risk.[36,52,65] Living alone substantially increases the risk for suicide, especially among adults who are widowed, divorced, or separated.[36] Social isolation from family, relatives, friends, neighbors, and co-workers also increases the chance of suicide.[50,65] Conversely, the presence of social supports is protective against suicide.[102]

Significant personal losses (including diminution of self-esteem or status[65,66]) and conflicts also place individuals, particularly young adults and adolescents, at greater risk for suicide.[3,112] Bereavement following the death of a loved one increases the risk for suicide over the next 4 or 5 years, particularly among people with a psychiatric history (including suicide attempts) and in those who receive little family support.[35,113] Unemployment, which may produce or exacerbate psychiatric illness or may result from psychiatric illness,[35] increases the likelihood of suicide and accounts for as many as one third to one half of completed suicides.[45,65] This risk may be particularly elevated among men.[35] Financial and legal difficulties also increase the risk for suicide.[12,36,114]

The annual number of suicides among soldiers on active duty in the Army, Army Reserve, and Army National Guard has reached a 28-year high, having risen steadily between the years 2004 and 2008.[115] One study of suicide risk among veterans of Operations Iraqi Freedom and Enduring Freedom showed that the overall risk was not significantly elevated compared to that in the general population, but suicide risk was increased for former active-duty veterans and for veterans diagnosed with a selected mental disorder.[116] However, a study of patients in the Veterans Health Administration in fiscal year 2001 found that the suicide rates were significantly higher than in the general population.[117]

The presence of one or more firearms in the home appears to increase the risk of suicide independently for both genders and all age groups, even when other risk factors, such as depression and alcohol abuse, are taken into account.[6,112,118] For example, adolescents with a gun in the household have suicide rates between 4 and 10 times higher than other adolescents.[23,119]

Past and Present Suicidality

A history of suicide attempts is one of the most powerful risk factors for completed and attempted suicide.[12,120] As many as 10% to 20% of people with prior suicide attempts complete suicide.[10,17,121] The risk for completed suicide following an attempted suicide is almost 100 times that of the general population in the year following the attempt; it then declines but remains elevated throughout the next 8 years.[35] People with prior suicide attempts are also at greater risk for subsequent attempts and have been found to account for approximately 50% of serious overdoses.[122] The clinical use of past suicide attempts as a predictive risk factor may be limited in the elderly because the elderly make fewer attempts for each completed suicide.[19–21,65]

The lethality of past suicide attempts slightly increases the risk for completed suicide,[35] especially among women with psychiatric illness.[42] The dangerousness of an attempt,

however, may be more predictive of the risk for suicide in those individuals with significant intent to suicide and a realization of the potential lethality of their actions.[123]

The communication of present suicidal ideation and intent must be carefully evaluated as a risk factor for completed and attempted suicide. As many as 80% of people who complete suicide communicate their intent either directly or indirectly.[65] Death or suicide may be discussed, new wills or life insurance policies may be written, valued possessions may be given away, or uncharacteristic and destructive behaviors may arise.[65]

People who intend to commit suicide may, however, be less likely to communicate their intent to their health care providers than they are to close family and friends.[48] Although 50% of people who commit suicide have consulted a physician in the month before their death, only 60% of them communicated some degree of suicidal ideation or intent to their physician.[3,48] In a study of 571 cases of completed suicide who had met with their health care professional within 4 weeks of their suicide,[124] only 22% discussed their suicidal intent. Many investigators believe that ideation and intent may be more readily discussed with psychiatrists than with other physicians.[124,125]

Hopelessness, or negative expectations about the future, is a stronger predictor of suicide than is depression or suicidal ideation,[126,127] and may be both a short-term and long-term predictor of completed suicide in patients with major depression.[48]

Contact with Physicians

Nearly half of the people who commit suicide have had contact with their primary care provider (PCP) within 1 month of committing suicide.[36,48,128] Approximately three quarters of people who commit suicide have seen a PCP in the year before the suicide.[128] Many of these individuals have sought treatment from their PCP for somatic rather than for psychiatric complaints.[129] Rates of psychiatric encounters in the period before completed suicides are lower than those for primary care contacts.[128] In the month before a completed suicide, approximately one fifth of suicide-completers obtained mental health services, and in the year before a completed suicide, approximately one in three suicide completers had contact with a mental health professional.[128]

PATHOPHYSIOLOGY

Suicide is a behavioral outcome with a large number of contributing factors, rather than a disease entity in itself. Therefore, in order to understand the pathophysiology of suicidality, it is necessary to examine the differences between individuals with a given set of predisposing factors who do not attempt or complete suicide and those who do. Research has focused on a wide array of neurobiological and psychological topics in an attempt to better understand the pathophysiology of suicide. Neurobiological inquiries have included neurotransmitter analyses, genetic studies, neuroendocrine studies, biological markers, and imaging studies.[16]

Of all the neurotransmitters, the relationship of serotonin to suicidality has been most widely studied.[16] Specifically, an association between reduced serotonergic activity, as indicated by lower levels of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA), and serotonin dysfunction and suicidality has emerged since the 1970s.[30,102,130–141] This finding is independent of underlying psychiatric diagnoses.[131,132] Changes in norepinephrine transmission in suicide have also been investigated, but although there may be some association between a decreased number of noradrenergic neurons and suicidality,[142] overall, CSF studies have shown no significant difference in norepinephrine metabolites in those with suicidal behavior.[102,143] Data regarding the role of dopamine in suicide are inconclusive.[102,141,143,144] Lastly, heightened hypothalamic–pituitary–adrenal (HPA) axis activity has been implicated in the pathophysiology of suicide, although not all studies of the relationship between the HPA axis abnormalities and suicidal behavior have reached the same conclusions.[16,30,102,132,141]

Psychological aspects of suicide typically focus on psychodynamic and cognitive perspectives, and they have contributed to a vast literature on the topic. Suicide can be conceptualized as anger turned on oneself or anger toward others directed at the self.[145–147] Suicide has also been seen as being motivated by three driving forces: the wish to die, the wish to kill, and the wish to be killed.[147] Deficits in ego function have also been postulated to predispose to suicide,[145] as have poor object relations.[147] Hopelessness is a central psychological correlate of suicide, and extensive study on it has suggested that hopelessness may be the best overall predictor of suicide.[102] Shame, worthlessness, poor self-esteem, early traumatic relationships, and intense psychological pain are also key concepts in the understanding of suicide.[147,148] In addition, poor coping skills, antisocial traits, hostility, dependency or over-dependency, self-consciousness, and high intropunitiveness have also been associated with suicide.[147,149] Finally, research has postulated correlations between observed neuroanatomical, neurotransmitter, and neuroendocrine findings in suicide and attendant cognitive traits of loser status, no escape, and no rescue as central to understanding suicidal behavior.[132]

CLINICAL FEATURES AND DIAGNOSIS

The patient at risk for suicide varies along a continuum (from an individual with private thoughts of wanting to be dead or to commit suicide, to a gravely ill individual who requires emergent medical attention as the result of a self-inflicted injury aimed to end his or her life). There is no characteristic presentation for a suicidal patient. As a result, suicide risk must be assessed in all patients, and it depends on a thorough clinical assessment; the patient who has contemplated, threatened, or attempted suicide requires special consideration. The thoughts and feelings of the individual must be elicited and placed in the context of known risk factors for suicide.

Although useful as a guide to populations who may be more likely to commit or to attempt suicide, risk factors alone are neither sensitive nor specific in the prediction of suicide. Their pervasive prevalence in comparison with the relatively low incidence of suicide in the general population may also lead to high false-positive rates. A multiple logistic regression model that used risk factors (e.g., age, gender, psychiatric diagnoses, medical diagnoses, marital status,

family psychiatric history, prior suicide attempts, and suicidal ideation) failed to identify any of the 46 patients who committed suicide over a 14-year period from a group of 1906 people with mood disorders.[150] Similarly, a multiple regression analysis aimed at predicting risk classification by treatment disposition of individuals after a suicide attempt had only slightly more than a two-thirds concordance with the decisions made by the treating clinician.[151]

An evaluation for suicide risk is indicated for all patients who have made a suicide attempt, who have voiced suicidal ideation or intent, who have admitted suicidal ideation or intent on questioning, or whose actions have suggested suicidal intent despite their protests to the contrary. All suicide attempts and thoughts of suicide should be taken seriously, regardless of whether the actions or thoughts appear manipulative in nature. The work group on suicidal behaviors of the American Psychiatric Association has outlined the four critical features of a comprehensive assessment of patients with suicidal behaviors in its 2003 practice guideline: a thorough psychiatric evaluation, specific inquiry about suicidality, establishment of a multiaxial diagnosis, and estimation of suicide risk.[147] The key facets of each of these components are detailed in Table 40–3.

The approach to the patient at risk for suicide should be nonjudgmental, supportive, and empathic. The initial establishment of rapport may include an introduction, an effort to create some degree of privacy in the interview setting, and an attempt to maximize the physical comfort of the patient during the interview.[52] The patient who senses interest, concern, and compassion is more likely to trust the examiner and to provide a detailed and accurate history. Often ambivalent about their thoughts and plans, suicidal patients may derive significant relief and benefit from a thoughtful and caring evaluation.[50,52]

The patient should be questioned about suicidal ideation and intent in an open and direct manner. Patients with thoughts of and plans for suicide are often relieved when they find someone with whom they can speak about the unspeakable. Patients without suicidal ideation do not have the thoughts planted in their mind and do not develop a greater risk for suicide.[50,52,152] General questions concerning thoughts about suicide can be introduced in a gradual manner while obtaining the history of present illness. Questions such as "Has it ever seemed like things just aren't worth it?"[52] or "Have you had thoughts that life is not worth living?"[50] may lead to a further discussion of depression and hopelessness. "Have you gotten so depressed that you've considered killing yourself?"[52] or "Have you had thoughts of killing yourself?"[49] may open the door to a further evaluation of suicidal thoughts and plans.

Specific questions concerning potential suicide plans and preparations must follow any admission of suicidal ideation or intent. The patient should be asked when, where, and how an attempt would be made, and any potential means should be evaluated for feasibility and lethality. An organized and detailed plan involving an accessible and lethal method may place the patient at higher risk for suicide.[45] The seriousness of the wish or the intent to die must also be assessed. The patient who has begun to carry out the initial steps of a suicide plan, who wishes to be dead, and who has no hopes or plans for the future may be at greater risk. The last-mentioned domain (plans for the future) may be assessed by asking questions such as, "What do you see yourself doing 5 years from now?" or "What things are you still looking forward to doing or seeing?"[52]

Many clinicians have addressed the issues of lethality and intent by means of the risk/rescue ratio.[147,153] The greater the relative risk or lethality and the lesser the likelihood of rescue of a planned attempt, the more serious is the potential for a completed suicide. Although often useful, the risk/rescue ratio cannot be applied as a simple formula; instead, one must examine and interpret the particular beliefs of a given patient. For example, a patient may plan an attempt with a low risk of potential harm but may sincerely wish to die and believe that the plan will be fatal; the patient may thus have a higher risk for suicide. Conversely a patient may plan an attempt that carries a high probability of death, such as an acetaminophen overdose, but may have little desire to die and little understanding of the severity of the attempt; the patient may thus have a lower risk.[45,147]

The clinician must attempt to identify any possible precipitants for the present crisis in an effort to understand why the patient is suicidal. The patient who must face the same problems and stressors following the evaluation or who cannot or will not discuss potential precipitants may be at greater risk for suicide.[45] The clinician must also assess the social support in place for a given patient. A lack of outpatient care providers, family, or friends may elevate a patient's risk.[50,65]

The examiner who interviews a patient after a suicide attempt needs to evaluate the details, seriousness, risk/rescue ratio, and precipitants of the attempt. The patient who carries out a detailed plan, who perceives the attempt as lethal, who thinks that death will be certain, who is disappointed to be alive, and who must face unchanged stressors will be at a continued high risk for suicide. The patient who makes a calculated, premeditated attempt may also be at a higher risk for a repeat attempt than the patient who makes a hasty, impulsive attempt (out of anger, a desire for revenge, or a desire for attention), or the patient who is intoxicated.[52]

TABLE 40–3 Components of the Suicide Evaluation

Conduct a thorough psychiatric examination
• Establish initial rapport
• Combine open-ended and direct questions
• Gather data from family, friends, and co-workers
• Conduct a mental status examination
Suicide assessment
• Ask specifically about thoughts of suicide and plans to commit suicide
• Examine the details of the suicide plan
• Determine the risk/rescue ratio
• Assess the level of planning and preparation
• Evaluate the degree of hopelessness
• Identify precipitants
Establish a multiaxial diagnosis
• Obtain history
• Use data from a psychiatric examination
• Incorporate data from prior or current treaters
Estimate suicide risk
• Evaluate risk factors
• Evaluate available social supports

A thorough psychiatric, medical, social, and family history of the patient who may be at risk for suicide should be completed to evaluate the presence and significance of potential risk factors. Particular attention should be paid to the presence of MDD, alcohol or drug abuse, psychotic disorders, personality disorders, and anxiety disorders. The presence of multiple significant risk factors may confer an additive risk.

A careful mental status examination allows the clinician to detect psychiatric difficulties and to assess cognitive capacities. Important aspects to evaluate in the examination include level of consciousness, appearance, behavior, attention, mood, affect, language, orientation, memory, thought form, thought content, perception, insight, and judgment.[153,154] A psychiatric review of systems aids in the detection of psychiatric disease.

The clinician should interview the family and friends of the patient at risk to corroborate gathered information and to obtain new and pertinent data. The family may provide information that a patient is hesitant to provide and that may be essential to his or her care.[45,50,52] A patient who refuses to discuss an attempt or who insists that the entire event was a mistake may speak in an open and honest manner only when confronted with reports from his or her family. The evaluation of suicidal risk and the protection of the patient at risk are emergent procedures, which may take precedence over the desire of the patient for privacy and the maintenance of confidentiality in the physician–patient relationship. Concern over a life-or-death situation may obviate obtaining formal consent from the patient before speaking to family and friends.[52]

TREATMENT OF SUICIDE RISK

The treatment of suicide risk begins with stabilization of medical sequelae of suicidal behaviors. Attention to current or potential medical conditions must be prompt, and medical evaluations must be complete. The severity of the psychiatric presentation should not distract a clinician from his or her obligation to provide good medical care.[45] Once the patient is medically stable, or if the patient is suicidal but has not acted on suicidal impulses, the focus of treatment can shift to initiation of treatment for the underlying causes of the desire for death. Components of the treatment of suicide risk include providing a safe environment for the patient, determining an appropriate treatment setting, developing a treatment plan that involves appropriate somatic and psychotherapeutic interventions, and reassessing safety, suicide risk, psychiatric status, and treatment response in an ongoing fashion (Table 40–4).[147]

Throughout the evaluation and treatment of the suicidal patient, safety must be ensured until the patient is no longer at imminent risk for suicide. Appropriate intervention and the passage of time may aid in the resolution of suicidal ideation and intent.[45,52] A patient who is at potential risk for suicide and who threatens to leave before an adequate evaluation is completed must be detained, in accordance with statutes in most states that permit the detention of individuals deemed dangerous to themselves or others.[155] Patients who attempt to leave nonetheless should be contained by locked environments or restraints.[45]

TABLE 40–4 Treatment of Suicide Risk

Stabilize the medical situation
Create a safe environment
• Remove potential means for self-harm
• Provide frequent supervision
• Use restraints as needed
• Detain involuntarily if necessary
Identify and treat underlying mental illness
Identify and modify other contributing factors

Potential means for self-harm should be removed from the reach of a patient at risk. Sharp objects (such as scissors, sutures, needles, glass bottles, and metal eating utensils) should be removed from the immediate area. Open windows, stairwells, and structures to which a noose could be attached must be blocked. Medications or other dangerous substances that patients may have in their possession must be secured by staff in a location out of the patient's access.[45] Appropriate supervision and restraint must be provided at all times for a patient at risk for suicide. Frequent supervision, constant one-to-one supervision, physical restraints, and medications may be used alone or in combination in an effort to protect a patient at risk. The least restrictive means that ensures the safety of the patient should be used.

A decision about the appropriate level of care and treatment setting for the suicidal patient is critical. The patient's safety is paramount, and decisions about level of care—from discharge home with outpatient follow-up to involuntary hospitalization—should be based on risk determinations and methods most likely to protect the patient from self-harm, even when the patient disagrees. Those who are at high risk for suicide, or who cannot control their suicidal urges, should be admitted to a locked psychiatric facility. A patient who is at high risk but who refuses hospitalization should be committed involuntarily.

A patient who requires psychiatric hospitalization should be informed of the disposition decision in a clear, direct manner. Possible transfers should proceed as quickly and efficiently as possible because a patient may become quite tense and ambivalent about the decision to hospitalize. Those who agree to voluntary hospitalization and who cooperate with caregivers may have the highest likelihood of successful treatment.[52] A 3-year study of patients at a university ED in Zurich found that older patients were more likely to be hospitalized after a suicide attempt and that nearly half of patients admitted for psychiatric treatment were voluntary.[151] In a regression analysis of the same sample, more aggressive methods of suicide attempt (defined as not overdose or cutting), a history of previous inpatient treatment, and a current diagnosis of psychosis or schizophrenia were associated with inpatient admission.[151]

The clinician should always take a conservative approach to the treatment of suicidal risk and the maintenance of patient safety, and err, if necessary, on the side of excess restraint or hospitalization. From a forensic standpoint, the clinician sued for battery secondary to the use of restraints or to involuntary commitment would be easier to defend than the clinician sued for negligence secondary to a completed suicide. Acting in accordance with good clinical judgment in the best interest of the patient brings little danger of liability.[52] Adequate documentation should include the thought processes behind decisions to supervise, restrain, discharge, or hospitalize.[52]

Although managed care may place pressure on a clinician to avoid hospitalization through the use of less costly alternatives, there is no substitute for sound clinical judgment.[147] In particular, safety contracts or suicide prevention contracts, while intended to manage risk, are generally overvalued and of limited utility.[147,156] Specifically, suicide contracts depend on the subjective beliefs of the psychiatrist and the patient and not on objective data; they have never been shown to be clinically efficacious.[147,156] In addition, many suicide attempters and completers had suicide contracts in place at the time of the suicidal act.[147,157,158] Finally, a suicide contract is not a legal contract and it has limited utility, if any, if litigation should ensue from a completed suicide.[147,159,160]

Somatic therapies to target underlying psychiatric illness are a mainstay of the management of the suicidal patient. However, though psychiatric illness is a significant risk factor for suicide and treatment of underlying psychopathology is associated with decreased suicide risk, with few exceptions psychiatric medications have not independently been associated with a decrease in suicide. The two notable exceptions are long-term treatment with lithium (in affective illness)[161,162] and clozapine (in schizophrenia).[163,164]

Because depression is the psychiatric diagnosis most associated with suicide, psychopharmacologic treatment of depression is a central facet of management of suicide risk. However, antidepressants have not been shown to decrease suicide risk.[147,165] Although one recent study found a higher rate of suicide after discontinuation of antidepressants compared with ongoing antidepressant treatment, the study was small and further investigation is required.[166]

Controversy regarding the relationship of selective serotonin reuptake inhibitor (SSRI) antidepressants and suicide has now spanned more than a decade. In the early 1990s, reports of a possible increase in suicidal ideation and suicidal behavior in both adults and children on SSRIs emerged.[167,168] In 2004, the Food and Drug Administration (FDA) issued a black box warning for all antidepressants related to the risk of suicide in pediatric patients.[169] In 2007, the FDA proposed that makers of all antidepressants update the existing black box warning to include warnings of increased suicidal ideation and behavior for adults ages 18 to 24 years during the first 2 months of treatment.[170] Nonetheless, controversy about SSRIs and suicide persists in both adults and children. For example, in 2004, before the FDA advisory opinion, the American College of Neuropsychopharmacology's Task Force on SSRIs and Suicidal Behavior in Youth failed to find an association between SSRIs and increased suicidality in children; this was confirmed and extended in their final report.[171,172] Another study also showed an improvement in depression and a reduction in suicidal thinking when fluoxetine was combined with cognitive-behavioral a therapy (CBT), compared with placebo and CBT.[173]

The controversy has extended to the issue of whether the publicity surrounding the black box warning has had a significant effect in decreasing physician prescription of antidepressants for children and adolescents[174] and whether there are spillover effects on community treatment for adults with depression. One study found a spillover effect into community treatment for adults with depression, including a lower rate of diagnosis of depression than would have been expected by historical trends and a reduction in antidepressant prescription rates for adults with depression.[175] However, others have argued that the black box warnings had modest and targeted effects limited to the pediatric population.[176] One study that examined the U.S. data on prescription rates for SSRIs from 2003 to 2005 in children and adolescents found an association between decreased prescription rates and increases in suicide rates in children and adolescents.[177] However, making such an association has been heavily cautioned against and contested.[178] A meta-analysis of randomized controlled trials emphasized that the risks of suicidal ideation and suicidal attempts must be weighed in the context of the benefits of antidepressants for pediatric MDD, OCD, and non-OCD anxiety disorders.[179]

In adults, there has been similar controversy about a possible relationship among use of SSRIs and increased suicidality and self-harm. Multiple large studies that assessed the risk of suicide and self-harm have been completed; they largely concluded that SSRIs were not associated with a greater risk of suicide or violence.[147,180–183] However, debate has continued.[184] Most recently (in 2005), three papers published in the *British Medical Journal* reached varying conclusions and raised some questions about the data used in a previous analysis.[185–187] One analysis of 477 randomized control trials of more than 40,000 patients found no evidence that SSRIs increased the risk of suicide, but found weak evidence of an increased risk of self-harm.[185] A second review of randomized controlled trials with a total of 87,650 patients reached the opposite conclusion, finding an association between suicide attempts and the use of SSRIs.[186]

A case-control study of 146,095 individuals with a first prescription for depression found no greater risk of suicide or nonfatal self-harm in adults prescribed SSRIs as opposed to those prescribed tricyclic antidepressants (TCAs), although there was some weak evidence for increased nonfatal self-harm with use of SSRIs in patients under age 18 years.[187] A case-control study of Medicaid beneficiaries aged 19 to 64 years who had been hospitalized for depression found no association for suicide and suicide attempts with antidepressant drug use.[188] An observational study of over 225,000 U.S. veterans with a new diagnosis of depression found patients who received monotherapy with SSRI had approximately one third the risk of suicide attempts compared to those who received no medication.[189] A study of 1,264,686 people over 66 years of age, which matched 1138 suicide cases with four comparison subjects for each case, found that the use of SSRIs compared to other antidepressants was associated with an increased risk of completed suicide only for the first month of use.[190]

What is clear from review of the data on SSRIs is that more study is needed. Because SSRIs are prescribed for treatment of an underlying illness characterized by anxiety, agitation, and suicidality, it is difficult to separate out drug effect from illness effect.[147] Whether the medication might affect the patient's threshold for reporting ideation, rather than the actual occurrence of suicidal ideation itself, has also been raised.[191] Notwithstanding the continuing controversy, SSRIs do have the obvious advantage over TCAs and monoamine oxidase inhibitor (MAOI) antidepressants of being relatively safe in overdose.

Finally, because pharmacotherapy for depression typically requires several weeks for onset of efficacy, electroconvulsive therapy (ECT) may be indicated in cases in which suicide risk remains high or antidepressants are contraindicated.[147,192] ECT is associated with a decrease in short-term suicidal ideation.[147] Its use is best established for depression, and it may also be recommended for pregnant patients and for patients who have not responded to pharmacological interventions.[147]

Psychotherapeutic interventions are widely used to manage suicide risk, although few studies have addressed psychotherapy outcomes in the reduction of suicidality. Nonetheless, clinical practice and consensus supports the use of psychotherapy and other psychosocial interventions, despite the need for further study.[147] There is emerging evidence of the efficacy of multiple psychotherapeutic modalities in the treatment of depression, borderline personality disorder, and suicide risk *per se*, including psychodynamic psychotherapy, CBT, dialectical behavioral therapy, and interpersonal psychotherapy.[147]

DIFFICULTIES IN THE ASSESSMENT OF SUICIDE RISK

Clinicians may encounter obstacles with certain patients, or within themselves, during the evaluation of suicide risk. They must be adept in the examination of patients who are intoxicated, who threaten, or who are uncooperative, and they must be aware of personal feelings and attitudes (e.g., anxiety, anger, denial, intellectualization, or overidentification) to allow for better assessment and management of the patient at risk (Table 40–5). A survey study found that only 25% of patients who had self-disclosed suicidal ideation on a computer survey had suicidal ideation or other mental health issues documented in the chart; a majority of these patients were discharged to their home.[193]

A patient who is intoxicated may voice suicidal ideation or intent but retract such statements (frequently) when sober. A brief initial evaluation while the patient is intoxicated, and when his or her psychological defenses are impaired, may reveal the depth of suicidal ideation or the reasons behind a suicide attempt.[52] A more thorough final examination when the patient is sober must also be completed and documented.[45,52]

A patient who threatens should be evaluated in the presence of security officers and should be placed in restraints as necessary to protect both the individual and the staff.[52] Those who are uncooperative may refuse to answer questions despite all attempts to establish rapport and to create a supportive and empathic connection. Stating "I'd like to figure out how to be of help, but I can't do that without some information from you" in a calm but firm manner might be helpful. Patients should be informed that safety precautions will not be discontinued until the evaluation can be completed and that they will not be able to sign out against medical advice. Their capacity to refuse medical treatments should be carefully questioned.[52] A patient who refuses to cooperate until restraints are removed should be reminded of the importance of the evaluation and should be enlisted to cooperate with the goal of removing the restraints. Statements such as "We both agree that the restraints should come off if you don't need them. I am very concerned about your safety, and I need you to answer some questions before I can decide if it's safe to remove the restraints" might be helpful.[52]

TABLE 40–5 Common Reactions of Clinicians to Suicide

Anger
Anxiety
Denial
Depression
Helplessness
Indifference
Intellectualization
Overidentification
Rejection

A clinician may experience personal feelings and attitudes toward a patient at risk for suicide, which must be recognized and which must not be allowed to interfere with appropriate patient care.[145] Clinicians may feel anxious because of the awareness that an error in judgment might have fatal consequences. They may feel angry at a patient with a history of multiple gestures or at a patient who has used trivial methods, often resulting in poor evaluations and punitive interventions. Angry examiners may inappropriately transfer a patient with a low risk for suicide to a psychiatric facility or may discharge a patient with a high risk to home.[52] Attitudes of ED staff toward patients who have attempted suicide may vary based on gender, age, and hospital site.[194]

Some clinicians are prone to experience denial as they evaluate and treat patients at risk for suicide. They may conspire with the patient or family in the stance that voiced suicidal ideation was "just talk" or that an attempt was "just an accident." Others may practice intellectualization and choose to believe that suicide is "an act of free will" and that patients should have the personal and legal right to kill themselves.[45]

Clinicians commonly overidentify with patients with whom they share personal characteristics. The thought "I would never commit suicide" may become translated into the thought "This patient would never commit suicide," and serious risk may be missed.[52] The examiner may try to assure patients that they will be fine or may try to convince them that they do not feel suicidal. Patients may thus be unable to express themselves fully and may not receive proper evaluation and treatment.

A clinician who performs evaluations for patients who have made suicide attempts and who have been admitted to general hospital floors has to be aware of his or her own reactions to the patient, as well as to those of the staff. In addition, medical and surgical staff often develop strong feelings toward patients who have attempted suicide, and at times they wish that these patients were dead. The clinician must diffuse such charged situations, perhaps by holding group meetings for those involved to make them more aware of their negative feelings so that they are not acted out.[195] Such intervention may prevent mismanagement and premature discharge. Institutions should be aware of the need for guidelines for and management of immediate, short-term and long-term responses in the event of an in-hospital suicide.[196]

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41 Care at the End of Life

Rebecca W. Brendel, M.D., J.D.
Marlynn Wei, M.D., J.D.
Lucy A. Epstein, M.D.
Ned H. Cassem, M.A., Ph.L., M.D., S.J., B.D.

With more than 2 million deaths each year in the United States,[1] providing both competent and compassionate care for patients at the end of life is a crucial task for physicians. The Institute of Medicine has identified end-of-life care as one of the priority areas for improvement of quality of care, and it has specifically identified pain control in advanced cancer and care of patients with advanced organ failure as areas of focus.[2] In addition, professional organizations including the American College of Physicians have issued guidelines for improving end-of-life care, including recommendations for clinicians to regularly assess patients for pain, dyspnea, and depression.[3,4]

Caring for patients at the end of life occurs amid an often complex background of medical, psychiatric, ethical, and legal concerns. Psychiatric issues (such as depression, anxiety, delirium, substance dependence, and coping difficulties) are common conditions encountered in the treatment of dying medically ill patients. This chapter provides an overview of the central principles of care, diagnosis, and treatment of patients at the end of life from the psychiatric perspective. It also examines current concepts in ethics and legal precedents that surround this evolving area of medicine, where advances in medical technology and practice have extended the human life span and led to the emergence of both opportunities and conflicts at the end of life.

GOALS OF TREATMENT

Psychiatrists face multiple challenges when caring for a dying patient, encompassing issues of diagnosis and treatment as well as larger ethical and legal considerations. Psychiatrists may be uniquely effective in helping a dying patient by ensuring optimization of palliative care and by assisting the patient and the family in the dying process. An important first step in the treatment of the dying patient is for the psychiatrist and the patient to define treatment goals. According to Saunders,[5] the primary aim of care is to help patients "feel like themselves" for as long as possible. Care at the end of life also offers an important opportunity, according to Kübler-Ross, to address and to complete "unfinished business."[6] Common themes in this category include reconciliation with estranged friends or family, resolution of conflicts with loved ones, and the pursuit of remaining hopes. Additionally, according to Kübler-Ross,[6] patients who are dying go through a transformational process (which includes stages of denial, anger, bargaining, guilt/depression, and eventual acceptance). These stages may occur in a unique order, may occur simultaneously, and may last variable amounts of time. Psychiatrists and other physicians may assist the dying patient in the transition through these often difficult stages toward acceptance.

Hackett and Weisman[7] also developed five goals for "appropriate death" that may focus therapeutic efforts for the treatment of a dying patient. These goals include freedom from pain, optimal function within the constraints of disability, satisfaction of remaining wishes, recognition and resolution of residual conflict, and yielding of control to trusted individuals. Perhaps the most important principle in the treatment of the dying patient is that the treatment be individualized. That is, within these general goals and paradigms, each patient's unique characteristics will necessitate careful tailoring of clinical interventions. This case-by-case approach can be accomplished only by getting to know the patient, by responding to his or her needs and interests, by proceeding at his or her pace, and by allowing him or her to shape the manner in which those in attendance behave. There is no one best way to die.

Hospice can provide an important function for the dying patient by incorporating spiritual and family support, pain management, respite services, and a multidisciplinary approach to medical and nursing care. When St. Christopher's Hospice opened in 1967 with Saunders as medical director, it was dedicated to enabling a patient, according to Saunders, "to live to the limit of his or her potential in physical strength, mental and emotional capacity, and social relationships."[5] Saunders viewed hospice as the "alternative to the negative and socially dangerous suggestion that a patient with an incurable disease likely to cause suffering should have the legal option of actively hastened death, that is, euthanasia."[5]

Currently, hospice provides home nursing, family support, spiritual counseling, pain treatment, medication, medical care, and some inpatient care for the terminally ill. In 1994,[8] this numbered approximately 340,000 dying persons, and by 2007, approximately 1.4 million patients received services from hospice.[8] A decade ago, the average patient was enrolled roughly 1 month before his or her death, and the vast majority of patients had cancer.[9–11] According to 2007 data, cancer diagnoses now account for less than 50% of hospice admissions, and growth in these admissions has been attributable to dementia, stroke or coma, and lung diseases.[8] The average length of hospice enrollment in 2007 was 67 days, with a median length of

service of 20 days.[5] Women were found to use hospice services more than men, whites more than blacks, and, overall, close to one in three older Americans used hospice services.[8] Higher hospice utilization rates were found for diseases that impose higher burden on caregivers or diseases with more prognostic accuracy.[8] The three causes of death with highest hospice utilization rates were malignancies, nephritis or kidney disease, and Alzheimer's disease.[8] Medicare pays for the vast majority of hospice services; in 2007 more than 80% of hospice patients received services through their Medicare benefits.[8] To qualify for hospice benefits, potential recipients of hospice care must have their physician and the hospice medical director certify that they are terminally ill and that they will live 6 or fewer months if their illness runs its normal course.[12]

THE ROLE OF THE PSYCHIATRIST

Psychiatrists can play a crucial role in the effective management of patients at the end of life because of their abilities to appreciate the medical aspects of disease, to understand the highly subjective and individual factors that contribute to the personal significance of illness, to understand personality styles and traits, and to engage with patients to modulate maladaptive responses to illness.[13,14] To this end, the psychiatrist may serve many functions, including facilitating medical treatment, augmenting communication between the patient and the caregivers, and modeling those qualities that may be helpful for the patient. Above all, the psychiatrist's primary goals are the diagnosis and management of psychiatric symptoms and illnesses. As for all other patients, a consideration of all factors that contribute to psychiatric suffering, including biological illnesses (Axis I and III), psychological style (Axis II), psychosocial factors (Axis IV), and functional capacity (Axis V), is essential. Studies indicate that psychiatric morbidity in the setting of terminal illness is very high.[15] The most common issues that lead to psychiatric interventions for the dying patient include major depression, anxiety, personality disorders, delirium and other organic brain syndromes, refractory pain, substance abuse, and difficulties surrounding bereavement.[16,17]

Depression

The more seriously ill a person becomes, the more likely the person is to develop major depression.[18] The prevalence rates of clinically significant depression in the terminally ill range from 20% to 50%.[15,19] Studies of terminally ill cancer patients have suggested rates of adjustment disorders of from 9% to 35% and rates of major depression of from 8% to 26%.[20–26] Depression has also been associated with poor quality of life in amyotrophic lateral sclerosis.[27,28] Careful vigilance for depression is necessary, as both symptoms of depression and the impact of depression on other aspects of the patient's life and medical care are challenging. For example, Weisman formulated the wish to die as an existential signal of the person's conviction "that his potential for being someone who matters has been exhausted."[29] Ganzini and colleagues[30] documented that severely depressed patients made more restricted advance directives when depressed, and they changed them after their depression remitted. At Memorial Sloan-Kettering Cancer Center, Breitbart and Holland[31] studied terminally ill patients with cancer and acquired immunodeficiency syndrome (AIDS) who had suicidal ideation and compared them to similar patients *without* suicidal ideation. The primary difference was the presence of depression in the patients with suicidal thoughts.[31] Thus, aggressive treatment of depression is a cornerstone of care, as it dramatically decreases suffering and improves quality of life. In terms of specific treatments, psychiatrists may consider the use of rapidly acting treatments that target specific symptoms. In addition to antidepressants, stimulants are another useful class of agents; their advantages include the rapid onset of improved mood and potentiation of coadministered narcotics (with less accompanying sedation). Suicidal ideation, if it appears, should not be thought of as an "understandable" response but rather as a condition that warrants immediate investigation and treatment.[17]

Desire to Hasten Death

It is also important to differentiate suicidal ideation from a stated desire to hasten death. In one study, suicide was distinguished from life-ending acts and end-of-life decisions in the literature based on patients with chronic kidney disease and dialysis.[32] The desire to hasten death has been identified consistently among a minority of terminally ill patients.[33–36] Among patients with advanced AIDS, the desire for hastened death has been found to be 4.6% to 8.3%, significantly lower than the rate found in studies of patients with advanced or terminal cancer.[37] Although the desire to hasten death is frequently associated with depression, other factors (such as pain, existential concerns, loss of function, and social circumstances) also play critical roles.[33,38–44] The psychiatric consultant needs to listen carefully to the patient who desires hastened death, to treat any underlying psychiatric or physical problem, and to take steps to lessen distress.[41,45]

Anxiety

Anxiety frequently occurs at the end of life and requires psychiatric attention.[17,19] Impending death can generate severe anxiety not only in those who face death themselves but also in their family members, friends, and caregivers. The patient who experiences anxiety surrounding death may not necessarily be able to articulate his or her fears, although anxiety may be related to prior losses or experiences that involve the death of others. Common fears associated with death include helplessness or loss of control, ideas of guilt and punishment, physical pain or injury, and abandonment.[16–18,46,47] The psychiatrist can be helpful by addressing these fears and by exploring issues of isolation, abandonment, and suffering. Appropriate attention should also be directed toward psychopharmacologic management of anxiety symptoms.

Personality Considerations

The terminally ill patient who has a personality disorder (such as narcissistic or borderline personality disorder) or other coping difficulties can present a particular challenge for care providers. For such a patient, help is hard if not impossible to accept and trust, which can interfere with his or her ability to take the comfort that is offered.[13,16,17]

For such a patient, much of the situation is out of his or her immediate control; this elicits regression and the use of more primitive defenses (such as splitting). This may manifest as poor communication with treaters, inadequate pain control, and difficulty in the resolution of interpersonal conflicts.[17] Psychiatrists may find it useful to call on psychodynamic diagnostic and treatment skills to assist such a person in accepting palliative care.[17] Treaters can help to transform the negative countertransference (on the part of caretakers) into an understanding of how best to help the patient undergo the dying process.[16,17] Working closely with family and friends of the patient, as well as the medical team, is important in these situations.[16,17]

Delirium and Cognitive Changes

As terminal illness progresses, medical complications (such as delirium and other cognitive changes) can occur.[48–52] These complications can manifest as confusion, psychosis, agitation, or a multitude of other symptoms and can be caused by the medical illness, its treatment, or both. Palliative care interventions should also be considered earlier in the course of deterioration from dementia, and goals of care for patients with dementia should include quality of life, dignity, and comfort.[48,53] Effective management of changes in affect, behavior, and cognition resulting from delirium or dementia is critical, as it can indicate worsening of medical illness and can greatly affect the quality of time spent with friends, family, and caretakers.[16,17,54]

Pain

Pain management can be a complex challenge requiring extensive expertise. Freedom from pain is basic to every care plan, and it should be achievable in most cases,[16] but management of breakthrough pain requires detailed assessments and management.[55–57] For a multitude of reasons, pain is often undertreated by medical staff.[58–62] Pain management may be particularly challenging for a patient with a history of substance dependence; patients with a history of addiction are more likely to receive inadequate pain management than patients without a history of substance abuse or dependence.[14,63,64] The reasons for this can include concerns about higher-than-expected (and escalating) dosages of opiates, potential misuse or diversion, and fears of legal consequences of prescribing narcotics to a patient with substance dependence.[63,65] Evidence of abuse may include unexpectedly positive results on toxicology screens, frequent requests for higher dosages, recurrent reports of lost prescriptions, and multiple visits to various providers or emergency departments for prescription refills.[66]

Physicians who prescribe to such patients may have divergent opinions about the treatment of substance dependence in the terminally ill. Some physicians feel that carefully monitoring a terminally ill patient on an opiate or actively treating the patient's substance dependence deprives the patient; however, optimal relief of suffering mandates acknowledgement and treatment of active substance abuse issues.[67] The goal of care requires the physician to separate the management of the patient's pain from the management of addiction, and to treat both.[14,68] Careful monitoring of a patient's narcotic use, use of a multidisciplinary team, encouragement of substance abuse treatment, limitation of prescribing power to a single provider, and use of screening tests (e.g., urine toxicology) may all be useful in the management of the terminally ill person with substance dependence.[69] Complementary therapies as part of end-of-life care for improvement of quality of life or moderation of pain distress are also being studied.[70]

Psychosocial Considerations

Optimal end-of-life care includes an understanding of the major areas of psychosocial concern (such as family, work, religion, faith, ethnicity, and culture). The presence of the family is crucial to help a patient resolve long-standing conflicts (if possible) and to provide a context for honoring and remembering the patient.[16] Psychiatrists can aid the family by encouraging the sharing of feelings among family members and by helping to create specific plans for the family (such as the compilation of commemorative items).[17] At the same time, an understanding of the complexities of family interactions (both positive and negative) helps prevent harm to a potentially fragile family system. For example, a recent randomized clinical trial of family-focused grief therapy found that it could help prevent pathologic grief in family members; however, it also had the potential to increase conflict in families where the level of hostility was high.[71]

As with family relationships, a sense of vocational identity can help create meaning for a patient at the end of life.[16] For some, work can be critical for self-esteem. As a patient can begin to feel less valuable when work ceases or retirement arrives, the presence of former and current colleagues can be quite supportive.

Similarly, thoughtful discussion about a patient's beliefs and faith can provide an opportunity for a patient to further his or her sense of meaning and thoughts about an afterlife.[17] Many patients are grateful for the chance to express thoughts about their faith. The patient's own clergyperson, if available, can often provide valuable information and insights about the patient and family and help smooth the course before death. Writers such as Allport[72] and Feifel[73] have contrasted an extrinsic religious orientation (in which religion is mainly a means to social status, security, or relief from guilt) with an intrinsic religious orientation (in which the values appear to be internalized and subscribed to as ends in themselves). Experimental work[74] and clinical experience[16] indicate that an extrinsic value system, without internalization, seems to offer less assistance in coping with a fatal illness than an intrinsic religious commitment (which can offer considerable stability and strength).

Last, patients from underserved communities or minority populations in the United States may have needs that are not served by the current health care system. Unfortunately, the same institutional, cultural, and individual factors that generate disparities in care for minority populations in general also affect care at the end of life.[75] These factors include lack of access to care, undertreatment of pain, and mistrust of the health care system.[75–77] Furthermore, important differences between ethnic groups and cultures can be found at all segments of end-of-life care. For example, several studies have shown that African American patients, as well as older individuals from other ethnic backgrounds (such as Latino, Asian, or Native

American), are somewhat less likely to have arranged for an advance directive as compared with Caucasion patients.[78] There are also important differences in terms of preferences for life-sustaining treatment. For example, in a study involving multiple ethnic groups, African Americans had the highest rate of preferring life-sustaining treatment, and European Americans had the lowest rates.[79] Multiple other studies have demonstrated a preference by African Americans to choose more life-sustaining treatment and cardiopulmonary resuscitation in the face of terminal illness.[75,80–83]

Additionally, culture may influence the decision-making process.[84] For example, family-centered (rather than individual) decision-making is common in certain ethnic groups in the United States, which challenges the traditional Western model of the importance of individual autonomy. Studies have found a higher use of family-centered decision-making among Latino and Asian groups in the United States, which may include the decision to disclose (or not to disclose) the diagnosis of a terminal illness to an individual patient.[78] Thus, attention to cultural competency by psychiatrists plays a significant role in mediating end-of-life care for patients from all ethnicities and cultures.

CHALLENGES FOR CARE PROVIDERS

The emotional intensity associated with providing empathy and support for the dying patient during a time of need may challenge and tire caregivers (such as family and professional staff). A critical skill in end-of-life care is being able to hold end-of-life discussions[85] and to listen to the patient and families, asking open-ended questions.[86–89] End-of-life discussions with physicians have been associated with fewer aggressive interventions, which, in turn, is associated with improved quality of life and caregiver bereavement adjustment.[90] Structured, proactive, multidisciplinary communication systems that include an ethics consultation and palliative care teams have also been shown to improve communication during critical care and end-of-life care for patients and their families.[91–95] Barriers to patient–physician communication about end-of-life care include physicians' own perception that the patient is not ill enough or is not ready to have the conversation.[96] Special considerations should be given to pediatric populations.[97]

Caregivers may also experience helplessness and despair in the face of their powerlessness over a patient's approaching death.[98] If left unaddressed, these feelings in caregivers can cause the caregiver to avoid the patient, to retreat, or even to convey to him or her how burdensome he or she is to caregivers. This could be devastating to the helpless patient who looks to the caregiver for hope. Hence, among the greatest psychological requirements for caregivers is to learn to live with negative feelings and to resist the urge to avoid the patient—actions that convey to the patient that he or she no longer matters. Certain traits make these empathic difficulties hazardous for some caregivers. Dependent persons who expect patients to appreciate, to thank, to love, and to nurture them are unconsciously prone to exhaust themselves regularly because they "can never do enough." This creates a pattern that may be sustainable for a patient with the capacity to nurture the caregiver, but it could have a disastrous outcome if the patient is depleted or intractably hostile. The harder the caregiver strives, the less rewarding the work becomes. Exhaustion and demoralization follow. Some caregivers want to please every physician they consult, and they come to a similar state of exhaustion because many of these patients cannot improve.

ETHICS AND END-OF-LIFE CARE

Principles

End-of-life care carries, inherently, a host of ethical questions that the psychiatrist is likely to encounter. A brief discussion of principles is not intended to supplant the need for concrete individualized judgments for every patient. Principles provide anchor points from which clinical reasoning can proceed—specifically, when limitation of life-supporting treatment is proposed.

The primary obligation of the physician to the patient in traditional medical ethics has been expressed in both positive and negative terms. The negative goal, always referred to first, is not to harm the patient *(primum non nocere)*. The positive obligation is to restore health, to relieve suffering, or both. Our contemporary dilemma, as Slater[99] has pointed out, arose because we now have many situations in which these two aims come into conflict (i.e., the more aggressive the efforts to reverse an incurable illness, the more suffering is inflicted on the patient). For example, if a 70-year-old man with large cell cancer of the lung is found to have metastatic spread of the disease to the other lung and to his liver, any treatment of the cancer is likely to make him feel worse and would be unlikely to prolong his survival.

A related problem is the difficulty in distinguishing treatments administered to relieve pain and suffering from those intended to hasten death.[100] The principle of double effect is commonly used to allow the administration of narcotics and sedatives with the intent to relieve suffering of dying patients, even though such administration may hasten death, but it is a principle that remains widely debated.[101–103]

Second, modern medicine respects patients' right to autonomy. This principle guarantees any competent patient the right to refuse any treatment, even a lifesaving one. This was the emphasis of the medical ethics of the 1970s and 1980s and it focused on refusing life-prolonging treatment, such as mechanical ventilation, and more recently, nutrition and hydration. Honoring such refusals presupposes that the patient is competent. It is important to remember that competent patients may make decisions that providers may view as irrational.[104] However, a patient cannot insist that the physician provide treatment that is considered futile.[105–109] Defining futility continues to be a goal of medical ethics as a balance is forged between the autonomy interest of patients to opt for aggressive treatment and concern by physicians that there is a duty not to offer or provide treatments that are ineffective.[110–112]

Another area of debate concerns the right for terminally ill patients with cancer to have access to investigational drugs.[113] A case was brought against the U.S. Food and Drug Administration by an alliance named after Abigail Burroughs, a young woman who had been diagnosed with

squamous-cell carcinoma of the head and neck at age 19 and had unsuccessfully attempted to obtain investigational drugs on a compassionate-use basis. In 2006, the U.S. Court of Appeals for the District of Columbia Circuit initially held that patients with cancer have a constitutional right of access to investigational cancer drugs.[114] On a rehearing, however, the Court of Appeals reversed the decision and found that there is no fundamental right of access to experimental drugs for the terminally ill.

Limitation of Life-Sustaining Treatment

One salient concept for psychiatrists to understand is the limitation of life-sustaining treatment. Whenever the risks or burdens of a treatment appear to outweigh the benefits, use of that treatment should be questioned by both physician and patient. Limitation of life-prolonging treatment is generally reserved for three categories of patients. First, patients whose illness is judged to be irreversible, who are moribund, and who need to be protected from needlessly burdensome treatments may refuse life-sustaining treatment. This is widely accepted for patients who will die with or without treatment (such as the patient with advanced metastatic cancer). Second, because of the right to refuse treatment, competent patients who are not moribund but who have an irreversible illness have also been allowed to have life-sustaining treatments stopped. Last, competent patients with a reversible illness have the right to refuse any treatment, including life-saving treatments.

However, complications emerge when a patient is not able to make or voice a decision regarding his or her wishes. In these situations, the state has a recognized legal interest in preserving life, and it may be difficult to ascertain whether the patient had a countervailing autonomy interest. One historical example is the case of Karen Ann Quinlan, a 21-year-old woman who in 1976 fell into an irreversible coma while at a party. This case became a legal battle between the right of Quinlan's mother (who, as her guardian, wished to withdraw life-sustaining treatment from her daughter and allow her daughter to die with dignity) and the state's interest in preserving life. In the end, the Supreme Court of New Jersey decided that, if it was believed, to a reasonable degree, that the coma was irreversible, life-sustaining treatment (e.g., with a respirator) could be removed.[115] Now, more than 30 years later, the standard medical recommendation in the case of irreversible coma is to stop all treatment (including nutrition and hydration). This judgment is made on the principle of the inevitability of death and the futility of any treatments to prevent it.

For patients in a persistent vegetative state (a state in which patients have a functioning brainstem but total loss of cortical function), a complicated scenario emerges.[116,117] The many clinical dilemmas in this condition are perhaps best exemplified by the Nancy Cruzan case in 1990. Seven years after the automobile accident that left her in a persistent vegetative state, Nancy Cruzan's feeding tube was removed. She died 12 days later. Her parents' request that the tube be removed initiated a journey that took them through the state and federal court system, up to the U.S. Supreme Court. The U.S. Supreme Court's decision[118,119] affirmed that competent patients have the right to refuse treatment, that foregoing nutrition and hydration is no different from foregoing other medical treatment (such as artificial ventilation or pressor agents), but that Missouri (and other states) could require "clear and convincing evidence" that the patient, while still competent, had rejected the idea of life-sustaining treatment under such circumstances. That is, the autonomy interest of the patient in a persistent vegetative state had to be weighed against the state's interest in protecting life. However, according to the U.S. Supreme Court, while Missouri could require clear and convincing evidence of a patient's wishes when that patient was previously competent, states could also adopt less rigorous standards.

The complicated scenario of the persistent vegetative state was more recently revisited in the Theresa Schiavo case of 2004.[120] In this case, Theresa Schiavo was determined to be in a persistent vegetative state, and her husband, who was her guardian, wished to withdraw life-sustaining nutrition and hydration from her, in accordance with what he believed her wishes would have been. However, her parents opposed removal of the life-sustaining measures. Although the Florida Supreme Court's decision upheld the decision to have her feeding tube removed, it did not revisit or alter the legal rights of patients, in that it rested on a narrow legal analysis of the proper powers of each branch of the state government. Nonetheless, the case revived public debate about withdrawal of care at the end of life. After the case, many states began debating the amount of proof required to establish that an incompetent patient, when competent, would have opted to have his or her life-sustaining care withdrawn, and clinicians have had to revisit the guidelines for the appropriate use of artificial nutrition and hydration.[121]

As a whole, the legal cases regarding end-of-life decision-making explicitly give patients the right to exercise their autonomy regarding what care they receive. For competent patients, these wishes may be expressed at the time that they are making decisions regarding end-of-life care through the use of advance directives that take effect in the event of future incapacity to make or express decisions about their care. These directives may be instructional, may appoint a substitute decision-maker, or both. Instructional directives placing limits on life-sustaining treatment, however, may be difficult to interpret on clinical grounds. For example, requests (such as the desire that "no extraordinary means" be taken to preserve life) may be difficult to interpret in actual clinical settings. Advance directives that appoint a substitute decision-maker with whom the patient has discussed his or her wishes may be a more flexible way to enact a patient's wishes. Specifically, a substitute decision-maker can use his or her knowledge of the patient's prior expressed wishes in combination with the actual clinical scenario in order to more reliably lead to the outcome that the patient would have wanted, if competent.

Physician-Assisted Suicide

Although patients have broad rights of autonomy in expressing their wishes for end-of-life care, there are limits on a patient's ability to control his or her death. A patient may express the wish to have a physician end his or her life (euthanasia). One study of terminally ill cancer patients

found that attitudes toward euthanasia and assisted suicide were determined by psychosocial traits and beliefs, including religious beliefs and perceptions of the amount of burden on families, rather than symptom intensity or disease severity.[122] Euthanasia, even when requested by the patient, is illegal in all 50 states and all U.S. districts and territories. Physicians are prohibited from administering life-ending medication or directly causing death through affirmative actions throughout the United States.

Unlike euthanasia, the practice of physician-assisted suicide, which allows physicians to help patients acquire the means to end their lives but does not permit the physician to actually administer those means, has begun to gain acceptance in the United States. Specifically, physician-assisted suicide is legal in the state of Oregon and has survived numerous legal challenges in the U.S. Supreme Court. Most recently, in 2006, the Supreme Court in *Gonzales v Oregon* held that the U.S. Attorney General did not have the authority under federal law to prohibit doctors from prescribing regulated drugs for use in physician-assisted suicide in the setting of state law authorizing the practice.[123]

Under the Oregon Death with Dignity Act (DWDA),[124] physicians in Oregon are permitted to write prescriptions for lethal doses of medications to patients who request to die and meet the other requirements of the state law. Overall, the practice has contributed to a small proportion of deaths in Oregon (0.01%): from 1998 to 2008, there were 401 deaths by ingestion in Oregon.[125] The specific prevalence of psychiatric symptoms in individuals requesting physician-assisted suicide has not been extensively characterized. One study of 58 Oregon residents who had requested aid in dying from a physician or had contacted an aid-in-dying advocacy organization found that 15 participants met criteria for depression and 13 for anxiety.[126] Three of the 18 participants in the study who received a prescription for a lethal drug under the DWDA met criteria for depression.

Although Oregon has legalized the practice, organized medicine (and psychiatry) oppose the practice. Nonetheless, a second state, Washington, in 2008 passed an initiative for the Washington Death with Dignity Act[127] modeled on the Oregon DWDA. The debate[128–130] over physician-assisted suicide will no doubt continue as other states consider passing laws that authorize it.

CONCLUSION

The aim of end-of-life care is to maximize the quality of life and to minimize the suffering of patients who are terminally ill. For many patients, the end of life marks an important opportunity to reflect, reconcile, and pursue remaining hopes. The psychiatrist can play an important role in the diagnosis and treatment of psychiatric illness in this setting, as well as in facilitating treatment, enhancing communication, and modeling caregiver qualities for families. From a psychiatric perspective, major depression and anxiety are commonly seen; suicidality should not be considered "understandable" or "normal" in this setting. Delirium, pain, and difficulties with coping are also common reasons for consultation requests. As in all other forms of psychiatric evaluation and treatment, it is crucial to consider any medical contribution to psychiatric symptoms. Aggressive treatment of depression, anxiety, and other psychiatric symptoms is a crucial part of holistic management. Additionally, psychosocial factors may play an important (and, at times, complicating) role in the care of these patients. Psychiatrists also should be aware of, and prepared to manage, many of the complex ethical and legal issues that arise in the care of these patients. Physicians have clear obligations in caring for their patients, and patients have rights to autonomy in their decision-making.

Sound clinical and ethical practice requires that the physician assist the terminally ill patient in the complex and often simultaneous processes of grieving and celebrating, reconciling conflicts and completing unfinished business, achieving last hopes and accepting that some goals are unrealized, while alleviating suffering and maximizing autonomy and personhood until death.

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Pediatric Consultation

Brian P. Kurtz, M.D.
Anna C. Muriel, M.D., M.P.H.
Annah N. Abrams, M.D.

Psychiatric consultants are called on to respond to a diverse set of needs originating with the child, the family, and the hospital staff. The child psychiatrist consults directly with the pediatric patients and their families, acts in a liaison capacity with medical and nursing staff, manages the needs and demands of difficult parents, and helps a divided treatment team understand divisive dynamics and unite around common goals of quality care.

Stocking and associates[1] found that 64% of children on their pediatric wards had emotional problems that warranted psychiatric consultation, even though only 11% were referred for such consultation. In a more recent study of pediatricians, Burket and Hodgin[2] found that more than half of the pediatric staff stated that they rarely or never referred to child psychiatry, yet these same pediatricians estimated that more than 30% of their patients had emotional problems.

Fritz and Bergman[3] surveyed more than 1000 members of the American Academy of Pediatrics; they questioned pediatricians about their experiences with psychiatric consultation during residency training. They found that 68% of those who had had an interaction with a psychiatrist remembered the consultation as helpful. However, although the experiences were positive and the need identified was substantial, half of the pediatricians rarely consulted psychiatrists. As identified in the survey, there were several obstacles to referral (the corresponding percentage of pediatricians agreeing with the statements is shown in parentheses): "Patients are reluctant to see psychiatrists" (51%), "No one will pay for it" (46%), "There are too few interested, competent psychiatrists" (44%), and "Other mental health professionals are more readily available" (39%).[4] Burket and Hodgin also found that the pediatric house staff reported referring to child psychiatry somewhat more often than did their attending physicians. This pattern suggests that less-experienced staffers are more comfortable requesting psychiatric consultations.

Potential barriers to psychiatric consultation are abundant. One factor is that child psychiatrists are unavailable in many pediatric hospitals. However, early identification of children in need of consultation remains crucial. To overcome resistance to consultation requests, routine psychiatric consultations for specific diagnoses (such as cancer, diabetes, cystic fibrosis, and failure to thrive), as well as for protracted or frequent hospital stays, nonadherence, and psychosocial dysfunction, may be initiated. A psychosocial screening tool, such as the Pediatric Symptom Checklist (PSC)[5] or the Psychosocial Assessment Tool (PAT2.0),[6] can also help identify high-risk patients. Once consultation has been initiated, pediatricians highly value accessibility and timeliness of child psychiatry consultants. Close follow-up, liaison work, and provision of specific recommendations are also valued.[2]

The consultant needs to be attuned not only to the needs of the child and the family but also to the dynamics of the pediatric unit.[7] Assessment of how the child's situation is experienced by the pediatric team requires an awareness of the patient mix on the unit, recent deaths or other traumas, and attitudes toward certain diseases and presentations that can evoke strong emotions among staff (e.g., irritation when caring for a patient whose problems are perceived as "self-induced," such as with an eating disorder or intentional overdose). At times, the consultant might identify a psychologically vulnerable team member who needs referral for additional support.

The consultant needs to make assessments and treatment plans quickly, to facilitate rapid high-quality communication between members of the health care delivery team, and to create seamless transitions from inpatient to outpatient care (involving follow-up and specific recommendations). These goals are facilitated by creating relationships between the consultant and the pediatricians, interacting with community resources, and appreciating the medical challenges from within the child's developmental frame of reference.[8,9]

DEVELOPMENTAL AND FAMILY-CENTERED APPROACH TO CONSULTATION

In assessing a hospitalized child, the consultant must appreciate the child's phase of development and recognize that the child's presentation can be understood only in the context of his or her previous level of function and behavior. The task for the consultant is to place what is learned about an individual child and his or her family into a general context and to understand the challenges faced by all children at that particular developmental level.

The consultant uses a developmental perspective, informed by collateral data regarding temperament, premorbid personality, and the family's function, to evaluate the child's behavior, emotional state, and defensive style. Knowledge of defense mechanisms is often used to help children and their families cope with illness and hospitalization. In general, the maturity of a child's defensive style helps when coping with anxiety; however, defensive patterns are complex. Defenses (including denial, isolation of affect, and intellectualization) help with modulation of

anxiety.[10] For example, a teenager with cystic fibrosis might use isolation of affect and intellectualization when discussing what is needed for lung transplantation. An example of effective denial is the 10-year-old with metastatic cancer who is invested in completing his schoolwork and getting promoted to the fifth grade. Use of an array of defenses that permits adherence with the health care and facilitates investment in age-appropriate activities should be supported. Denial, when used by a withdrawn child, can mask psychopathology and prevent referral.[11]

Infancy

For the hospitalized infant, the key developmental challenge is to maintain the quality of the attachment between parent and child. The parental component of attachment begins while anticipating the infant's birth or adoption. An infant is a parent's most personal product, embodying the hopes that the child will ultimately possess the strengths and values the parent most values in himself or herself, and the wish that the child will have capacities that offset the parent's self-perceived deficiencies. No infant can meet all of the parents' conscious and unconscious expectations, yet most infants are accepted and loved when they enter the world. Parents adapt to the reality of the infant and embark on the lifelong process of attachment that enables child and parent to weather the stresses and strains of caretaking and growing up while remaining committed and connected.

Parents with affective illness (including postpartum depression), anxiety disorders, psychotic disorders, character pathology, or intense guilt can have difficulty achieving the attunement that is necessary for attachment. The psychiatric consultant may be called on to differentiate among depression, character pathology, or anxious adjustment in the setting of inadequate parental attachment. Infants with medical conditions that interfere with feeding, limit access to holding and soothing, affect appearance, or cause irritability present special challenges to the process of attachment. Ill infants require parents to be more mature because the unexpected circumstances can leave a parent feeling incompetent or unloved by the newborn. The medical staff can play a crucial role in successfully supporting new parents through this difficult early phase.

Infants and toddlers are largely nonverbal, and they rely on a small, consistent number of caretakers who know them well enough to be attuned to their nonverbal communications. Therefore, the infant's experience of the stress of hospitalization is exacerbated by separations from the mother or primary caretaker. Bowlby's classic work on attachment[12] described the three phases of separation anxiety seen in infants:

1. *Protest:* The infant acutely, vigorously, loudly, and thrashingly attempts to prevent departure of the mother or rapidly attempts to recapture her. In the older child, this phase can appear as clinging, nagging, or bargaining as a parent is about to leave.
2. *Despair:* The infant is less active, might cry in a monotone with less vigor, begins to withdraw, and appears hopeless. Sometimes the withdrawal phase is mistakenly seen as a good adjustment because the infant is quieter.
3. *Detachment:* The infant seems more alert and accepting of nursing care. These new attachments are superficial, however, and the infant concomitantly shows a loss of affect or positive feeling when the mother appears. With chronic disease that requires numerous prolonged hospitalizations, the infant or young child might make many brief, inconsistent attachments and suffer numerous losses if the primary caretaker is regularly absent and many different surrogate caretakers interact with the child. Spitz[13] referred to the overwhelmed infant's state as *hospitalism*.

Tronick and co-workers[14] found antecedents of Bowlby's more pronounced phases of separation occurring over minutes when a mother is unresponsive to her infant's attempts at relating. In response to these findings of short-term and long-term consequences of maternal separations, hospitals are increasingly encouraging mothers to stay overnight with children and to participate in their child's care.[10,14] In addition, nursing departments have instituted a primary nursing model to limit the number of nurses who care for each child.

Preschool Age

Medical conditions in the preschool phase (ages 2.5 years to 6 years) are affected by three important aspects of the child's emotional and cognitive development: egocentricity, magical thinking, and body image anxiety. Egocentricity is the child's perception that all life events revolve around him or her. The child cannot imagine that others see the world from a vantage point different from his or her own. Magical thinking is the creative weaving of reality and fantasy to explain how things occur in the world.

The combination of egocentricity and magical thinking can lead the preschool-age child to imagine that medical conditions are punishment for the child's own bad thoughts or deeds. For example, a 4-year-old with leukemia reported he got his "bad cells" from eating too many cookies. The young child needs ongoing support from family and medical staff to understand that the medical condition is not punishment or secondary to some unrelated experience. Without this support, the child's anxiety is likely to be much greater and be expressed as inhibition and withdrawal, or as behavioral outbursts.

One understanding of the cause of body image anxiety comes from the preschooler's cognitive development, which leads the child to envision the body as a shell (skin) filled with blood, food, and stool, which could ooze out of any hole in the skin. This concept of the body being like a tire or water balloon that can be punctured with dire results may explain the preoccupation with bandages at this age, as well as fear of needle sticks and surgical procedures that seem to exceed what can be explained by painful experiences alone.

Some regression is to be expected in the stressed preschooler.[11,15] This can take the form of enuresis in a previously toilet-trained child, increased dependence on parents for help with dressing or eating, and episodes of unwillingness to use words to express wishes or use of baby talk. Each of these regressed behaviors serves to engage parents and nursing staff in a style of caretaking that may be more commonly associated with a baby or toddler.

Treatment approaches can assist the preschooler with adjustment to medical illnesses and interventions and can

minimize regression. Pain should be controlled or eliminated whenever possible, even when it is not the fastest way to proceed. Procedures should be explained in simple terms to the child. The child needs to hear in the most basic terms what will be done, why it is needed, and what parts will be uncomfortable or painful. Children will want to know where their parents will be before, during, and after the procedure. Interventions should be performed in designated locations, such as treatment rooms, and there should be safety zones, usually the child's hospital room and the playroom, in which no procedures are done. It is crucial for children of all ages to have safe places within the hospital setting, so that they are not on high alert at all times. Similarly, warning children about impending procedures can lead to protest acutely but over time allows children to relax and not be constantly anticipating an unpleasant surprise attack.

School Age

School age (6 to 12 years), also referred to as latency, is characterized by a host of new and developing skills in many arenas: academic, athletic, and artistic. The world outside the family becomes more important with the advent of best friends and status in friendship or interest groups. In the context of medical illness, the age-appropriate investment in mastery of skills can lead to improved coping, with a better understanding of medical illnesses (although still rudimentary), pride in learning to anticipate regular treatments, medications, and procedures, better capacity to verbalize needs, and establishment of relationships with nursing staff and physicians. Children with premorbid competencies might weather the stress of illness somewhat better than their less-capable peers.

The stress of medical conditions, however, routinely leads to regression in all age groups, so the improved coping skills of latency might not be observed in the hospital setting. Regression is common early in a chronic illness, with the potential for developing better coping after there has been time for adjustment. The level of function fluctuates according to the individual stressors (e.g., mood, malaise, pain, procedures, and prognostic changes) and family function. Offering age-appropriate activities (such as board games, video games, computers, puzzles, arts and crafts) and school tutors helps children to function closer to their premorbid level and serves as a counterweight to the regressive pull of dependency, helplessness, and loss of control that often accompanies hospitalization.

Later in a chronic illness, flexible denial can be a healthy component of coping. Flexible denial denotes the child's ability to suppress thoughts about the illness and invest in an array of activities without abandoning the appropriate measures necessary for treatment of the illness.

It is common for school-age and older children to have distorted or magical notions of the cause of the illness, which are typical of the thinking of younger children. It is helpful to invite all questions—by saying things like "I like to hear what children wonder about" or "There is no such thing as a silly question" and invite fantasies about the medical condition by direct questions such as "What do you think might have caused your cancer?" Some children may be uncomfortable expressing themselves in a direct dialogue but may be willing to draw a picture of their cancer or to write a story about a child with an illness. Any outlet for expression can be helpful to elucidate the fears that underlie the child's anxiety.

In chronic illness, the school-age years offer a less conflicted opportunity to foster positive health-related behaviors. The child should be able to give a simple, accurate explanation of the illness. The child should be learning the names of medications, their purpose, and when they are to be taken. At this age, a partially independent relationship between the child and the treating physician can be developed. Psychiatric intervention is warranted if the child is resistant to learning about the illness, if the child is regressed, if parents are noted to be intrusive or overinvolved in the health care regimen, or if nonadherence to the medical treatment plan has become a means of fighting between child and parent. Allowing these patterns to proceed into adolescence will likely increase risk of dysfunction and make intervention more difficult.

Adolescence

The adolescent, similar to an adult, enters the medical setting with the capacity to understand the meaning of an illness, including its possible ramifications. Developmentally, adolescents venture out with a more independent posture and leave behind the intense dependency on parents that is seen in younger children. This brings with it a particular sensitivity and vulnerability. The multiple demands of hospitalization, including deciphering the meaning of diagnoses and treatments and bearing the physical discomfort, limitations, pain, impact on appearance, and fears about the present and future, can overwhelm the adolescent's ability to exercise newly acquired independence in a developmentally appropriate way. The physical limitations imposed by illness can put adolescents at risk for major depression, especially when the illness interferes with activities that are key to the adolescent's emerging self-image.[16]

The assault on the teenager's autonomy may be particularly difficult to bear because it coincides with the strong developmental pull to individuate from parents and to establish an independent identity. Often the illness occurs at a time when other tensions between the adolescent and parent make relying on the parents uncomfortable or unacceptable. Faced with this emotionally complex dilemma, some teens become sullen, aggressive, nonadherent, or withdrawn, whereas others are able to negotiate the discomfort of returning to a more dependent, supportive relationship with parents.

Interview styles should respect the adolescent's wish for autonomy. One should engage the adolescent first before looking to the parents for their input. Adolescents should also be offered private time to share information that might not be easily shared in the company of parents. Sexual experiences or concerns and worries about parental coping or even death may not be voiced without privacy. The risks and benefits of treatments need to be presented to the adolescent with the recognition that his or her adherence is central to the success or failure of any treatment plan.

Family-Centered Care

The concept of family-centered care has emerged as a care philosophy that highly values effective collaboration

among patients, families, and health care providers and promotes principles and practices that improve this collaboration.[17] It can be helpful to use this term when communicating with pediatric health care providers, who may be less accustomed than child psychiatrists to thinking about the family in a systemic manner, in order to share a common language about the need to include families in psychiatric assessments and treatment planning.

The child cannot be understood separately from the family. Serious or chronic illness in a child is a family crisis. The parents must cope with the uncertainty and the highs and lows associated with hospitalization. Abnormal laboratory results, adverse reactions, life-threatening crises, limitations on the child's future, and the specter of death suddenly become their reality. They observe their child in distress and they often feel fundamentally unable to protect the child.

The hospital environment brings with it a host of medical professionals with as many personalities as there are consultants and caretakers; often, each seems to hold a crucial piece of the puzzle. Small nuances in the presentation of data or differing styles of optimism or pessimism among staff can radically shift the family's mood. There is rarely much privacy and sometimes none at all, whether in a shared room or an intensive care unit. Parents' anxiety negatively affects the child's capacity to cope; to expect a parent to be other than anxious is unthinkable.[18,19]

Parents are the child's most trusted and valuable resource; therefore, strategies to support the parents are crucial. Most parents evoke staff empathy and appreciate the skill and compassion of the treatment team. Certain parents are particularly challenging to support because of a combination of personality difficulties and coping style. Their distress, often fueled by a sense of helplessness, is typically expressed either as devaluing staff or as apparent insensitivity to the sick child's needs. The consultant helps the team of caregivers understand the psychological meaning of the parents' troubling behavior so they can continue to provide optimal care.[20,21]

Siblings are often the forgotten sufferers in the context of chronic or life-threatening illness.[22] They not only have worries about the sick sibling, but often they also lose the support of their parents. The parents may be physically absent, spending time at the hospital with the ill child and attempting to meet at least minimal work demands to support the family financially. They are often emotionally absent, depressed, or drained by the emotional demands of the sick child. Many parents feel angry at the well siblings for making any demands and for not selflessly understanding the seriousness of the ill child's predicament. This compounds the well siblings' guilt at the expectable feelings of resentment and jealousy toward the ill child who is receiving so much attention and so many gifts. If the illness results in death, the feelings of guilt and responsibility may become overwhelming.

Family interviews can aid in the assessment of the physically ill child and help the consultant target areas in the family system that might benefit from support. Families of ill children need to express their feelings about hospitalization and to obtain emotional support. Siblings often have distorted concepts of the child's illness that need to be corrected. A carefully planned family meeting can begin to clarify distortions, reduce family turmoil, improve coping skills, and dispel conflict between family and staff. During the meeting, the ward staff or the psychiatrist should evaluate the family's psychological state, including an assessment of coping mechanisms, anxiety level, available support, and ability to comprehend information.

INITIAL STEPS IN THE CONSULTATION PROCESS

The first step in any consultation is to fully understand the consultation questions (e.g., "Who initiated the consultation?," "What concerns underlie the question?," "What feedback does the consulting person need to be satisfied, and within what time frame?"). Once the questions are clarified, the consultant must gather the necessary history including data provided by members of the medical team, the hospital record, and clinical interviews with the child and parents, as well as social agencies or nonparental caretakers, when appropriate.

Some pediatricians are especially sensitive to psychological concerns and have known the patient and family for several years. In university-affiliated hospitals, the consultant often deals with less-experienced house staff on monthly rotating schedules, and discussion with the referring physician is shifted toward teaching. A crucial function of ongoing consultation is the trusting relationship that should develop among the pediatrician, unit personnel, and the consultant. This trust creates an atmosphere in which the psychological needs of children are recognized and the consultant's recommendations are carried out even when these take additional time and effort.

In the review of the medical record, it is especially important to note the observations of the nurses and child-life specialists, who often have a wealth of information from sustained contact with the child and the family. They often have had considerable experience with other children of similar age and with the same diagnosis; thus, they have a sense of how this child is coping as compared with a relevant peer group. The nurse usually takes a self-care and daily habit history on admission that emphasizes the child's premorbid level of function. The nurse may also record the most careful observations of the child's level of anxiety, state of aggression, and temperamental characteristics.[23,24] The role of the child-life specialist, trained in development, is to help children cope with the stress of hospitalization by organizing individual and group play activities in the recreation room. The child-life specialist often has the opportunity to observe children interact with peers and to use special hospital play materials.[25] The staff's input is a critical adjunct to the consultant's impression, which is based on one or two interviews. Many pediatric inpatient services have a social worker who reviews all or some of the admissions; this expanded social history may be helpful before the consultant meets the family and child.

Techniques of Child Psychiatric Consultation

The child and family should be prepared for the consultation. The referring physician should discuss the reasons for the referral with both the child and the parents so that

the child feels more included and does not feel that information is being withheld. Parents of a preschool-age and young school-age child (younger than 8 years) should be interviewed by the psychiatric consultant before the child is interviewed. The interview of the young child requires largely indirect means of expression of feelings and concerns via play rather than by direct questioning.

In the initial interview, the psychiatrist needs to create an environment as normal as possible as he or she gets to know the child. The consultant's interactive style should be active, interested, and playful. The assessment room should contain some toys and not be the site of painful procedures. First, one should carry out an unstructured observation, after which a gross developmental assessment is conducted.

In the child younger than 3 years, observations of the parent–child dyad are crucial. One should note: "What is the eye contact like between parent and child?," "Does the parent respond to cues in the child and vice versa?," "Are the parent and child in sync?," "Does the child look to the parent for reassurance and comfort?," "What is the child's temperament like, and how does the parent handle frustration?," "How do the child and parent handle separation?," "How does the child respond to strangers?" Stranger anxiety in the very young is expected, and the lack of any stranger anxiety may be a sign of attachment difficulties.

The 3- to 6-year-old child might still require that a parent be present throughout the interview. That request should be respected, although at some point in the interview an attempt should be made to have the parent leave the room. Developmental assessment, including language, social interaction, and gross and fine motor coordination, is a mandatory part of the interview. Drawings become a more important tool for some children to express troublesome thoughts and feelings. The psychiatrist should not expect to complete the evaluation in one visit. It can take several sessions, and the sessions may be short because of the child's fatigue or because other tests have been scheduled. The consultant might need to arrange visits to coincide with appropriate times for observing key behaviors, such as around meal times or dressing changes.

The school-age child can be a more verbal participant in the interview. The child should be questioned about current and previous school attendance, school behavior, school performance, after-school activities, friends, health (including mental health) of family members, family problems, and interaction of family members in response to traumatic events. The mental status examination should initially focus on the manner of relating. The child may be active and verbal or shy and inhibited. The consultant's approach should be flexible depending on the child's way of relating. The active verbal child can be approached in the more traditional interview. The shy child may be engaged through drawings or games, such as checkers or video games. These activities can prove helpful in facilitating an alliance and in demonstrating organic deficits. The first several sessions may be necessary for the child to trust that the consultant will not be performing invasive or painful procedures. Many helpful observations of the child can occur in this initial phase, including assessment of pain, anorexia, and insomnia, assessment of coping strategies, and supportive comments about ways to deal with symptoms and difficult feelings.

Interviewing an adolescent can be most challenging with regard to building an alliance. Some adolescents flatly refuse to talk, and others substantially distort their psychosocial histories. Adolescents are often labile and experience emotions intensely. The consultant should not become discouraged by an adolescent's initial silence. This response might represent anxiety and vulnerability. The adolescent should be given a thorough explanation and reason for referral. The consultant should clarify the limits and expectations of the interview as well as his or her knowledge of the adolescent's medical condition. The consultant can present himself or herself as a member of the medical treatment team with expertise in trying to understand what is most taxing about an illness or situation and working with the patient and the team to find the best approach for helping the patient.

Confidentiality should be addressed, and the interview should be conducted in a private setting. In general, the consultant should be patient and easygoing. It may be helpful to initiate the conversation with some safe topics, such as a sporting event, television show, or question about a photo or other belonging in the hospital room. The consultant should let the adolescent know the intended length of the visits, initially giving the adolescent some control over length and timing when possible. Over time, questions about body image, school, family relationships, friendship patterns, goals, and sexuality need to be addressed.

The role of the family interview as the initial interview for the assessment of a child is somewhat controversial. Many clinicians believe that a family evaluation is mandatory to understand the child,[26] but that the timing of the family assessment may vary. A family evaluation is necessary in certain disorders, specifically somatoform disorders, anorexia nervosa, school phobia, or recurrent abdominal pain, in which family interaction can precipitate or maintain the symptoms. In the pediatric intensive care unit, we routinely prescribe family evaluation sessions for families with the following characteristics: when the response to the child's hospitalization is inappropriate (either excessive or severely constricted), when there is a history of psychiatric illness in family members, when there is a question of maltreatment, or when there is a question of whether the family is able to comprehend the clinical information adequately.[27] For other families, the assessments are less urgent.

REASONS FOR CONSULTATION REQUESTS

Consultation may be requested for assessment and treatment planning of primary psychiatric disorders, somatoform illness, psychiatric factors affecting a medical illness, behavioral difficulties contributing to hospitalization, behavioral difficulties during hospitalization that compromise optimal medical care, child maltreatment in the form of physical or sexual abuse or factitious disorder by proxy, and supportive interactions in children and families who must cope with life-threatening or chronic illness.[8,9]

Primary Psychiatric Illnesses

Depression

Depression is a prevalent disorder in hospitalized children. It may be a secondary response to acute or chronic

illness, or it may be the primary diagnosis and manifest with somatic symptoms or behavior problems. One of the obstacles to making the diagnosis of depression in the hospitalized child is the misconception that the child's dysphoric mood is appropriate to the stress of the situation and therefore does not deserve to be called depression. On the contrary, stress increases the likelihood that depression will occur; it does not invalidate the diagnosis.

Depression may be used to refer to a mood, a symptom, or a syndrome. As a syndrome, depression in childhood is characterized by a persistent mood disorder or dysfunctional behavior, or both, and in older children it is characterized by self-deprecatory ideation. These symptoms or behaviors should represent a significant change in the child's premorbid function and not be a long-standing temperamental trait. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*[28] (DSM-IV-TR), characterizes a depressive episode as prolonged depressed or irritable mood, with the loss of interest in all or almost all activities and other associated symptoms. Although the criteria are the same for children and adults, there are some differences. Associated symptoms that are particularly common in prepubertal children with an episode of major depression are separation anxiety, somatic complaints, irritability, or behavior problems.[29]

Making the diagnosis of depression is difficult in children who are sick because many of the symptoms they exhibit (e.g., decreased energy or loss of appetite) may be attributed to their illness.[30] Also, children who are sick often use denial as a coping mechanism and underreport their symptoms of depression.[31] Prepubertal children cannot give an accurate self-assessment of sustained mood, so dysphoria must be observed by caretakers over a prolonged period. For children younger than 6 years, the hallmarks of depression include poor appetite or failure to grow and gain weight appropriately, disturbance of sleep, hypoactivity, and indifference to the surroundings and to primary caretakers.[32]

Treatment involves use of antidepressants in conjunction with psychotherapy to support the child and family, as well as child-life and recreational therapy. There has been significant attention to the question of whether antidepressant treatment increases the likelihood of suicidal ideation, and in October 2004 the U.S. Food and Drug Administration (FDA) issued a black-box warning related to this concern. Patients, families, and medical providers often benefit from education about the impact of this warning on decisions about the risks and benefits of pharmacotherapy. (See Chapter 35 for further discussion of the use of psychopharmacologic agents in children.)

Suicide Gestures and Attempts

Suicide is one of the leading causes of death among adolescents.[33,34] In 2005, suicide accounted for 11.6% of all deaths in the United States in persons between the ages of 15 and 19 years.[35] Although the incidence of completed suicide among children aged 6 to 12 years may be relatively low, suicidal threats and attempts by children in this age group are not uncommon.[33] In most cases, children who have made a suicide gesture must remain in the hospital or another secure facility until a thorough evaluation and disposition are completed. This can occur via admission to the pediatric ward, in conjunction with crisis intervention services in the emergency department, or in some cases by transfer directly to a psychiatric facility.

During the assessment of a potentially suicidal child, one should:

- Gather details of the suicide attempt.
- Assess the risk of an attempt: What did the child imagine would happen? What was the likelihood of rescue?
- Determine the child's mindset at the time of the attempt: Was there a clear precipitant? Was it an impulsive or a planned act?
- Determine whether there is a history of suicide attempts in the child, family members, or peers.
- Pursue the child's understanding of death and fantasy of what his or her death would elicit in the family or other significant person (such as a boyfriend or girlfriend).
- Ask about the child's feelings of remorse about the attempt or regrets about having survived.
- Assess whether the child expresses feelings of hopelessness, helplessness, or despair.
- Determine whether the child used drugs or alcohol at the time of the attempt.
- Determine whether the child is depressed, manic, or psychotic.
- Determine whether the child identifies with someone who has committed suicide.
- Assess the probability of physical or sexual maltreatment.
- Conduct a family interview. Determine whether the parents are sad and frightened by the attempt or angry at the child for being manipulative.
- Learn about therapeutic interventions that have been tried in the past. What is in place currently, and how good has adherence been with outpatient treatment?

Family issues should be assessed, including a family history of depression or suicide, tension in the family, and real or imagined rejection of the suicidal child by the parents. If maltreatment is suspected, the appropriate child protective services agency must be contacted.

The consultant is initially asked to decide on the appropriate safety management for the suicidal child. This can include one or more of the following: one-to-one supervision, use of physical restraints, sedation, and the presence of or separation from the parents. Ultimately the consultant needs to determine whether the child or adolescent should be psychiatrically hospitalized or managed as an outpatient (while either living at home or in another setting). Criteria for psychiatric hospitalization include serious risk of death through suicide, little wish to be rescued, psychosis, identification with someone who has committed suicide, co-morbid drug or alcohol abuse, intense feelings of hopelessness and helplessness, intense anger or severe depression, lack of support systems, history of inability to use help, and vulnerability to further losses. Appropriate outpatient or day treatment will be required if the patient is not transferred to a psychiatric facility. In this case it is important to educate and engage the patient and his or her family in safety planning. This includes developing a plan for dealing with a crisis (e.g., having contact information for treaters and access to hotlines), directing attention to limiting availability of lethal means of suicide (e.g., guns

and medications, including over-the-counter medications such as acetaminophen) and emphasizing the need for vigilance about likely environmental contributors to suicidal behavior (e.g., substances and psychosocial stress).

Anorexia Nervosa

Anorexia nervosa (AN) is an illness characterized by significant weight loss or absence of appropriate weight gain for age and height in the context of a fear of gaining weight and a distorted perception of the thin body as fat. Amenorrhea is also a symptom of AN in postmenarcheal girls. Onset of AN is typically in mid to late adolescence (14 to 18 years), and it is predominantly seen in girls; it may be associated with a stressful life event.[28]

Hospitalization of afflicted children is usually associated with severe weight loss, cardiovascular abnormalities (usually bradycardia), hypothermia, or electrolyte imbalance. Electrolyte imbalance can reflect binging or purging, which can include vomiting or abuse of laxatives or diuretics. The goal of pediatric hospitalization is medical stabilization; additional interventions in the hospital are nutritional assessment and treatment, psychological assessment of the child and family, and recommendations for appropriate levels of psychiatric intervention after medical stabilization.[36] The assessment as to whether or not medical stabilization must be followed by intensive day or inpatient psychiatric treatment includes determination of the adolescent's recognition that he or she has a problem with eating behavior and self-image, the adolescent's motivation to participate in psychotherapy (e.g., is he or she in denial about the eating disorder and resistant to eating the adequate nutrition presented in the hospital diet), and the parents' ability to support the adolescent and the need for psychotherapy (e.g., are they angry, intrusive, or controlling of the teen, or do they want to deny that the eating disorder is a problem?).

The consultant will be called on to make a recommendation about disposition once the patient is medically stable. Placement is based on whether the adolescent can live at home safely while consuming adequate calories and attending outpatient treatment appointments (e.g., psychotherapy, nutrition, and pediatric) versus the need for a more intensive and structured program such as a day treatment or residential eating disorder unit. Often, the consultant, in conjunction with the social worker, spends a significant amount of time helping the parents accept the plan for psychotherapeutic treatment, especially if the team recommends that the adolescent not return home.

Somatoform Disorders

Some patients present to the pediatrician with intense somatic complaints (such as headaches, abdominal pain, constipation, dysmenorrhea, or fatigue). In general, when cases are referred for psychiatry consultation, the pediatrician suspects that the intensity or the nature of the complaints is more likely to be an expression of emotional factors than medical conditions. Somatoform disorders, as described in DSM-IV-TR, refer to a clustering of physical symptoms suggestive of a medical condition, but the severity of the symptoms or the level of functional impairment is not fully explained by the medical condition.[28] Although the DSM-IV-TR lists specific disorders, including somatization disorder, conversion disorder, pain disorder, hypochondriasis, and body dysmorphic disorder, the criteria for these conditions were established for adults; children rarely meet full criteria for these specific diagnoses. Recurrent somatic complaints are common in the pediatric population and are a common reason for psychiatric consultation. There may also be developmental considerations, with prepubertal children most often presenting with recurrent abdominal pain or headache and older children presenting with other pain and neurologic symptoms.[37]

The pediatrician's assessment that symptoms are emotional in origin is often at odds with the patient's and the parents' assessment. In psychosomatic illness, the child and family are highly invested in a medical cause to explain the somatic complaints. They are not reassured by routine medical work-ups and they pressure the physician to continue to search for a medical cause. Although the families of somatizing children have been found to have higher rates of anxiety and depression and to be more dysfunctional than other families,[37] they are typically resistant to psychiatric assessment.

Parents might view any suggestion of the important role of psychological factors as an insult and an indication that the clinician does not believe that the symptoms are real. These families prefer to have the child radiographed and endoscoped for abdominal pain, rather than to discuss stressors, such as the child's increasing difficulty at school, the death of a grandparent, or parental discord. Often the child and parents focus on borderline test findings and they pressure the physician to pursue these findings. They might connect a series of irrelevant bits of data to create a medical causal theory that is not supported by the pediatrician. Commonly, families consult multiple specialists in an attempt to find one who will support their medical theory. Unfortunately, if the parents search long enough, they will find either a specialist who will ignore the psychological factors and validate the parents' perspective or a more junior clinician who lacks the clinical experience to stop the rule-out approach. If the psychological issues are not attended to, the condition is likely to become chronic and result in significant morbidity.

The presenting somatic symptoms serve as a solution, albeit a maladaptive one, to an emotional dilemma. For example, it may be easier for a child to get his recently divorced mother to focus on his needs by vomiting and by complaining of relentless abdominal pain than by articulating his deep sadness at his father's absence. Moreover, it may be easier for the mother to champion the cause of discovering a medical cause for her child's vomiting than to support and acknowledge the child's level of distress about the divorce.

The psychiatric consultant is well poised to advocate for a balance of attention to medical and psychiatric factors in the consideration of somatization. This includes keeping in mind that it is not necessary to make the whole diagnosis the first day, week, or month, despite the wishes of the family. Restraint is called for in the pursuit of equivocal organic findings, without sacrificing a complete and appropriate medical work-up. It is often helpful to minimize the importance of a final diagnosis and instead to focus on reducing dysfunction.

Campo and Fritz[38] have proposed a method for assessing and managing pediatric somatization that includes the following key elements in the assessment: acknowledge the patient's suffering and the family's concerns, explore prior assessment and treatment experiences, investigate the patient's and family's fears provoked by the symptoms, remain alert to the possibility of unrecognized physical disease and communicate an unwillingness to prejudge the etiology of the symptom, avoid unnecessary tests and procedures, avoid diagnosis by exclusion, and explore the timing, context, and characteristics of the symptoms. Mainstays of management include honesty, reassurance, emphasis on the rehabilitative approach (as opposed to the curative approach) to symptoms, consideration of family and group interventions in addition to individual management, and consolidation of care.

Therapeutic interventions for the somatizing patient include a medical–psychiatric team approach that emphasizes a consistent relationship among the clinicians, the child, and the family. It is important to foster the continued presence of the pediatrician, because there may be a tendency for the pediatrician to withdraw after psychiatric referral has been made. If the family believes the presence of the psychiatrist leads to diminished access to the pediatrician, there may be escalating anxiety about physical symptoms, and it becomes difficult for the psychiatrist to maintain the critical alliance with the family. Pediatric re-examination without retesting helps calm the family's medical anxiety and reduces the likelihood of continued doctor-shopping. Ongoing psychoeducation from team members can help the family reframe the medical symptoms and enhance communication with caregivers. Inpatient pediatric rehabilitation is sometimes necessary to address the physical components of the presentation and allow the child to regain strength and function in a supportive environment.

Often the child and family need different forms of psychotherapy to allow the child to let go of somatic symptoms and to move on to a healthy role. The child's medical symptoms often serve to stabilize the family system; therefore, family therapy may be required to change patterns of interactions. Couples therapy may also be used to help parents strengthen their adult relationship so the child's illness is not needed to hold the couple together or to distract from their discord. A child's individual therapy helps to build self-esteem and allows the child to engage in developmentally appropriate activities that can increase his or her sense of agency or mastery, which leads to greater confidence and less need to rely on the sick role. Co-morbid psychiatric disorders in the child or family members must also be identified and treated appropriately, with the use of pharmacologic agents as needed.

Psychiatric Factors that Affect a Medical Illness

Medical illness and psychiatric illness are often co-morbid. Studies have shown higher rates of mental health problems in youth with a variety of chronic medical illness,[39] such as asthma,[40,41] diabetes,[42,43] epilepsy,[44-46] and inflammatory bowel disease.[47] In addition to the impact of illness-related symptoms and impairments on psychological function, complex interactions can arise between psychiatric factors and the symptoms, severity, complications, and even treatment of a medical illness. For instance, in youth with type 1 diabetes, depression is associated with poorer glycemic control,[48,49] need for hospitalization,[50,51] and retinopathy.[52] In adolescents with asthma, there is an association between severity of anxiety and depressive disorders and asthma symptom burden.[53] The co-occurrence of mental retardation in children with epilepsy predicts increased behavioral problems.[45,54] In children and adolescents with inflammatory bowel disease, both disease-related inflammation and steroid treatment have been hypothesized to affect the presence and expression of psychiatric symptoms, posing additional challenges in detection and treatment of psychiatric illness.[55,56] And in patients and families who have experienced fear and helplessness in the course of life-threatening medical illness and treatment, pediatric medical traumatic stress can result in posttraumatic symptoms of intrusive thoughts, hyperarousal, and avoidance.[57] Future medical care can then be complicated by posttraumatic symptoms that have been triggered by the medical setting.

Pediatricians rely on parents' reports in young children and self-reports in older children to assess the need for intervention in many chronic conditions. When anxiety, dysphoria, emotional lability, or apathy is present, this increased distress often leads to more medical interventions. In a study of asthmatic patients, it was found that steroid prescription was correlated with the patient's expressed anxiety about an exacerbation and not with the degree of change on pulmonary function tests.[58] Apathy or dysphoria in a patient with severe lung disease, as may be seen in a child with cystic fibrosis, can lead to less therapeutic coughing and to significant pulmonary compromise. Apathy as a result of frustration or helplessness in a child undergoing rehabilitation after a cerebrovascular accident (CVA) or car accident can prevent physical therapy from being optimal. Motivation is often a function of mood, and it is an essential feature of the sense of mastery and agency that we associate with striving toward maximal health. To help children be invested in their own best level of function, it is necessary to understand the emotional issues that impede the health-seeking process.

To understand the psychiatric factors involved in coping one should:

- Ask the child what aspects of the illness and treatments are most difficult or scary for him or her.
- Invite the child to describe his or her own treatment goals and any disappointments in reaching those goals.
- Pursue the child's experience of how the illness and treatment affect his or her life outside the hospital.
- Learn whether the child feels someone understands what it is like to be him or her.
- Find out whether there is someone the child is particularly disappointed in for not understanding. Has the child felt deceived by anyone?
- Determine whether the child knows someone with this condition, and how that person's condition has evolved and why.
- Know the condition and its evolution.
- Learn about the worst thing that could happen.

The goals of the physicians are sometimes at odds with the goals of the child. For example, a teenage girl who suffered

a stroke but did not want to walk "like an old lady" with a cane was sullen in rehabilitation because she did not want to give up her crutches. The many disappointments during hospitalization and unexpected rehospitalizations are compounded when a patient feels his opinion was not sought or her best efforts still resulted in setbacks, leading to anger, frustration, mistrust, anxiety, or apathy.[59] Engaging the child in voicing his or her experience may be therapeutic in itself. There may be ways of altering the hospital protocols to suit the child or adapting the child's treatment program to accommodate home-life priorities. The consultant is asked to assist the child during the hospital stay and to determine whether outpatient psychotherapy is warranted. Knowing how time is spent outside of the hospital and what the content of the frustrations covers informs this decision. Psychopharmacologic interventions can also be helpful, depending on the symptoms and the psychiatric diagnoses.

Behavioral Difficulties that Contribute to Hospitalization

Accidents and nonadherence are the two major categories of behavioral difficulties that lead to the hospitalization of children. Accidents are a leading cause of pediatric emergency department visits and childhood deaths. It is not uncommon to find multiple accident-related emergency department visits for the same child; therefore, identifying the accident-prone child and gaining a better understanding of the causes of accidents can serve to prevent future and possibly more disabling injuries. Medical nonadherence is pervasive, but it runs along a spectrum from benign to potentially life-threatening. As a result, many cases of nonadherence (such as an incomplete course of antibiotics for an ear infection) go undetected; some cases of nonadherence can lead to death, such as a diabetic teen who skips his or her insulin and embarks on a drinking binge.

Accidents

All children experience accidents, but they are more likely to occur in children who are reckless, active, impulsive, or inadequately supervised. Predisposing conditions include attention-deficit/hyperactivity disorder (ADHD), fetal alcohol syndrome, and lead exposure. Adolescents tend to view themselves as invulnerable and therefore may be prone to greater risk-taking and to accidents. It is necessary to gather the following information about the child's behavior before the accident:

- Has the child had behavioral difficulty in school, at home, or with peers?
- Has there been a change in the child's mood?
- Is there evidence of a thought disorder?
- Have there been problems leading to legal interventions?
- Are these worrisome behaviors new or are they longstanding?

Supervision, particularly in younger children, plays a significant role in maintaining child safety. When a child presents with an accidental injury, an assessment must be made as to whether the supervision has been adequate for the child's age; this usually involves an assessment of the parents or other caretakers. It is necessary to entertain the possibility that an accidental injury could be the result of maltreatment (see the section on child maltreatment), a suicide gesture, or an act of self-destructiveness (see the section on suicide). These causes should be part of the clinician's routine consideration for an injured child.

Nonadherence

Nonadherence may be secondary to an inadequate understanding of, or capacity to implement, the intended medical regimen. Often nonadherence is not an active decision to defy treatment recommendations. Rather, it can result from the patient's being overwhelmed by a medical regimen or being tired of the chronicity of one. Some children leave the hospital on numerous medications that are to be administered several times each day. It is crucial for the pediatrician to review the medications with the family before planned discharge. Simplifying medication regimens as much as possible and having honest dialogues with parents and children about what is realistic at home is recommended. Highlighting critical medications and the consequences of not taking them engages the child and family as educated collaborators in the child's health care.[60,61] Patients and families who are refractory to simple educational interventions to improve adherence might benefit from a more-intensive intervention to address the issue, and the medical team can seek the consultant's input. A meta-analysis of psychological interventions to promote adherence in pediatric chronic illness concluded that adherence was most likely to be improved by interventions that emphasized applied behavioral methods, such as problem-solving or parent training, or multicomponent interventions, usually incorporating combined behavioral and educational treatments.[62]

In contrast to the passive nonadherence just described, some children or parents actively disregard medical recommendations. There are many emotional issues that underlie such a course of action. Denial on the part of either the child or the parent can result in nonadherence. In this scenario, the child or caretaker has the conscious or unconscious notion that if the prescribed medication or prescribed restrictions are ignored, it is as if the illness does not exist. The clinician might hear from the child, "Taking my pills makes me feel like I am sick," or from the parent, "I cannot make myself bring him in for his doctor's appointments because sitting in the clinic reminds me he has a bad liver." Suppression of thoughts about illness can be a healthy defense, allowing medically ill children and their families to cope with the stress of the illness, but denial when it leads to nonadherence is maladaptive and warrants psychotherapeutic intervention to minimize serious medical consequences.

Sometimes, nonadherence is an expression of anger, be it the child's anger at the parent or the child's or family's anger at the physician or at the illness itself. When the child is angry at the parents, nonadherence becomes a foolproof weapon guaranteed to elicit the parent's distress, which is then emotionally satisfying for the child. Psychologically absent in this schema is the child's awareness that he or she is actually harming himself or herself. The consultant can assist in altering the medical relationship from a physician-to-parent-to-child relationship toward a more direct relationship between physician and child. By diminishing

the parent's role in the communication of the health care regimen and of policing adherence, to the extent possible depending on the child's age, the pediatrician has the opportunity to build an alliance with the child that fosters a wish to please and thus to enhance adherence.

Psychotherapy serves the function of allying with the healthy part of the child and helping the child or adolescent appreciate that this style of acting-out anger and frustration with parents is self-injurious. Similarly, when the anger being acted out is against the illness or the physician, the psychotherapeutic goal is to ally with the healthy part of the child, helping the child articulate the frustration with words rather than by acting them out in a self-destructive way. The consultant is called on to assess what aspect of this goal can be achieved during the hospital stay and when outpatient psychotherapy is warranted. The nonadherent child may be resistant to the idea of outpatient psychotherapy. Hospitalization offers the consultant a valuable opportunity for alliance-building by letting the child experience how talking (therapy) can be helpful.

Behavioral Difficulties During Hospitalization

Some children are referred for consultation for the management of specific behavioral symptoms that interfere with medical care or with their own safety and the safety and comfort of other patients and medical staff. Their symptoms can include excessive activity, agitation, verbal or physical threats to staff and other children, seizure-like episodes, and temper tantrums. Assessment should include medical, developmental, and social history from the child and family, a neurologic examination, nursing and child-life observations, and school reports, as needed.

Psychopharmacologic interventions might also be appropriate. The child with generalized anxiety or separation anxiety might benefit from a trial of a long-acting benzodiazepine[63] (e.g., clonazepam). Children with anxiety in association with particular procedures might benefit from premedication with shorter-acting benzodiazepines (e.g., lorazepam). Anticipatory anxiety can be managed with behavioral interventions (e.g., relaxation and visualization techniques) as well as pharmacologic therapy.[64,65] When ADHD is diagnosed, the child might respond quite dramatically to the addition of stimulant medication. Occasionally an underlying psychosis may be discerned, and the appropriate antipsychotic agent should be instituted. (See Chapter 35 for in-depth discussion of pediatric psychopharmacology.) Agitation associated with delirium might require the use of antipsychotics to maintain a child's safety and to help clear the delirium.

Behavioral plans, especially for younger children, may be instrumental in establishing good behavior. The guiding principle underlying behavioral plans is to identify the key behaviors that are most problematic and provide incentives for the child to behave in positive ways. In younger children, sticker charts for swallowing pills and allowing blood drawing without a temper tantrum are examples of common behavioral interventions. Younger children may receive stickers as the full reward, or after receiving a predetermined number of stickers, a child may earn a toy. Older children may work toward special privileges (such as a trip to the gift shop, time outside with the child-life specialist, or a favorite meal brought in from outside the hospital). Other incentives (such as tickets to a hockey game), may be provided by the family. In addition to behavioral plans, children benefit from having a schedule for the day. An unstructured day increases uncertainty, boredom, and anxiety. Scheduling activity times, meal times, rest times, and procedure times can be helpful in providing the child with an increased sense of control over the hospital milieu.

Parents' interactions often play a major role in the child's behavior. Some behavioral outbursts might reflect the child's anxious response to a parent's escalating anxiety and inability to help the child feel safer in the hospital setting. Some parents might find it difficult to set limits on the child in light of the sadness the parent feels at the child's medical condition. The child's behavior might represent an unconscious need to re-engage the parent in what had been the usual style of parenting. A parent's lack of limit-setting often feels to the child like emotional abandonment. In conjunction with the social worker doing family work or parent guidance, the consultant needs to help the parent feel competent to be an active parent again.

Children with behavioral difficulties invariably arouse negative feelings in the staff. There may be disagreements between staff members about how best to respond to particular behaviors, and the inconsistencies can foster further behavioral disturbances. Team meetings to develop a consistent plan and to facilitate good communication are essential. These team meetings are a good opportunity for the consultant to share his or her understanding of the psychological meaning of the behavior in a way that helps the staff feel more empathic with the child and the family.

CHILD MALTREATMENT

Child maltreatment is defined as any act or series of acts of commission or omission by a parent or other caregiver that results in harm, potential for harm, or threat of harm to a child.[66] Acts of commission constitute child abuse, in the form of physical abuse, sexual abuse, or psychological abuse. Acts of omission constitute child neglect, including a failure to provide (physical neglect, emotional neglect, medical neglect, or educational neglect) or a failure to supervise (inadequate supervision or exposure to violent environments).[66] In general, data collected from child protective service agencies by the National Child Abuse and Neglect Data System (NCANDS), overseen by the U.S. Department of Health and Human Services, have shown a significant decline in the rate of physical and sexual abuse, but not neglect, since data collection was initiated in 1990.[67-69]

Because the etiologic contributions to child maltreatment are diverse, a developmental–ecological perspective has been advocated in understanding the determinants of maltreatment, in which parenting behaviors are understood to be influenced by factors across multiple levels, including characteristics of the parent, the characteristics of the child, and the broader context.[70,71] Maltreatment can occur in the setting of multigenerational inadequate parenting, substance abuse, and multiple family stressors including domestic violence, a disrupted family unit, and cognitively limited or psychiatrically ill parents.[72] Low family income[73]

is a risk factor, particularly among single-parent families.[74] Risk factors notwithstanding, maltreatment occurs in all socioeconomic and demographic environments, demanding constant vigilance in those who work with children.

The consequences of child maltreatment, including mental health problems, can be far-reaching.[75] Psychiatry may be consulted in cases where maltreatment is suspected. In some health care settings, a specialized child protection team is also available to provide consultation and coordinate care. All physicians are mandated reporters of maltreatment, but only a suspicion is required; it is not necessary to prove maltreatment to file with the appropriate state child welfare agency.

Physical Abuse and Neglect

Physical abuse is defined as the intentional use of physical force against a child that results in, or has the potential to result in, physical injury.[66] Acts constituting physical abuse can include hitting, kicking, punching, beating, stabbing, biting, pushing, shoving, throwing, pulling, dragging, dropping, shaking, strangling or choking, smothering, burning, scalding, and poisoning.[66] The incidence of child physical abuse, based on data gathered by NCANDS, has decreased from 3.6 per 1000 in 1990 to 1.1 in 2007.[67,76] It occurs most commonly in the 4- to 15-year-old range, with a peak incidence in the 4- to 7-year-old range.[76] Specific determinants of risk for recurrent abuse include age of the child, the number of previous child protection services referrals, and certain caretaker characteristics such as emotional impairment, substance abuse, lack of social support, domestic violence, and a history of childhood abuse.[77] Children with disabilities have been thought to be at higher risk for maltreatment, but whereas there may be an association with emotional and learning problems, it is not clear that studies support an association between physical disabilities and maltreatment.[78,79]

Neglect, by comparison, is the failure by a caregiver to meet a child's basic physical, emotional, medical, or educational needs.[65] These children might present with failure to thrive or other consequences of inadequate nutrition, the occurrence of preventable accidents, dermatologic conditions related to poor hygiene, lack of routine and specialized medical appointments, and school absences.

Abuse and neglect must be suspected before they can be diagnosed. Certain types and locations of injuries are suspicious. Bruises that resemble finger or hand prints, and those that appear on body surfaces that normally do not bear the brunt of an accidental fall (such as welts on the back as opposed to anterior shin bruises), should raise suspicion. Multiple bruises in various stages of healing are suggestive of abuse that has been ongoing. Clinicians should be suspicious when bruises, broken bones, and accidents have occurred that are inconsistent with the caretaker's explanation, when the caretaker admits and then recants culpability, or admits having observed the abuse being perpetrated and then recants the story. The caretaker might blame the injury on the child, suggesting it was self-inflicted, or blame a sibling for an injury that appears beyond the developmental capability of the child. There may have been an inexplicable delay in seeking medical attention, or the person bringing the child for medical assistance may be vague or report having not been with the child during the injury and not knowing how it happened.

When physical maltreatment is suspected, the child at risk should be kept in a safe facility until the child welfare agency has determined the safety of the child's disposition. A full physical examination should be performed and well documented, checking the whole child for evidence of bruising or injury in various stages of healing. This is important both to ensure the child's safety and because there may be subsequent legal proceedings. A radiologic bone series should be performed to look for evidence of old and new fractures. A funduscopic examination should be performed for evidence of traumatic shaking of a young child. Siblings of a child suspected of having been abused must be assessed immediately because they are also considered to be at high risk for abuse.

Sexual Abuse

Sexual abuse is defined as any completed or attempted sexual act with, sexual contact with, or exploitation of (i.e., noncontact sexual interaction) a child by a caregiver.[66] This involves the exposure of a child to a sexual experience that is inappropriate for his or her emotional and developmental level and that is coercive in nature.[80] Like physical abuse, reported rates of sexual abuse have declined since the 1990s.[68,69] However, the incidence of sexual abuse is significantly underreported and there are many methodologic difficulties with estimating the prevalence of sexual abuse. The most common form of sexual abuse is father–daughter incest.[81] Incest is present when sexual contact occurs between a child and a family member, including stepfamily members or members of a surrogate (foster) family. The highest reported rates of sexual abuse (35.2% of sexual abuse reports) occur in the 12- to 15-year-old age range.[76] Sexual abuse tends to be so disturbing and so emotionally intense a topic that there is risk of medical professionals abandoning a logical approach to assessment.

There are three common presentations of sexual abuse in children: presentation with an unmistakable traumatic injury or a sexually transmitted infection, testimony that sexual abuse has occurred in the context of no physical evidence, and presentation of a patient who has physical or behavioral symptoms suggestive of sexual abuse but who has neither disclosed abuse nor implicated a perpetrator.[82]

In the first two presentations described, assessment and documentation of the sexual abuse and disclosure must be approached with the assumption that legal proceedings are likely to follow. In these cases, there is ample information to make mandated reporting of the suspicion of abuse a requirement. The fewest people should question the child to minimize further trauma to the child and to decrease distortions. Ideally a single interview of the child should be conducted by a mental health professional with expertise in child sexual abuse and the appropriate police agency representative. The child psychiatry consultant's role may be as the interviewer or as the supporter of the child on the pediatric unit, without being involved in the sexual abuse examination

In the third scenario, the child might present with medical symptoms, such as a urinary tract infection or vaginitis, or behavioral changes, such as sleep problems

or depression.[80] These findings can arouse suspicion and should be followed up with a psychological assessment. A play therapy assessment of a preschooler may be helpful, looking for themes of abuse in the fantasy play. During the play, the young child might reveal new information about sexual experiences. In the school-age child, additional information may be gleaned from the child's drawings, especially self-portraits or pictures of the family. Children and teenagers should be invited to disclose sexual abuse to the consultant with questions such as, "Has anyone touched you in ways that made you feel uncomfortable or scared?" A follow-up question might be, "Would you tell me if they had?" and "Who could you tell, if someone was touching you or making you uncomfortable?" It is helpful to learn who a child feels he or she can talk to and to add new choices to the list, such as the pediatrician or schoolteacher as well as the consultant or another counselor. Even if a child is not yet ready to disclose, one hopes that it is therapeutic to assist a child in conceptualizing a plan for disclosing when he or she does feel ready.

In any case in which abuse is entertained, a family assessment is essential. There is no single personality profile of a perpetrator of sexual abuse. Perpetrators can come from within the family or the community. The task of the psychiatric consultant is to explore sensitively the meaning of general symptoms that can indicate sexual abuse without suggesting that nonspecific symptoms are pathognomonic of sexual abuse.

Factitious Disorder by Proxy

Factitious disorder by proxy, previously known as Münchausen syndrome by proxy, was first described as a pair of case reports in 1977.[83] It is a form of child maltreatment in which a parent, usually a mother,[84] consciously distorts her description of her child's symptoms or does things to the child to fabricate a picture of medical illness and then seeks hospitalizations and medical interventions for the child. The parent might report periods of apnea or seizures at home that have not occurred or might cause life-threatening illness by injecting the child with medication, blood, or feces to ensure that a medical work-up continues.

Some of the persons with this syndrome have had medical training in a health-related profession, such as nursing,[84,85] and they use their medical knowledge to create "illness" in their child. The mother is usually at the infant's or young child's bedside. She tries to establish friendships with the nursing staff and is content as long as continued hospitalization and medical procedures are being scheduled and performed. She may become angry and agitated if she receives a report that her child is well and should be discharged home. Often she appears earnest and less anxious when serious diagnoses of the child are being entertained. If discharged, she may return within hours or days to the emergency department with an escalation of symptoms. The psychological understanding of this syndrome is that the mother needs the child to be sick to maintain her role as a "nurturant" mother in the protected, supported environment of the pediatric ward. She may gain a "curious sense of purpose and safety in the midst of the disasters which [she herself has] created."[84] She perceives the nurses to be her friends and the male physicians as caretaking men in her life. She lacks the empathy to be troubled by the pain and suffering she is inflicting on her child.

Factitious disorder by proxy is a difficult diagnosis to make without observing the mother doing something to the child. It may be suspected when a child's medical condition does not follow the expected course and the symptoms are persistently inconsistent. The symptoms may be observed only by the mother or might occur in conjunction with the mother's presence and may be consistent with an intentional action. Undertaking the investigation of this diagnosis, and seeking concrete evidence of risk to the child at the hands of a parent might require input from hospital legal counsel and administration.

It is crucial to protect the child's safety if this diagnosis is suspected. The reporters of this syndrome have described mortality rates and significant morbidity.[86,87] The hospital legal department and child protective services should be notified of this diagnosis to protect the best interest of the child. If the parent thinks that she is being suspected of having hurt her child she might become angry and leave against medical advice (sometimes going straight to another hospital under the same or an assumed name). Perpetrators of factitious disorder by proxy are difficult to treat due to their psychological difficulties, persistent denial, and capacity for deception; recidivism is common.[88]

LIVING WITH CHRONIC ILLNESS

The vast majority of children with chronic illnesses cope well. They are not defined by their illnesses but rather by their individual strengths, weaknesses, personalities, and age-appropriate developmental issues. However, children with chronic illnesses are more likely than their peers to have a psychiatric disorder.[8,39,89] There is no one personality that coincides with a particular illness, but each chronic illness, such as asthma, diabetes, rheumatoid arthritis, cystic fibrosis, and sickle cell anemia, presents particular challenges. These challenges include coping with the symptoms, such as pain or shortness of breath; the timing of diagnosis at birth, childhood, or adolescence; and the requisite health care regimen, such as inhalers, IV antibiotics, or dietary restrictions. The meaning of the illness evolves according to relevant developmental issues throughout the child's life. The consultant's task is to understand the meaning of the illness to the individual child and family at this moment in development. The earlier section on development provides some general principles for understanding the effect of chronic illness throughout childhood, but the consultant must assess the unique experience of a particular child and family.[90-92]

The consultant needs to ask many questions to elucidate the child's subjective experience of living with the chronic illness. Diagnostic instruments used in physically healthy children might not be useful in children with chronic illnesses.[8] Some useful questions include what the worst or hardest thing is about the illness and if there is anything good about the illness. Similarly, what is the child's personal experience of the health care regimen? How has the child's experience of the disease changed as the child has grown older, or what events in the future are of concern? What are the child's peer relationships like, and how, if at all, does the illness affect these relationships? Whom does the child tell about his or her illness, and when does the

child do so in the course of the relationship? How does the child explain the illness to others, and how can he or she explain it to the consultant? What is the child's perception of the parents' concerns about the illness? What are the areas of conflict between parent and child and between child and pediatrician or subspecialist?

Chronic illness requires adjustment on the part of the child, the family, and sometimes the school. The child's personal strengths, such as music, sports, or academics, are assets in maintaining self-esteem and building important peer supports. Some children enjoy peer group opportunities, such as specialized camps for children who share a particular illness. Temperament and interpersonal capacities are also factors in the ease of a child's adjustment. The parents' attitude toward the illness is crucial in setting the stage for the child's attitude. This can raise difficulties, because feeling worried, burdened, and isolated is a common experience among parents of children with chronic illness.[93] Excessive parental anxiety, anger, sadness, and guilt, however, are likely to impede the child's adjustment.[92]

The extent to which an illness interferes with age-appropriate activities, especially school, is an important factor in adjustment. Multiple hospitalizations are associated with greater emotional morbidity than is seen in an individual hospital stay.[94] Structuring the admissions to provide the child with protected times and protected places for play and dialogue, appropriate to the child's age, decreases the stress of the hospital environment. In-hospital tutoring for prolonged hospital stays and continued contact with friends in person, by phone, or online can assist the child's comfort in returning to school.

CARE AT THE END OF LIFE

The emerging subspecialty of pediatric palliative care has helped focus the attention of clinicians who participate in end-of-life care on the complex challenges to providing the best possible care to these children and their families.[95-97] Some treatment settings have specialized clinical services dedicated to pediatric palliative care, and the psychiatric consultant can work closely with these services to address psychosocial needs.[98] In circumstances where these services are not available, the psychiatric consultant may be called upon to aid the patient, family, and medical team in a variety of ways.

A request for consultation might stem from issues related to problem-solving and decision-making in the context of life-limiting illness.[99] This can include initiating a dialogue between the medical team and the patient and family of the patient with life-threatening illness, clarifying the goals and hopes of treatment, and assisting in the evaluation of pros and cons related to specific treatments or treatment settings, including end-of-life care outside of the hospital[100] and planning for location of death.[101] Because these issues are often accompanied by emotional distress on the part of patients, families, and caregivers, psychiatric expertise may be sought. The psychiatric consultant may help to facilitate affectively intense discussions and to help anticipate and interpret the reactions of children to issues around death and dying in the relevant developmental context.

In children, a mature conception of death can be viewed in components that might not be acquired simultaneously.[102] Key components include, in approximate order of typical acquisition,[103] concepts of universality, irreversibility, nonfunctionality (i.e., that the functions of life cease with death),[104] and causality. It should not be assumed that children either do not understand the concept of death or are too fragile to talk about it. The child's parents and the medical team might need education about whether and how to talk with the child about death and to involve the child in the plan of care.[105-107] In addition, helping the seriously ill child to communicate his or her many small preferences, from being called by a nickname rather than a formal name to whether or not to wake him or her for optional events or social activities, can create a greater sense of agency and help stave off the destructive force of helplessness.

Facilitating peer interactions in the hospital playroom for the child and encouraging both formal and informal support groups for children and their parents can be invaluable. Many parents and children feel that the immensity of the child's illness has so changed their lives that old friends feel inadequate. The worries of the well world can feel alienating and out of touch with the child and the family's new reality. This experience can be isolating. Sharing pleasures and frustrations with other families facing cancer, a terminal neurologic syndrome, or a metabolic disease can be an antidote to the isolation. Many family friendships that begin on the ward survive long after a child dies.

The consultant might also have a role in helping with the treatment of symptoms at the end of life, which may be underrecognized or undertreated. Studies of children who died of cancer have found that symptoms of pain, fatigue, and dyspnea occur in large numbers of patients, result in significant suffering, and persist despite attempts to treat.[108-111] In children with life-limiting illness of all kinds, the consultant may have a role in assisting with treatment of pain,[112-114] fatigue, dsypnea,[115] agitation,[116] anxiety, and depression.[117] Although the psychopharmacologic treatment of seriously ill or dying children is complicated, compassion dictates considering the use of psychiatric medications in this population if they may help relieve suffering.[118]

Families also need varying amounts of assistance to cope with the impending loss of a child, ranging from sympathy for their grief to guidance with how to make end-of-life decisions that reflect their values, preserve dignity, and minimize suffering. In a retrospective study of parents who lost children to cancer, the presence of unrelieved pain and a difficult moment of death were the most significant factors still affecting parents 4 to 9 years after the loss.[119] The same study also demonstrated that most parents had worked through their grief "a lot," and that factors that were associated with working through grief were sharing their problems with others during the child's illness, having access to psychological support during the last month of the child's life, and counseling being offered by health care staff within the last month of life.[120] Parents who reported that they had not worked through their grief reported more physical and psychological health problems, increased sick leave, and increased utilization of health care services.[121] Parents who felt that health care given to their children was inadequate, that anxiety or pain had gone unrelieved, or that the parents' own needs (such as support and communication) were not met reported more feelings of guilt in the year following the death of the child.[122] Although support

for grieving families at their time of loss can be beneficial, it is important to remember that grieving for the death of a child is a lifelong process and community resources for bereaved families can help to work through grief and find meaning in a tremendous loss.

The child's care team might also struggle with the loss of a patient. Commonly, feelings of sadness and helplessness can surface, and it can feel difficult to maintain empathy for patients and families whose circumstances appear trivial by comparison or whose disorders seem "less real" or self-inflicted. Even when these factors are not present, continuous compassion directed at those in crisis can create emotional exhaustion that is termed *compassion fatigue*.[123] The intensity of relationships formed in the course of providing care to children at the end of life can contribute to this phenomenon. The consultant may assist by educating members of the team about this phenomenon and dispelling stigma and by helping develop personal, professional, and organizational strategies to prevent and manage compassion fatigue.[124,125]

WORKING WITH STAFF

Child psychiatric consultation almost always involves more than the patient and the referring physician. Parents are inherently a part of treatment because they give critical information and need to be actively involved in implementation of recommendations. During hospitalization, nurses can assume some parental roles while the ward is the child's temporary home. Child and family behaviors have an impact on other patients and staff and are likely to evoke intense feelings. Because many pediatric units encourage parents to visit and room-in, the potential impact of a distraught or disturbed parent on the entire ward is substantial. Lastly, patients with chronic illness can return repeatedly to the same floor over a 5- to 10-year period. Thus, many children become well known, and the depth of the staff's involvement grows over the years. Child psychiatric consultation includes an essential liaison role that is relevant to patient and family care, to interstaff tensions, and individual staff stress.

Primary nursing encourages continuity of care as one or two nurses are assigned to the child during the hospitalization, often for repeated admissions. This practice is beneficial for the child's sense of trust, makes the nurse's role more personally satisfying, and can add a needed perspective if too many subspecialists forget the whole child's needs. Unavoidably, primary nurses become intensely involved in the child's personal and family life; thus they have critical information and share the stress of the child's illness. The child psychiatrist can provide suggestions and supervision for dealing with difficult families or crisis, review when psychiatric referral is indicated, and help in understanding the painful issues of chronic disease, suicide, and terminal illness.

For house staff, a basic stressor is being relatively inexperienced and yet forced to deal with complex medical and psychological circumstances. The source of stress is clearest in the intensive care unit, where frustration mounts rapidly as children do not respond to treatment or suffer life-long physical and neurologic damage. The consequences of multiple stresses (frustration with the patient's course, lack of sleep, and feeling incompetent) can lead to depression, substance abuse, or bitter tensions among house staff or nurses.

Part of the child psychiatrist's liaison function is to attend rounds, be aware of difficult clinical and family situations, get to know nurses and house staff through teaching and informal discussion concerning patients, and be aware of the early signs of behavior destructive to patient care and fellow staff. With sufficient credibility, the child psychiatric consultant can organize family or interstaff meetings that have a beneficial impact on the unit's functioning and can relieve family or staff suffering.

ETHICAL ISSUES

The psychiatric consultant faces many challenging ethical issues in the hospital. The consultant may be involved in helping children and families come to terms with psychologically complex decisions, such as pursuing continued aggressive treatments or assenting to do-not-resuscitate orders. Staff and families need help assessing the extent to which a child at a particular developmental level can understand and be included in such decision-making.

Confidentiality is complex in the hospital setting. The consultant must be clear about with whom information gathered in the consultation will be shared and what the limits of confidentiality are. What cannot be kept confidential may be clear, such as suicidal ideation, but what can be confidential, such as a child's worry about a parent's sadness or a parent's trauma history, may be less apparent. The medical record is open to the full medical and support staff, and some personal information may be disclosed that is not relevant to the child's medical care.

FUTURE CONSIDERATIONS

The long-term benefits of psychiatric intervention must be assessed through outcome studies examining the impact on quality of life and on further use of health care dollars. Professionals who work with children are called on to advocate for the special needs of the young because they are not yet able to do so for themselves. Interventions that improve the psychological well-being of children maximize their productivity long into the future, and interventions that support families strengthen the community. As managed care, critical pathways, and advances in care decrease lengths of stay, increasingly consultation work will bridge to or be centered in outpatient settings and schools.[126] Being accessible, responsive, and communicative with primary care pediatricians will continue to be essential in the future.

Efforts have resulted in closing some of the distance between pediatrics and child psychiatry. Some subspecialty clinics, including those treating cystic fibrosis, cancer, diabetes, and endocrine disorders, are more open to consultation at the time of diagnosis, at key points in the illness, and for nonadherence. For primary care settings, the Bureau of Child and Maternal Health of the Public Health Service and the American Academy of Pediatrics have collaborated on projects that emphasize the psychosocial needs of children. Bright Futures[127] integrates psychosocial issues into every recommended primary care visit. The *Diagnostic and Statistical Manual of Mental Disorders*—

Primary Care[128] bridges variations and problems common to pediatric practice with the DSM-IV-TR. Symptom checklists, such as the Pediatric Symptom Checklist,[129] are being used to screen for psychosocial dysfunction as part of ensuring comprehensive care and assessing mental health services. Sustained improvement in pediatric mental health services will require continuing and expanding collaboration between medical and child and adolescent psychiatric providers.

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43

Consultation to Parents with Serious Medical Illness: Parenting at a Challenging Time

Kristin S. Russell, M.D.
Paula K. Rauch, M.D.

Millions of children in the United States grow up in families in which a parent is medically ill. The National Cancer Institute estimates that 25% of cancer patients have at least one child 18 years of age or younger[1] and that one third of patients with breast cancer have dependent children.[2] Psychiatric consultants are often asked to consult with parents who have questions about how their medical illness will affect their children. The psychiatric consultant can assist medical and surgical teams by facilitating communication about these topics among the treating clinicians and the patient, providing specific guidance about parenting to the patient, and assisting with connections to community resources.[3–23]

FACILITATING COMMUNICATION WITH MEDICAL TEAM

In general, medical teams often err on the side of not talking to patients about parenting concerns (because they believe they lack the expertise, it isn't their place, and they do not have enough time). Consultants can help parents get the medical information they need to help with planning (e.g., what to expect regarding symptoms secondary to the illness and side effects of treatment). They can also guide patients to get information that will help answer a child's specific questions or concerns (e.g., how long they will have to be in the hospital, whether they will lose their hair as a result of chemotherapy, whether medications may interfere with driving, and how much energy they might expect after they return home).

PARENT GUIDANCE

The most common question that parents who face serious medical illness ask is, "How can I make all this easier for my child?" Given the limits of the current research in the field, the content discussed in this chapter is derived from the accumulated clinical experience of the team of clinicians who staff the Parenting at a Challenging Time (PACT) program at the Massachusetts General Hospital (MGH).[3–25] This chapter will address important ways to support childhood coping, including the following: using a developmental perspective to understand the child's current cognitive, emotional, and social abilities and needs; facilitating communication with the child about the illness and the treatment; and applying practical approaches to routines and family life.

RESOURCES

A list of community and online resources for patients can be found in Table 43–1. In addition to connecting parents with resources, clinicians can help parents assess when further intervention is needed; parameters to assist clinicians with this are discussed in the chapter and outlined in Table 43–6. Clinicians may be interested to read about a parenting-focused consultation-liaison (C-L) model, which has been used at the MGH for a number of years to serve the needs of parents with severe medical illness.

Although it is difficult when a parent develops a serious medical illness and perhaps dies, children and families are resilient, particularly when supported. For clinicians who have only recently begun to work with families facing medical challenges, the sadness and anxiety can feel overwhelming. However, our clinical experience compels us to underscore the strength, grace, and resilience that parents and children so often exhibit during and after exposure to illness. Indeed, many families return to us, sometimes years later, with memories and thoughts about this time in their lives. For many this experience has been not only one of pain but also one of enormous growth for themselves and their children. Through the process of pulling together, finding support in the community, prioritizing values, and appreciating each day and each other, they feel their children have learned to actively cope with challenges and appreciate their strength.

PARENTAL ILLNESS: A REVIEW OF THE LITERATURE

The body of research in the field of parental illness is relatively young; most studies have involved small numbers of parents and children, and some suggest conflicting results about the impact on the children. Much of the literature concerning parental illness has involved patients with cancer; several reviews provide recent summaries of this work.[15,21,26] We will highlight several areas of ongoing research.

TABLE 43–1 Resources for Patients

Resources for Cancer Patients

People Living with Cancer, from the American Society for Clinical Oncology (ASCO)
Offers educational information for patients and families (www.plwc.org)

American Psychosocial Oncology Society (APOS)
Provides a free help line to connect patients and families with local counseling services, as well as webcasts for professionals on topics such as "Cancer 101 for Mental Health Professionals" and "Psychosocial Aspects of Cancer Survivorship" (co-sponsored by the Lance Armstrong Foundation) (www.apos-society.org)

American Cancer Society (ACS)
Provides information on talking to children about cancer, as well as numerous other cancer-related topics (www.cancer.org)

The Wellness Community
A national, nonprofit organization that provides free online and in-person support and information to people living with cancer and their families (www.thewellnesscommunity.org)

Living Beyond Breast Cancer
A national education and support organization with the goal of improving quality of life and helping patients take an active role in ongoing recovery or management of the disease (www.lbbc.org)

Young Survival Coalition
Through action, advocacy, and awareness, this nonprofit seeks to educate the medical, research, breast cancer, and legislative communities and to persuade them to address breast cancer in women 40 and younger—and serves as a point of contact for young women living with breast cancer. (www.youngsurvival.org)

Breast Cancer.org
Offers medical information about current treatments and research in breast cancer care and survivorship (www.breastcancer.org)

Hurricane Voices Breast Cancer Foundation
Among other breast cancer–related resources, this organization offers a family reading list of books and stories for children of all ages dealing with cancer, in particular with breast cancer. (www.hurricanevoices.org)

CancerCare
The mission of this national nonprofit is to provide free professional help to people with all cancers through counseling, education, information, and referral and direct financial assistance. They offer online, telephone, and face-to-face support groups to those affected by cancer. (www.cancercare.org)

Lance Armstrong Foundation (LAF)
LAF offers information and services to cancer survivors and the professionals who care for them. (www.livestrong.org)

The Life Institute
This organization's online publication "Conversations from the Heart" provides an annotated list of resources for parents and professionals who want to learn more about how to have developmentally appropriate conversations with children about serious illness and death. (www.thelifeinstitute.org)

Resources for Other Illnesses

American Heart Association (www.americanheart.org)
American Diabetes Association (www.diabetes.org)
ALS Association (www.alsa.org)
Brain Injury Association of America (www.biausa.org)
Colitis Foundation (www.colitisfoundation.org)
Cystic Fibrosis Foundation (www.cff.org/home)
Epilepsy Foundation (www.epilepsyfoundation.org)
National Multiple Sclerosis Society (www.nmss.org)
National Neurofibromatosis Foundation (www.nf.org)
Pulmonary Fibrosis Foundation (www.pulmonaryfibrosis.org)

Stress and Family Function

Parental cancer is a significant stressor for children.[27–31] Parents often underestimate their children's level of psychological distress.[31,32] Re-establishing normal routines is key to successful family coping.[33] Interestingly, families with parental cancer perceive themselves as functioning in a positive fashion compared with the norm (believing that they are more expressive and social, better organized, less controlling, and with less conflict).[34] Maternal depression negatively affects marital relationships, a child's coping, and family function.[35,36] Moreover, patients with dependent children were more likely to meet criteria for panic disorder; their spouses were more likely to meet criteria for major depressive disorder and generalized anxiety disorder.[37]

Childhood Coping

Children move in and out of their worries about a parent's cancer.[38] Their developmental stage affects their style of coping and their response to a parent's illness.[39] Children employ a range of coping strategies when facing parental illness (e.g., relying on normal activities, the support of friends, and family cohesion; understanding the medical situation).[40] Among children, distraction and maintenance of normality were common strategies for coping. Noticeable changes in children's lives included increased responsibilities and decreased social activity; positive aspects of the experience were stronger relationships and learning to value important people and things.[41] Some children used coping strategies that included helping others, parentification (i.e.,

acting like a parent) distraction, internalization, and wishful thinking; in these children communication patterns and parental coping were highly correlated with a child's coping repertoire.[42]

In a number of studies, approximately one fourth of children who faced parental cancer experienced clinically significant depression, anxiety, or somatic symptoms compared with approximately 10% to 15% in normative samples; of note, some studies demonstrated no difference between groups.[21] Adolescent girls of an ill parent may be at greater risk for distress than other demographic groups.[43] In particular, it may be adolescent daughters with ill mothers who are at the highest risk.[44]

Communication

Parents desire developmentally sophisticated assistance to facilitate communication about their illness with their children.[45,46] Moreover, better communication helps children cope.[47–50] Children want honest communication about their parent's illness and its treatment, as well as any genetic implications of the disease for them; communication stalls because they worry about upsetting parents by asking them directly.[51]

SUPPORTING CHILDHOOD COPING

The following discussion pertains to three key ways to support a child's coping. The first is to use a developmental perspective to understand the child's current cognitive, emotional, and social abilities and needs. The second is to facilitate communication with the child about the illness and treatment. The third is to apply specific practical approaches to routines and family life.

Developmental Considerations

A developmental perspective helps inform parents and clinicians. Although there are many factors that contribute to variations among children (e.g., temperament and environment), the vast majority of children pass through common developmental stages at fairly predictable ages. Familiarity with these stages and the cognitive, emotional, and social implications of each can lead to a more nuanced understanding of the impact of the illness on the child, facilitate communication, and guide decision-making to best support the child (Table 43–2).

Infants and Toddlers (0–2)

Attachment and self-regulation are the primary tasks of infants and toddlers. Accordingly, it is likely that infants will be distressed by separation from familiar caregivers and changes in routines. They also tend to be affected to some degree by the emotional tone in the home, and they may be more irritable during times when the family is most distressed. Parents can help infants and toddlers feel more secure and comfortable by maintaining regular routines, using familiar blankets and animals, and providing detailed instructions to caregivers to keep care as consistent as possible. In this vein, minimizing the number of caregivers is optimal. Helping the parent who is ill feel engaged (to the extent that this is feasible) in the care of the child is beneficial, and sharing videotapes or hearing voicemail messages with caregiver updates can be ways to help maintain a connection. Children of this age cannot understand explanations about illness, and the narrative of the experience will occur later. To help prepare for this, parents can create photo albums, videos, or letters for the child to read.

Preschoolers (3–6)

It is likely that preschoolers will be affected more profoundly by the changes in daily routine than by the idea of the illness. Alterations in the family rhythms (e.g., the parent being unavailable to tuck them in at night, changes in the dinnertime routine, new caregivers in the home) are likely to be distressing. Cognitively, preschoolers use magical thinking to intermingle fantasy and reality, and they lack a clear understanding of cause and effect. They remain largely egocentric at this age, and the combination of these factors can lead them to conclude that something they did, said, or thought caused the illness. For instance, a 5-year-old girl, after learning her father "has cancer in his stomach," might conclude that the rough hug she gave him before he went to work caused his illness. Children may feel powerful and dangerous, which may lead to anxiety; alternatively, they may react to the overwhelming feelings by becoming aggressive and ignoring limits. It is useful to check in with children this age to discuss what they think caused the illness and correct misconceptions; preschoolers need to be reminded repeatedly that nothing they did caused the illness. In any discussions about death and dying, it is important to recognize that children this age see death as reversible and temporary.

It is not uncommon for preschoolers to regress (e.g., beginning to wet themselves again) or to complain of stomachaches or headaches from time to time. Usually these changes do not persist. As with infants and toddlers, maintaining daily routines and familiar surroundings for preschoolers is crucial. Caregivers may be tempted to relax discipline because the child is already going through so much; however, consistent limits are in fact essential to remind the child that the world is a predictable and safe place.

Latency/School-Age Children (7–12)

School-age children are focused on the mastery of skills. They feel strongly that everything, including illness, should be fair and follow rules; they can get very angry with unexpected changes. Although they are cognitively able to connect cause and effect, they may regress under stress and feel responsible for a parent's illness. Also, their cause-and-effect logic is fairly simplistic and inflexible, and they may insist, for instance, that illnesses must be contagious or that cancer is always caused by cigarettes. It is common for latency-age children to care deeply about appearances as they strive to figure out where they fit into their social world; as a consequence, they may be particularly embarrassed about the ill parent's appearance (e.g., if the parent has lost his or her hair as a result of chemotherapy, they may insist that the parent wear a wig). In conversations about death, school-age children are able to understand that death is both permanent and universal. They may be surprisingly matter-of-fact about death, intellectualizing about the topic rather than being immersed in the feelings. They may also be particularly curious about the details of death and dying; preparing parents for these questions may help them feel more comfortable engaging with their child.

TABLE 43–2 Key Points and Parenting Tips by Developmental Stage

DEVELOPMENTAL STAGE	KEY POINTS	PARENTING TIPS
Infancy (birth to 2.5 years)	Concern with attachment and self-regulation	Maintain familiar routines. Keep number of caretakers to a minimum
Preschool years (ages 3 to 6 years)	Egocentricity + magical thinking = "I am to blame" Death is temporary and reversible	Maintain routines and loving limit-setting Repeatedly remind the child that the illness is not his or her fault
Latency (ages 7 to 12 years)	Mastery of skills Rules and fairness; simple cause-and-effect logic Peer-focused and image-conscious Intellectualization of death	Protect family time by limiting visitors and turning off the phone at meal times Set regular times for the child to show the ill parent the accomplishments of the week; attend to the details
Adolescence (ages 13 to 18 years)	Abstract thinking and behavior are not on the same plane Separation is developmental task but complicated by vulnerability of parent	Be cautious about assigning teens a parenting role with younger siblings Support relationships with trustworthy nonparental adults Foster safe independent behavior
Young adults (19 to 23 years)	Living away from home Serious relationship formation Longer time frame with regard to decision-making	Provide enough information to allow for decision-making Encourage balance between pursuing new life experiences and putting these on hold to spend precious time with the ill parent

Adolescents

Adolescents have the capacity to think in a more mature way and use abstract thought. For instance, they are cognitively able to understand more of the nuances of the illness and the potential consequences of death (e.g., less money for college or the sorrow of the other parent). However, there is often a lack of connection between their cognitive ability and its translation into behavior. Adolescents may respond to their emotional distress by spending more time away from home, with peers, or in non–family-related activities. This may leave parents feeling that the teen is self-absorbed or uncaring, when in reality he or she is trying to cope with the painful awareness of the parent's vulnerability.

This is a particularly poignant time in the child's life for illness to strike a parent. One of the primary developmental tasks of adolescents is to negotiate comfortable separation from their parents; their feelings about separation and family may become intolerably complex at times, with the developmental pull to separate mixed up with the intense fear of losing the parent. The adolescent will likely need an adult's help (and limit-setting) to find an appropriate balance between engaging in (safe) independent behavior and spending time with the ill parent and the family. Although teens should be expected to help with chores at home, caution should be exercised when shifting a parenting role with younger siblings to teens. This is particularly common with adolescent girls. Adolescents often seek nonparental adults to confide in, and it is important for parents to foster these relationships when they are with adults whom they trust. Intense feelings about death are often the rule; many adolescents make use of existential conversations or readings, journaling, and peers to absorb some of these feelings.

Young Adults

Given their stage of life, young adults may be away at college or living on their own. They may feel unsure about whether, and when, to come home. They may feel conflicted about having a separate life outside the family (on the one hand relieved, and on the other somewhat isolated from the family). There may be particular strain among siblings, some of whom may still be at home and facing struggles that the older sibling is not. Young adults who are themselves parents may have complicated feelings such as anger, fear, and loss because they do not have access to the help and guidance with their own parenting that they had expected to receive from the ill parent or family members who are now absorbed by the illness.

Communicating About Parental Illness

It is important to begin a dialogue. Children cope better when parents initiate communication about the illness (e.g., asking what questions they have, finding out what they understand and what kind of information they do and do not want). The worst way for children to find out about bad news is to overhear discussions between others. There are multiple reasons for this. Children may think that they are not being told because the information is too awful to discuss with them. Alternatively, they may believe that they are not sufficiently valued to be involved in the discussion. Finally, if they overhear it, they often will be confused by the information and reluctant to tell the parent that they were listening, so the opportunity to clarify the situation may not come until a long period of anxiety has elapsed for the child.

It may be best to wait a short time to communicate so that the parent is calm enough to help the child process his or her emotions. It helps to make it clear from the beginning that the parent trusts the child by sharing honest information. Parents should start by calling the illness by its real name (e.g., "breast cancer" as opposed to "a lump"). Children will not trust future information if they think their parents are not being straightforward, and they

will tend to search for clues that their parents are lying to them. It is also important not to make promises that cannot be kept. Instead, parents should say that they are just not sure of something; comfort with uncertainty is a helpful trait to model. It is also all right to take time to think through responses to questions (e.g., a parent could say, "That's a good question. I need to think about that, and I'll get back to you."). One of the most dreaded questions is, "Are you going to die?" Children can be reassured by hearing that their parent plans to get the best treatment possible, take good care of himself or herself, and live as full a life as possible in the meantime. As with other questions, it can be helpful to find out what the child really wants to know (e.g., what will happen to the child, who will care for the child).

Although parents should give children ample opportunities to talk about the illness, children should not be pushed if they resist. Some children tend to be talkers, whereas others are not, and the illness is unlikely to change these qualities. At the same time, for children who are less inclined to share their thoughts, parents can help by wondering aloud about some of the questions that the child might have and noticing whether the child becomes engaged and interested. If so, parents can continue talking, while taking particular notice of the child's nonverbal signals. Children are generally able to indicate whether they want the conversation to stop, and if they do, this desire should be respected. Parents may want to consider the time at which they bring up the topic, because children often are most communicative when the intensity is lessened in some way (e.g., when cooking or doing a craft project together, driving in the car, or getting ready for bed with the lights out).

Children often do better with more specific questions (e.g., "Did it annoy you to miss your play rehearsal last week because dad was driving me to the hospital?") rather than open-ended "feeling" questions (e.g., "How are you feeling about my illness?"). When children do ask questions, helping them refine the question so that the appropriate amount of information is given in response is important. For instance, a child who asks, "When is Mom getting out of the hospital?" may be thinking about whether she ever will (or whether she is going to die), or the child may be thinking about whether she will be home in time to attend the child's upcoming play performance. Very different responses would be appropriate in these two situations, and understanding what the child is really asking will help keep the child from feeling overwhelmed with more information than he or she can handle as well as convey the parent's concern and sensitivity.

Parents should encourage children to share what they hear from others about the illness and not to worry alone. Sometimes people with good intentions share their (unhelpful) observations about the parent's illness or their own (frightening) experiences with illness, and it is easy for the child to become overwhelmed or scared. Parents should tell children how much the illness varies among different people and how much misinformation exists. Anticipating these moments together and planning to talk about them if they happen can make a big difference. Table 43–3 summarizes some of these communication tips for parents.

TABLE 43–3 Tips for Communicating with Children About Parental Illness

Be honest.
Remember that the worst way to hear difficult news is to overhear it.
It is not necessary to answer questions immediately.
Welcome all questions warmly.
Encourage elaboration of the question.
Notice the child's best times for reflection and discussion.
Encourage children to share everything they hear from others about the parent's cancer.
Remind children not to worry alone.

Routines and Family Life

The following sections outline practical suggestions for parents regarding daily routines and family life. General principles include keeping routines as consistent as possible, preserving family time, and using support wisely.

Routines

Following regular daily routines (as much as possible) helps let children know that despite the illness, there is stability and thus security. Particularly for young children, parents should keep the schedule the same from day to day (e.g., mealtimes and bedtime) with just a few familiar caretakers. It is best if older children continue their activities to the extent possible (e.g., school, soccer practice). It helps to post schedules, make lists, and use calendars to help children and caregivers know what each day holds. For childcare or driving help, parents of the child's friends are often available and accepted by the child.

As much as is feasible, parents should keep family routines as consistent as possible. Children are highly attuned to any shifts at home (e.g., new people answering the phone or cooking, new smells, and dinnertime patterns done in a different way). Many children identify these types of changes as the most upsetting part about the illness. Remembering how important this consistency is to children can help parents set priorities that may initially seem inconsequential; for instance, even though doing so might be difficult, it may really matter that dinner begin at 6:30 and continue without interruptions, with dinner clean-up chores maintained the way they were before the illness.

In addition to trying to maintain routines, parents should look for ways to create new, predictable family time, such as having a certain meal each day of the week (e.g., Monday is pasta; Tuesday is tacos). It helps to elicit input from children about fun activities (e.g., watching cartoons in bed on Saturdays). It can lift everyone's spirits to find opportunities to celebrate. Taking videos and photos may become an important part of the family record for the future.

Keeping family time off-limits from visits, phone calls, and technology (e.g., e-mailing and texting) is crucial. This keeps the focus on togetherness and prevents children from overhearing conversations about the illness that are not intended for their ears. It is important to have ample time when the illness is not the focus of conversation. Staying as up-to-date as possible about the child's

friendships, schoolwork, and daily activities helps the child feel that his or her world remains right-side-up and gives the child permission to pursue these things even though the parent is ill.

Captain of Kindness

Appointing a "captain of kindness" to organize support so that volunteers are not directly contacting the family can be beneficial. There can be an overwhelming swell of support in communities when a beloved member has a life-threatening illness, and it quickly becomes a time-consuming task to coordinate the kind offers to help. Having a designated person to organize these efforts allows the family to conserve their resources and focus on the children. An additional benefit is that the captain of kindness can ensure that the support is concentrated on tasks that would be most helpful for the family (e.g., making lunches for the kids, providing a vegetarian dinner on Wednesdays).

Minister of Information

Designating a "minister of information" to organize the flow of communication, providing updates to concerned family and friends so that the immediate family is able to save precious time and energy for family time, can be valuable. It is also helpful to have volunteers in each of the family's communities (e.g., school, church, neighborhood, and work friends); these volunteers can help keep well-wishers informed and spare the family the trouble of providing individual updates. They can also help by organizing or diverting visits (so the family is not in the position of having to explain that they need quiet time).

School

Parents should tell the child's teachers about the illness and outline the approach they would like the teacher to take. Typically, school should be a protected place in which the child can have life go on as usual. Although teachers sometimes think that they are helping by trying to engage the child about the topic, it is best for the child to lead the way. The parents should let the teacher know that they would like to be informed if the child volunteers his or her worries about the illness (most children do not). Likewise, the teacher should keep the parents apprised of any other struggles, including academic ones, that the child is having so that these can be addressed promptly. Teachers sometimes consider it a kindness to withhold upsetting information, but it is in fact a disservice to the child and the family who need—more than ever—to stay on top of any developing problems.

Self-Care

Parents with medical illness and their co-parents need to take sufficient care of their own physical and emotional needs. For instance, it is critical to take time to get necessary medical care and to follow treatment recommendations to minimize physical and emotional stressors and setbacks. If the ill parent or spouse is feeling overwhelmed, panicked, or hopeless, seeking additional support in a timely way is important. Children look to their parents as models; demonstrating care during times of physical and emotional challenge provides an important lesson. Children feel more secure when they see that their parents are taking care of themselves.

Hospital Visits

With a few exceptions, children who want to visit a parent in the hospital should be allowed to do so. Parents often worry about their child seeing them looking ill and wonder if it is better for them to stay home. In reality, children seem to do much better with the actual—rather than the imagined—images. Preparation for the visit is important and should include a description of how the parent looks (e.g., what he or she is wearing, what tubes he or she might have) and how the hospital room looks (e.g., presence of a roommate) (Table 43–4). If there will be multiple agendas for the visit (e.g., if there are several children wanting to visit, or if the other parent wants to visit with the ill parent as well), an additional, familiar adult should come along and be available to take the child for a break when he or she is ready. For younger children, or when longer visits are anticipated, quiet activities (e.g., drawing pictures, coloring) can be planned and snacks can be packed. The child may want to bring something to do with the parent or show the parent during the visit (e.g., a new toy, a grade on a test). After the visit the child should be given the opportunity to discuss his or her impressions of the visit and ask questions.

There are a few exceptions to consider. For instance, when parents are delirious, children may be frightened or confused by the parent's agitation or disorientation. Or, if a parent is recovering from an intervention and is expected to be feeling or looking much better in a short time (e.g., 24 hours), it may be sensible to defer the visit. If an in-person visit is not possible, phone calls or even videophone calls can be very helpful.

Preparing for Death

End-of-Life Care

When a parent's care shifts from life-extending treatment to end-of-life care, the parent may be able to choose where to receive this care. Common options include institutional care (at a hospital or a hospice) or home care. There are pros and cons to each; some of these are detailed in Table 43–5.

Home-based hospice care is one way that families who want the parent at home but need help with the medical and nursing care can sometimes find a balance.

These choices are complicated and fraught with emotion. Although having this conversation is incredibly difficult, it is important for children to be able to participate in the process so they can express their feelings and concerns.

Saying Goodbye

It is helpful to have a conversation in advance of death about how the child wants to be told about a parent's death. For instance, if it happens in the night, does the child want

TABLE 43–4 Tips for Hospital Visits

Describe what the child will see before entering the room.
Let the child determine the length of the visit.
Bring a familiar adult who is available when the child is ready to go.
Bring play materials.
Discuss the visit after leaving.

TABLE 43–5 Pros and Cons of Institutional and Home Care

TYPE OF CARE	PROS	CONS
Institutional (Hospital/Hospice)	Less burden of caretaking on family	More difficult to visit May be less comfortable for patient
Home	Easier to visit More comfortable in own home	Concern about nursing needs, pain control, and medical equipment Best to have room with a door to allow privacy; ideal to not disrupt children's space Concern about death happening in home (e.g., what children will be doing, what happens when the coroner comes, possibility of discomfort in the room after the patient dies there)

to be awakened? If it happens during a school day, does the child want to be told at the end of the day?

When possible, children should have the opportunity to visit with a parent at the end of life. If children are reluctant to see a parent at this time, they can be encouraged to be nearby, such as in the waiting room. If a parent is unresponsive by this time, it is often helpful to let children know that we do not know what someone can hear when in this state, but we believe that the person may sense that loved ones are nearby. Children may want to say something to the parent, hold the parent's hand, or think something they want the parent to know. It is important for others to articulate that the parent was loved by the child and that the child was loved by the parent. If the relationship was strained or conflicted in some way, it is helpful to acknowledge this and then to say that despite these arguments, the parent loved the child and knew that he or she was loved by the child. It is this expression of love, rather than the word "goodbye," that is important to share in these final hours or days.

Leaving a Legacy

Many parents feel moved to leave behind something for their child. Parents have different ideas about what to leave and what leaving something represents. Much of the impetus is for the parent to communicate to the child that the child was loved. There may be moments for this in the final days, but the parent may also want to write a letter to the child describing his or her feelings. A letter affords the opportunity to provide details that may be cherished by the child, such as a description of the way the parent felt when the child was born, took his or her first steps, or went to kindergarten for the first time. A letter may also provide an opportunity for the parent to let the child know that he or she can form attachments to, and love, other adults without feeling disloyal.

Parents may find other means to convey these feelings. Some leave belongings, such as a favorite piece of clothing or jewelry. Others leave funds dedicated to something particular for the child to experience (e.g., a trip after graduation). Still others leave scrapbooks, CDs, recipe boxes, or lists of friends to contact to learn more about the parent at different phases of his or her life.

Financial and Legal Planning

For families facing serious medical illness, taking time out to attend to financial and legal issues is an important part of creating security for their children. This may be a task they can take on themselves, or they may need to employ the help of a friend, relative, or professional. These are weighty issues and thus ones that are often avoided by healthy families. In cases of illness, however, it is even more critical to confront these issues directly to minimize the likelihood of negative, and even catastrophic, consequences. Even when difficult circumstances prevail, it is crucial for children to be able to feel that their parents worked hard to create as much safety and security as they could.

Medical illness can have many financial implications (e.g., shortening the time a parent is able to generate income, depleting savings because of the cost of medical care or additional help). It can be helpful to start the process by getting a handle on current income and expenses and then working through several scenarios (e.g., parent becoming disabled or dying), including modifying the family budget. Looking carefully at benefits and insurance policies (e.g., medical, disability, and life insurance) is a critical part of this process.

Legal issues to consider include preparation of documents such as a will, health care proxy, power of attorney, and living will. Consultation with an attorney may be necessary, particularly if issues of custody are at play. Although custody is a complex topic and varies from state to state, there are several rules of thumb that are commonly followed. First, if the parents of a child are married and one dies, the child will remain in the custody of the surviving parent. If the parents are not married, custody typically will go to the surviving parent unless there is a very clear reason for the judge to decide against this. In situations in which the custodial parent is approaching death and feels strongly that the noncustodial parent is an inappropriate primary caregiver, one option is to contact that parent and ask him or her to voluntarily relinquish parental rights (i.e., giving up right to custody and responsibility for financial support). Another option is to seek help from the court in requesting a guardian *ad litem* to evaluate the best interests of the child.

Funerals and Memorial Services

Ideally, planning for a service should begin before the parent's death. This allows the parent to share his or her wishes about the service and helps minimize family conflict that might arise after the fact. It can be helpful for children to have a familiar person preside over the service and to have the service in a familiar location (where their friends can attend).

Many of the suggestions (e.g., having an adult prepare the child with as many specifics as possible about the event and answering any questions the child may have) that apply to hospital visits are appropriate for funerals and services as well. An adult should be available to talk with the child after the event to discuss his or her feelings and questions. Younger children should have a familiar adult who is specifically designated to support them and take them outside, if needed. The usual recommendation is for children age 4 and older to attend the ceremony. Preschool children often are not taken to the cemetery (after the ceremony) because they may have trouble understanding the fact that death is irreversible and therefore may become especially distraught at the image of the parent being buried.

Memorial services provide an opportunity for children to see that the community valued their parent. Children should be allowed to participate in whatever ways they are comfortable. Some may want to speak, play an instrument, or choose a song; others may just want to listen. If a child does not want to participate actively, this should be accepted and the child should not be made to feel that he or she is failing to meet an expectation.

WHEN TO RECOMMEND FURTHER INTERVENTION

One of the most rewarding aspects of working with children is their resilience; most children are able to adjust to a parent's illness or death relatively well with supportive caregivers. However, in some situations children struggle, and further evaluation and perhaps support by pediatric mental health providers may be helpful. An important role of the psychiatric consultant is to help parents determine when this is necessary; the following discussion and the guidelines in Table 43–6 may help guide the consultant.

When a child specifically requests to speak to someone, this should be facilitated. Because children with previous psychiatric challenges are at higher risk for difficulty when a parent is ill, it is often prudent to reconnect these children with their previous providers when possible. Children with symptoms of depression or anxiety that interfere with their daily activities (e.g., school, friendships, family life) for more than a few weeks should be referred for consultation. These symptoms may include depressed, anxious, or irritable mood for more than a few weeks; a change in sleep, appetite, energy, and concentration; or feelings of guilt or anhedonia. Suicidal ideation should be evaluated on an urgent basis. Finally, children who are engaging in risky behaviors (e.g., substance abuse, promiscuity, fighting, reckless driving) should be referred for consultation. There are many types of mental health supports for children, and access to services varies by location. A reasonable place to start is to ask the child's pediatrician or school guidance counselor.

TABLE 43–6 When to Recommend Further Intervention

When the child requests to speak to a counselor
When the child has previous psychiatric issues
When the child has symptoms of depression or anxiety that interfere with daily activities (e.g., school, friendships, family life) for more than a few weeks (Suicidal ideation should be evaluated on an urgent basis.)
When the child is engaging in risky behaviors (e.g., substance abuse, promiscuity, fighting, reckless driving).

PACT TEAM: A PARENTING-FOCUSED CONSULTATION–LIASION MODEL

The Parenting at a Challenging Time (PACT) program at the MGH Cancer Center was started in 1997 to provide expert consultation to parents with cancer. Referrals are made through any member of the medical team or by patients themselves. Typically, consultations consist of 2 to 10 visits; patients or families may choose to pursue further consultation if the cancer recurs, if a new parenting concern emerges, or after the patient dies. Indeed, the most common times for consultation include after the initial diagnosis, at the recurrence of illness, and at the end of life. The content of the meetings is generally focused on three general areas: communication with the child or children, behavior issues of the child or children, and general family coping. Clinicians (child psychiatrists and psychologists) meet with the patient and, if the situation warrants, with children, spouses, and other family members. Consultations occur on inpatient units, in outpatient offices, during chemotherapy infusion or dialysis, or by telephone. Patients and families who need more extensive intervention or psychiatric treatment are referred for treatment.

The PACT team (Table 43–7) meets during weekly rounds to coordinate care and discuss challenging cases. Oncology team members attend these rounds to collaborate in the care of complicated patients and families. When appropriate, PACT clinicians work more extensively with the oncology, medical, or surgical teams. Liaison work also includes education, outreach, and advocacy. Consultations are provided free of charge, and funding is secured through the MGH Cancer Center and through philanthropic donations (see www.mgh.pact.org).

CONCLUSION

Clinicians who care for patients with a serious medical illness must recognize that many of them are parents with pressing concerns about how the illness and treatment may affect their children. The psychiatric consultant can assist the team by facilitating communication about these topics among the treating clinicians and the patient and providing specific guidance to the patient and family about support-

TABLE 43–7 Parenting at a Challenging Time

Free to patients
Staffed by child psychiatrists and psychologists
Patient or any member of team can request a consult
Usually consist of 2 to 10 visits
Meet at patient's convenience (e.g., on inpatient floor, outpatient office, infusion unit or by phone)
Sometimes include the child or children
Contact information: www.mgh.pact.org

ing childhood coping. Use of a developmental perspective to understand a particular child's cognitive, emotional, and social capacities will inform both the approach to communication about the parental illness and the specific parenting interventions that may be helpful. General principles include keeping daily routines as consistent as possible, preserving family time, and using support wisely.

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44 Care of the Geriatric Patient

M. Cornelia Cremens, M.D., M.P.H.
Ilse R. Wiechers, M.D., M.P.P.

The U.S. population over the age of 65 years has been increasing dramatically, reflecting improvements in health, nutrition, and medical care for the elderly. Illness (both medical and psychiatric) increases with advancing age in part due to stressful life events, the burden of co-morbid conditions, and combinations of medications used.[1] Roughly 40% to 60% of those hospitalized with medical and surgical illnesses are over the age of 65 years; such problems place them at greater risk for functional decline.[2] In addition, a reduction in hepatic, renal, and gastric function further impairs the elderly's ability to metabolize drugs.[3] By the year 2030, one in five Americans will be older than 65 years. Thus, psychiatric consultation to this group of patients is becoming ever more necessary while providing both complicated challenges and rewards.

CONSULTATION WITH GERIATRIC PATIENTS

Depression

Mood disorders associated with later life are a major public health problem. Depression is prevalent, unrelenting, immobilizing, and frequently fatal, especially in those with co-morbid medical illness.[4,5] In the United States, depression in the elderly accounts for higher rates of suicide than any other condition. Moreover, rates of suicide are higher in later life than they are in any other age-group.[6] More than 90% of older individuals who commit suicide have a risk factor for suicide (e.g., depression or other mental disorders, a personal or family history of substance abuse disorder, stressful life events, a prior suicide attempt or a family history of an attempt, family violence [including physical or sexual abuse], firearms in the home [the method used in more than half of suicides], incarceration, or exposure to the suicidal behavior of others [e.g., family members, peers, or media figures]).[7] In addition to having a higher prevalence of depression, older persons are more socially isolated and they use highly lethal methods more frequently. Suicide occurs early (often during the first 6 months) in the illness, but it can occur at any time, often in combination with other mental disorders.

Approximately 50% of those with neurologic diseases, cardiac diseases, or cancer have depressive symptoms. The risk for depression in the poststroke period is also high, with 25% to 50% developing depression within 2 years after a stroke.[8] Alzheimer's disease (AD) carries an increased risk of depression (found in 20% to 30% either before or at the time of diagnosis), and delusions are also prominent in depression associated with dementia.[9] Recent research confirms the association of depression with the increased risk of developing late-onset AD.[10] Fifty percent of patients with Parkinson's disease develop depression or have a history of depression with anxiety, dysthymia, or frontal lobe dysfunction.[11] Use of medications for medical problems often generates adverse effects and complicates the diagnosis of depression; moreover, medical illness may mimic depression and depression may mimic medical illness. In short, the elderly are at greater risk for depression due to the prevalence of these illnesses and their downstream sequelae.

Despite the fact that depression is a mood disorder comprising far-ranging symptoms (involving disordered sleep, diminished interests, guilt and ruminations, decreased energy or fatigue, impaired concentration, disturbed appetite, and suicidal thoughts or attempts), clinicians find that somatic complaints, rather than depressed mood, are often the reason for referral of the elderly and the medically ill.[12] These physical complaints lie on a continuum and can mimic medical problems (e.g., chest pain, headache, joint pain, nausea, dizziness, and weakness). Teasing out the symptoms of medical or surgical problems from the symptoms of depression can be a daunting task in the hospitalized patient. Physicians often misdiagnose or undertreat depression in the medically ill due to an overlap of these symptoms. The Geriatric Depression Scale (Table 44–1)[13] is a helpful tool in this regard; often the information provided by caregivers is crucial because elders may not be forthcoming with their symptoms.[14] The criteria for diagnosing depression at this time are the same as they are in the general population.

Substantial progress has been made in the treatment of elderly individuals with mood disorders, especially major depression.[15] Once the diagnosis has been established, prescription of an appropriate medication is part of the art of geriatric psychiatry. Since most of the antidepressants are equally effective for depression (Table 44–2), knowledge of how an antidepressant may alter the metabolism and therapeutic drug levels of other medications is crucial. For example, one may wish to start with an antidepressant agent with less cytochrome P450 drug interactions (e.g., citalopram). One needs to review the side effects of the antidepressant and then tailor its use to the patient's symptoms. For example, if a depressed patient is sleeping poorly and losing weight, one should select a sedating agent that is associated with weight gain. Drugs with anticholinergic effects and undue sedation should be avoided to reduce complications (e.g., falls, confusion,

TABLE 44–1 Geriatric Depression Scale

Choose the best answer for how you felt this past week:

1. Are you basically satisfied with your life?
2. Have you dropped many of your activities and interests?
3. Do you feel that your life is empty?
4. Do you often get bored?
5. Are you hopeful about the future?
6. Are you bothered by thoughts you can't get out of your head?
7. Are you in good spirits most of the time?
8. Are you afraid that something bad is going to happen to you?
9. Do you feel happy most of the time?
10. Do you often feel helpless?
11. Do you often get restless and fidgety?
12. Do you prefer to stay at home, rather than going out and doing new things?
13. Do you frequently worry about the future?
14. Do you feel you have more problems with memory than most?
15. Do you think it is wonderful to be alive now?
16. Do you often feel downhearted and blue?
17. Do you feel pretty worthless the way you are now?
18. Do you worry a lot about the past?
19. Do you find life very exciting?
20. Is it hard for you to get started on new projects?
21. Do you feel full of energy?
22. Do you feel that your situation is hopeless?
23. Do you think that most people are better off than you are?
24. Do you frequently get upset over little things?
25. Do you frequently feel like crying?
26. Do you have trouble concentrating?
27. Do you enjoy getting up in the morning?
28. Do you prefer to avoid social gatherings?
29. Is it easy for you to make decisions?
30. Is your mind as clear as it used to be?

Scoring

1. no	6. yes	11. yes	16. yes	21. no	26. yes
2. yes	7. no	12. yes	17. yes	22. yes	27. no
3. yes	8. yes	13. yes	18. yes	23. yes	28. yes
4. yes	9. no	14. yes	19. no	24. yes	29. no
5. no	10. yes	15. no	20. yes	25. yes	30. no

This is the original scoring for the scale: One point for each of the correct answers.

Normal—0-9; mild depressives—10-19; severe depressives—20-30.

Adapted from Yesavage JA, Brink TL, Rose TL, et al: Development and validation of a geriatric depression rating scale: a preliminary report, *J Psychiatr Res* 17:37-49, 1983.

poor compliance). Moreover, since depression can complicate one's recovery from the medical or surgical problems, treatment should be swift and aggressive. Often, stimulants are used alone or in conjunction with a traditional antidepressant, such as a selective serotonin reuptake inhibitor (SSRI).[16] Electroconvulsive therapy (ECT) should be considered (and discussed with the patient and his or her family members) if a patient is not responsive to medications.[17]

Bipolar Disorder

Patients over the age of 65 years with bipolar disorder (BPD) may not have developed their affective illness early in life[18]; for many the illness began in middle age or later life, often in association with co-morbid neurologic insults.[19] Those patients with co-morbid neurologic diseases have a significantly later age-of-onset of their affective illness and are less likely to have a family history of a mood disorder. Snowdon[20] reported that 25% of patients whose mania arose after the age of 50 had a history of a neurologic disease and had significantly fewer genetic (familial) risk factors. A number of biological risk factors (including genetic factors and medical illnesses, particularly vascular conditions) have been identified for BPD in the elderly.[21]

Symptoms of mania or hypomania are manifested differently in the elderly, with more anger, irritability, aggressivity, delusions, and paranoia. In addition, less grandiosity and euphoria appear, episodes of mania are longer, and cycling may be more rapid. Treatment response is inconsistent, although lithium, anticonvulsants (e.g., divalproex sodium, carbamazepine, and lamotrigine), atypical antipsychotics (e.g., olanzapine, quetiapine, and risperidone), and antidepressants have all been beneficial in the treatment of elderly patients with BPD. Moreover, the differential diagnosis of secondary mania warrants special consideration.[22] Many of those with dementia or delirium present with mania secondary to their underlying illness. Although the treatment of secondary affective symptoms is similar to those of primary affective illness, an accurate diagnosis is important.

Delirium and Dementia

The discussions of consultation involving individuals with delirium or dementia are handled separately in chapters elsewhere in this book (see Chapters 10 and 11 respectively, for detailed discussions of diagnosis and management). However, they also warrant discussion in this chapter, given that the prevalence of dementia increases as age advances (3% to 12% of patients over the age of 65 years, and 25% to 46% of those over the age of 85 years have dementia)[23] and patients with mild dementia are at greater risk for developing delirium (leading to serious behavioral problems) during a hospitalization.[24] Dementia and delirium are often confused in the geriatric population; when consultants are asked to assess a patient for one condition, they often find the other.

The elderly are more vulnerable to delirium because of the numbers of medical problems encountered, changes in brain function, brain disorders (such as dementia), reduced hepatic metabolism of medications, and multisensory dysfunction. The elderly are at the highest risk for delirium, as are those with brain damage (including dementia and strokes), cardiac surgery, burns, substance withdrawal, and autoimmune diseases.[25–28] The morbidity and mortality of elderly patients with delirium is high; 15% to 26% die, often as a result of the problem responsible for the delirium.[28]

Performing a comprehensive medical evaluation (e.g., with assessment of oxygenation and infections [such as urinary tract infections]) with an examination of the patient

TABLE 44–2 Treatments Recommended for Depression in the Elderly

DRUGS	DOSE RANGE (mg/d)	COMMENTS
Tricyclic Antidepressants		
Nortriptyline	10–150	Reliable blood levels, minimal orthostasis
Desipramine	10–250	Mildly anticholinergic
Monoamine Oxidase Inhibitors		
Tranylcypromine	10–30	Orthostasis (may be delayed), pedal edema, weakly anticholinergic, dietary restrictions
Stimulants		
Dextroamphetamine	2.5–40	Agitation, mild tachycardia
Methylphenidate	2.5–60	
Modafanil	50–200	
Selective Serotonin Reuptake Inhibitors		
Fluoxetine	5–60	Akathisia, headache, agitation, GI complaints, diarrhea/constipation
Sertraline	25–200	
Paroxetine	5–40	
Fluvoxamine	25–300	
Citalopram	10–40	
Escitalopram	2.5–20	
Serotonin–Norepinephrine Reuptake Inhibitors (SNRI)		
Venlafaxine	25–300	Increased systolic blood pressure (SBP), confusion, lightheadedness
Duloxetine	20–60	Diarrhea
Alpha-2 Antagonist/Selective Serotonin		
Mirtazapine	15–45	Sedation, weight gain
Atypical Antidepressants		
Trazodone	25–250	Sedation, orthostasis, incontinence, hallucinations, priapism
Bupropion	75–450	Seizures, less mania/cycling headache, nausea

(including a careful neurologic assessment, even if it has been done by another physician), review of medications, and review of medication compliance, are keys to uncovering the etiology of the delirium and directing appropriate management. Medications with anticholinergic effects are often responsible for cognitive dysfunction and should be avoided. Diphenhydramine, a medication commonly given to elderly patients for sleep, can be problematic because of its strong anticholinergic properties.

Agitation and behavioral symptoms occur frequently in geriatric patients with dementia and delirium. First-line treatment for behavioral and psychological symptoms of dementia involves use of nonpharmacologic strategies that manipulate environmental and behavioral features (such as regularly scheduled routines for meals, sleep, and bathing). For geriatric patients with delirium, whenever possible, a family member or a familiar person should stay with the patient to re-orient them; this may minimize the need for medications or restraints. However, in those with delirium, both restraint and medication may be necessary. Restraints may also be required as a reminder not to get out of bed without supervision, because falls and subsequent hip fractures are common in confused elderly. Hip fractures are associated with delirium and a poor prognosis for the elderly; they may never return to independent function following a hip fracture.[29] On the other hand, the risks associated with use of restraints are also greater among the elderly. Whenever possible, other ways to prevent falls should be entertained. Memory impairment in those with delirium persists in half of afflicted patients and becomes permanent.[30] Nursing home patients and patients with dementia are also at greater risk of delirium due to their impaired status.

Low doses of antipsychotics, either typical or atypical agents, are generally adequate to treat delirium in the elderly. One should increase the dose slowly, so as not to give more than is needed. Table 44–3 lists the types and doses of antipsychotics frequently used in the elderly. When patients are agitated and fail to cooperate with care or are unable to take oral medications, then IV haloperidol is often used to sedate and to reduce psychotic symptoms of delirium.[31,32] Elderly patients are initially started on lower doses (e.g., 0.5 to 2.0 mg of IV haloperidol). To adequately treat the delirium, the dose will need to be titrated.[30] While IV haloperidol can cause cardiac problems (with QTc widening and torsades de pointes), the etiology of polymorphic ventricular tachycardia is often difficult to determine.[33]

Atypical antipsychotics have been successfully used for treatment of delirium and agitation in elderly and in those who are critically ill.[34,35] Again, doses must be titrated slowly to minimize adverse effects. Patients are maintained on the optimal dose until their symptoms resolve. Symptoms of delirium in the elderly can last up to 6 to 12 months, and it may be necessary to discharge a patient home on an antipsychotic medication. Patients with underlying dementia are at greater risk for developing delirium; the impact of cholinesterase inhibitors have been studied in this population.[36,37]

TABLE 44–3 Antipsychotics Commonly Used in the Elderly

AGENT/DOSE (mg)	SEDATION	ANTICHOLINERGIC	EXTRAPYRAMIDAL	COMMENTS
Low Potency				
Thioridazine (Mellaril) 10–50	High	High	Low	Significant hypotension
Intermediate Potency				
Perphenazine (Trilafon) 0.5–5	Medium	Medium	Medium	
High Potency				
Haloperidol (Haldol) 0.25–2	Low	Low	High	
Thiothixene (Navane) 0.5–4	Low	Low	High	
Fluphenazine (Prolixin) 0.5–2	Low	Low	High	
Atypical Antipsychotics				
Clozapine (Clozaril) 12.5–100	High	High	Very low	White blood cell (WBC) count each week Excessive drooling Hypotension
Risperidone (Risperdal) 0.25–3	Low	Low	Low	More EPS than initially reported
Olanzapine (Zyprexa) 2.5–10.0	Moderate	Medium	Low	
Quetiapine (Seroquel) 12.5–200	High	Low	Low	
Ziprasidone (Geodon) 20–120	Moderate	Low	Low	
Aripiprazole (Abilify) 5–20	Low	Low	Moderate	

FDA ALERT (6/16/2008): FDA is notifying health care professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.

In April 2005, FDA notified health care professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics.

Antipsychotics are not indicated for the treatment of dementia-related psychosis.

Psychosis

Psychosis (manifested by hallucinations, delusions, disorganized speech, or disorganized or catatonic behavior) in the elderly has multiple etiologies. New-onset psychosis in the elderly should be rigorously worked up for possible organic causes, such as trauma (e.g., concussion, subdural hematoma, intraparenchymal hemorrhage), organ failure (e.g., hepatic encephalopathy, hypertensive encephalopathy, electrolyte abnormalities, stroke, and seizures), drugs and toxins, infections (e.g., pneumonia, urinary tract infections), and substrate deficiencies (e.g. hypoxia, hypoglycemia, vitamin B_{12} or folate deficiencies). Once organic causes have been ruled out, the remaining differential diagnosis of psychosis in the elderly includes: various types of dementias (e.g., AD, Lewy body dementia, vascular dementia, frontal lobe dementia [Pick's disease], Parkinson's disease), all of which can manifest with symptoms of psychosis at any point during the illness; delirium; delusional disorders; BPD; schizoaffective disorder; schizophrenia (either early-onset or late-onset); and major depression with psychotic features.

Psychosis is most commonly associated with schizophrenia and delusional disorders, but in the elderly, delirium and psychosis are more commonly associated with dementia and have behavioral complications that accompany these diagnoses. Psychosis in dementia is often manifested by one of three general categories (i.e., delusions, hallucinations, and misconceptions). Delusions often include the themes of stolen items, infidelity, imposters, disorientation, a lack of familiarity with ordinary items, and fear of being alone or abandoned. Hallucinations may relate to sensory losses and to the usual sensory domains (e.g., visual, auditory, tactile). Frequent misconceptions include the misperceptions of objects, not recognizing oneself, and believing that television scenes are real here-and-now events. Symptoms of psychosis are distressing to family members and to caregivers. They can become dangerous if the individual is frightened or energized by them.

Although schizophrenia usually begins before the age of 30 years, late-onset schizophrenia is not rare. More than 20% of cases are diagnosed after the age of 40 years, and at least 0.1% of the population over age 65 years has a diagnosis of schizophrenia that started late in life, with a prognosis that may be made worse by delay and avoidance of treatment.[38] Aggressive treatment of symptoms and supportive care for patients with this diagnosis is imperative. Schizophrenia remains plastic into later life, with more prominent negative symptoms than positive

symptoms. Numerous confounding factors (including cognitive decline, dementia, depression, medical co-morbidity, and use of medications for medical conditions) occur with aging. Further complications from treatment of psychosis include drug-induced side effects. In the elderly these side effects are often dramatic. Drugs with anticholinergic, orthostatic, sedative, and extrapyramidal symptoms (EPS) are relatively commonplace.[39] The elderly are more susceptible to tardive dyskinesia than are other age groups. The conventional antipsychotics have more adverse side effects than atypical agents, and higher potency agents may be more useful than lower potency ones. Atypical antipsychotics are often used in the elderly because of their sedative properties and their lack of EPS (when used at lower doses).[32,33] Atypical agents also reduce aggression associated with dementia.[40,41] However, they should be used with care, because there is a risk of adverse cerebrovascular events in patients with dementia.[42] The risk of death in patients taking typical antipsychotics is comparable to, or higher than, the rates in patients taking atypical antipsychotics.[43–45]

Dose equivalents of the atypical antipsychotics have been problematic, but a recent report by Woods[41] (using 100 mg/day of chlorpromazine as the standard), compared 2 mg/day for risperidone, 5 mg/day for olanzapine, 75 mg/day for quetiapine, 60 mg/day for ziprasidone, and 7.5 mg/day for aripiprazole, and outlined a more useful schedule. The caveat "start low and titrate up slowly" remains the gold standard; adding more medication is less harmful than is giving a large bolus of a drug with a long half-life. In certain instances, when agitation without psychosis is the primary problem, other medications to reduce anger (e.g., SSRIs, or other antidepressants that may cause sedation) are more apt to induce calm.[40,46]

Substance Abuse and Withdrawal

Patients of all ages should be asked about their use of alcohol and illicit substances. Alcoholism in the elderly is common; however, it often goes unreported by patients and overlooked by physicians.[47,48] Alcohol-related problems in the elderly are a growing public health concern. A life-long pattern of daily drinking, even in small amounts, is problematic. The National Institute on Alcohol Abuse deems one drink (12 oz beer, 1.5 oz spirits, or 5 oz wine) per day to be the maximum intake considered to be moderate alcohol use for men and women 65 years of age or older.[49,50] The prevalence of alcoholism in the elderly is about 10% to 18% and is the second most frequent reason for admission to an inpatient psychiatric facility.[50] As with those in the general population, the risk of suicide in the elderly who abuse alcohol is staggering; it is second only to major depression.[51]

Older alcoholics often refuse treatment due to perceived negative stigma and significant denial of the problem.[49] Screening tools have not been of significant benefit, but as in all aspects of geriatric care, use of the team approach to diagnosis and treatment is essential.[52] Symptoms of problem drinking include insomnia, memory loss, confusion, anxiety, and depression, as well as somatic complaints that may mimic medical illness, further delaying accurate diagnosis. Alcohol withdrawal is characterized by two or more of the following signs and symptoms: autonomic hyperactivity; tremor; insomnia; nausea or vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; or tonic–clonic seizures.[47] With the loss of lean body mass associated with aging, the volume of distribution for alcohol is reduced; this results in an increased peak ethanol concentration after any amount of alcohol is consumed.[3]

Co-morbid illnesses, both psychiatric and medical, confound accurate diagnosis of both alcoholism and medical presentations.[48] Patients seen in consultation often are admitted for infection, trauma, cardiac disease, gastrointestinal disorders, renal diseases, and pulmonary conditions. Treatment of withdrawal in the elderly is more complex and requires close monitoring. Shorter-acting benzodiazepines (e.g., lorazepam) are the medications of choice, and one should begin with low doses and increase them slowly, so as to avoid oversedation. In some older patients, larger doses and longer-acting benzodiazepines (e.g., diazepam or chlordiazepoxide) are indicated, especially with those who have a history of seizures or *delirium tremens* (DTs). Often in chronic alcoholics with a history of DTs or seizures, the gold standard remains chlordiazepoxide because its long-acting metabolites provide a slow taper and reduce the risk of seizures. Most important, aggressive treatment of symptoms limits the possibility of complications due to withdrawal or the development of DTs.

Anxiety

Recently, anxiety in the elderly (generally associated with normal aging and with medical, financial, and health-related hardships) has been recognized more often than it had been in the past. However, anxiety is not a direct consequence of normal aging, and the symptoms of anxiety should not be ignored. Beekman and associates[53] noted that loss of control and vulnerability to stress were the strongest risk factors for anxiety in later life. Both of these risk factors were common among elderly hospitalized patients. Anxiety co-exists with many other psychiatric diagnoses (such as depression, BPD, alcoholism, and dementia). Diagnostic challenges often arise when anxiety (e.g., worry, fear, apprehension, concern, foreboding) as well as somatic complaints (such as tachycardia, sweating, abdominal distress, dizziness, vertigo) develop in the context of a medical illness (e.g., diabetes with hypoglycemia, hyperthyroidism, or cardiac disease with hypoxia), because it can be manifested by similar symptoms.[54] Worries, fears, and concerns are often related to finances, dependency issues, loneliness, and memory loss. Manifestations of medical illness can mimic psychiatric symptoms; certain substances or medications (e.g., caffeine, stimulants, ephedrine, bronchodilators) produce anxiety-like symptoms. Withdrawal from a prescribed or an illicit drug can precipitate severe anxiety and panic; life-threatening withdrawal can result from sudden abstinence from alcohol, benzodiazepines, or barbiturates.

Fortunately, anxiety can be effectively managed in the elderly by use of medications, therapy, or a combination of the two.[54] In the general hospital, the treatment for anxiety involves use of benzodiazepines. However, because some older patients develop significant side effects (such as confusion, falls, oversedation, and paradoxical agitation) from benzodiazepines[55] they should be

used cautiously (while observing for exacerbation of other problems, such as sleep apnea). Other agents (including selected antidepressants, such as trazodone and mirtazapine) can be used as well.

SPECIAL CONSIDERATIONS IN THE GERIATRIC POPULATION

Pharmacotherapy

Polypharmacy, the treatment with many medicines for the same condition, is extremely common in the elderly.[56] Older patients are at higher risk for polypharmacy because of the increased rates of chronic and co-morbid medical illness in this age group. Thus concurrent use of multiple drugs does not necessarily connote inappropriate prescribing; it may in fact be sensible. Regardless, polypharmacy puts the elderly at increased risk for multiple adverse outcomes, including adverse drug reactions, falls, hospitalizations, nursing home placement, malnutrition, pneumonia, and death.[57–59]

The four key concepts relevant to polypharmacy in the elderly are the "prescribing cascade," the effects of aging, altered pharmacokinetics and pharmacodynamcis, and multiple co-morbidities.[3] The "prescribing cascade" begins when an adverse drug reaction is misinterpreted as a new medical condition, for which another drug is then prescribed, placing the patient at risk of developing additional adverse effects relating to this potentially unnecessary treatment.[60] Age-related changes may exacerbate medication side effects in the elderly. Of particular concern are side effects like orthostatic hypotension, anticholinergic reactions, parkinsonism, sedation, and cardiac conduction disturbances. Changes in metabolism, distribution, and excretion that occur with aging result in longer half-lives, increased or decreased drug effects, and increased occurrence of drug toxicity. All of these issues need to be taken into consideration with the increased medical co-morbidities in the older population, which at times necessitates the use of multiple medications.

One of the primary goals of the consultant is to prevent polypharmacy and its associated negative outcomes. One of the first and most critical steps of any geriatric psychiatry consultation should be a careful and detailed review of current medications and all recent medication changes, including both psychotropic and nonpsychotropic agents as well as over-the-counter medications. A new medication should be added only when there is a clear indication for its use; one should consider nonpharmacologic treatments when appropriate. When starting new medications, one should start with low doses and slowly titrate them to achieve a therapeutic response. Many clinicians will stop titration too soon, thus giving the patient an inadequate trial of a medication; this is also a negative outcome. Hence, remember the adage "start low, go slow, but go all the way."

Health Care Decision-Making

Consultants are often called to make determinations about the ability of elderly patients to make decisions regarding their health care. It is sometimes assumed that the elderly, regardless of the level of the cognitive impairment, cannot make such decisions. Although the details regarding capacity evaluations are dealt with elsewhere (see Chapter 48), it is worth noting the unique issues that surround surrogate decision-makers and the geriatric population.

As a rule, one should not assume that patients with cognitive impairment are unable to make their own health care decisions. Each case should be considered individually, taking into consideration the level of impairment, the medical decision being considered, and the risks of treatment versus nontreatment. As a result of the Patient Self-Determination Act of 1990, Medicare and Medicaid providers are required to educate all adult patients upon hospital admission about their right to participate in and to direct their own health care decisions, the right to accept or refuse treatment, and the right to prepare an advance directive. Geriatric patients should be encouraged to have conversations with family, friends, and caregivers about their wishes related to these issues, and should have surrogate health care decision-makers in place even if they are in the best of health.

Emergency Department Care

Emergency department (ED) visits are especially problematic for the elderly (who often manifest atypical presentations of illness); when elderly are evaluated by someone with geriatric expertise, outcomes are improved. EDs are chaotic, even more so for elderly patients with cognitive or functional impairment. In such settings the elderly often have extended waits, as those with more dramatic presentations are tended to; when this occurs, their symptoms may progress to a point where the physiologic reserves become exhausted. Although timely and accurate diagnosis is crucial, the diagnoses of delirium, depression, and dementia are frequently missed. One should remember that two thirds of all cases of delirium in this age group occur in those with dementia.

Physicians in the ED may not have access to the patient's history; as a result they often attribute the presenting complaints to chronic problems or to symptoms of aging. Acute symptoms that bring an elderly patient to the ED are not a direct result of normal aging, even though physiologic functions and reserves diminish with aging; a rapid decline is not typical of the aging process and it requires immediate attention. Communication with third parties (e.g., caregivers, family members, primary care physicians or nurses) is essential, because the elderly often deny or minimize their symptoms or situation. The elderly can be at risk for abuse or neglect, and be embarrassed or ashamed about their situation. The hurried, chaotic, and noisy ED environment exacerbates impairments in communication (that arise secondary to hearing loss, poor vision, and cognitive impairment).[61] Implementation of simple and compassionate interventions (such as providing warm blankets, keeping patients informed, re-orienting them, hydrating and feeding them, as well as attending to the needs of caregivers) improves care. Caregivers of elderly ED patients should also be mindful of the propensity for skin breakdown (when lying for protracted periods on hard surfaces). Psychiatric consultants with expertise in geriatrics can facilitate shorter stays and prevent iatrogenic complications. Education of ED staff with regard to the care of older patients in the acute setting (including management of end-of-life issues[62]) is still sorely needed.

It is also worth mentioning a fairly new initiative, medication reconciliation, outlined in the July 2006 Institute of Medicine (IoM) Report on Preventing Medication Errors.[63] This effort encourages development of a partnership between patients and their health care providers. It involves creation of a medication list (including new ones and those to be discontinued) that is provided to and discussed with older outpatients and their family members or caregiver. The IoM report found that a simple review of a patient's medications can eliminate numerous errors that increase the cost of care and improve communication with other healthcare providers. Use of electronic prescriptions (a recommendation of the IoM) is aimed at eliminating prescription errors and enhancing communication among providers about medications. According to a study cited in the IoM report, the annual cost of avoidable medication errors in Medicare enrollees (65 years and older) was over $887 million. Over and above the monetary issue is the impact on pain and suffering, the need for family or caregiver assistance, and the loss of earnings. Ensuring medication reconciliation (with clear and concise instructions about the medications, their indications and side effects, and their various names and acronyms), at the time of hospital (or ED) discharge can lead to improved adherence and to fewer adverse drug reactions.

ELDER ABUSE

Each year thousands of elderly are abused, neglected, and exploited by family members, caregivers, and others. Many of the victims are frail and vulnerable; they are unable to help themselves and they depend on those who abuse them to assist them with their basic needs. The psychiatric consultant often identifies these issues that may result in noncompliance with medications or with medical care. These issues may have contributed to the hospital admission and to ongoing medical or psychiatric problems.[53] All 50 states have reporting systems and toll-free hotlines to report concerns anonymously. Adult protective services (APS) agencies investigate the reports of suspected elder abuse and determine if abuse or neglect exists. Types of abuse are physical, sexual, psychological, financial, exploitative, and negligent. More than a half million cases were reported to the APS in 1996 during a national incidence study done through the Administration on Aging. The cohort at greatest risk were those 80 years of age and older. In 90% of the cases the perpetrator was a family member; in two thirds they were either adult children or spouses.[64]

The warning signs of abuse may be subtle, and the patient may not be willing to cooperate or to agree to go forward with an investigation. Family or caregivers may be overwhelmed, depressed, or physically unable to continue to care for the elderly patient; the APS can guide them to appropriate services.

Families and Caregivers

Families and caregivers are often an integral part of the evaluation of the elderly. The consultant should begin by gathering information directly from the patient. However, when the patient is unable to provide information (e.g., because of altered mental status or cognitive impairment), gathering further collateral information is essential. Caregivers often serve as a crucial source of information regarding medication regimens and the patient's baseline in terms of both cognitive and functional status.

Dementia often causes tremendous suffering for patients, their families, and society. Patients are forced to become more dependent and to lose their independence in basic caring for themselves, which complicates other comorbid conditions. An important part of any evaluation is the assessment of the health and well-being of the caregivers, family members, or employees of the patient, because they are at risk for developing anxiety and depression.[65,66] Caring for the caregiver is as important as is caring for the patient. The inordinate stress and burden can place the caregiver at risk for both medical and psychiatric crisis.

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Aggressive and Impulsive Patients

45

Guy Maytal, M.D.
Kathy M. Sanders, M.D.

Patients who display aggressive and impulsive behavior frequently come to the attention of the consultation psychiatrist.[1] Because aggression and violence are complex behaviors that occur both inside and outside of the medical setting, they require a systematic approach to evaluation and management. In the medical setting, aggressive behavior is associated with delirium, dementia, and other organic medical conditions; these conditions must be assessed before ascribing the behavior to a psychiatric condition, to a life circumstance, or to character pathology.[2]

Although an exhaustive review of aggression and violence in our society (as well as workplace violence and its economic and sociocultural impact) is beyond the scope of this chapter,[3–6] we will focus on the differential diagnosis of aggressive acts as it pertains to the medical setting and discuss the causes of impulsivity. However, in an era of growing sensitivity to the effects of terrorism and the residual psychological and behavioral effects on tortured patients, psychiatrists must recognize the complex biopsychosocial context of each patient who displays aggression or impulsive behavior.[7] Psychiatrists must accurately assess for the risk of violence and develop the skills to manage it.[8]

DEFINITIONS, EPIDEMIOLOGY, AND GENETICS

Aggression, defined as a "hostile, injurious, or destructive behavior or outlook especially when caused by frustration,"[9] can be classified in a number of ways: by the target of aggression (i.e., self-directed versus other-directed), by the mode of aggression (i.e., physical or verbal), or by the cause of the aggression (e.g., medical). However, the most widely used and clinically useful classification of aggressive behavior is that of premeditated versus impulsive aggression. Premeditated aggression (usually goal-directed) is not usually associated with frustration or an immediate threat. On the other hand, impulsive aggression is a response to a perceived stress or threat. It is labeled as pathologic when the aggression is out of proportion to the actual stressor. (When there is an imminent and dangerous threat, unplanned aggression can be defensive.) Because the lines between pathologic and more acceptable forms of aggression are unclear, some individuals with pathologic aggression can justify their violence as being within the bounds of normal behavior. It is the consulting psychiatrist's task to tease out motivation and response, and to manage the impulsivity of patients in the general hospital.[10,11]

Violence and aggression (particularly impulsive and irritable aggression) is extremely common. The World Health Organization estimates that each year, 1.43 million people die from violent acts (excluding war); many more individuals suffer after nonfatal acts of violence. Most of this violence is an outgrowth of impulsive aggression. After the age of 18, one fourth of all men and half of all women are the target of an act of impulsive aggression.[12,13]

Controversy exists regarding whether individuals with mental illness are at greater risk for violence than those in the general population.[14,15] Several large studies have shown that the majority of individuals seen in the mental health arena are not more violent than those in the general population. Rarely does violence in this population result in serious injury or death, and these individuals are less likely to use weapons.[16] In fact, a recent analysis from the National Epidemiologic Survey on Alcohol and Related Conditions found that severe mental illness did not independently predict future violent behavior. Rather, those factors associated with future violence are more likely to be reported by those with mental illness[17,18] (Table 45–1).

A growing body of literature reveals that individuals with chronic mental illness are far more likely to be victims of violence (25%) than the general population (3%).[17–19] Nonetheless, there is a small minority of mentally ill individuals who engage in regular violent behavior. The rates of violence differ across diagnostic categories, with untreated schizophrenia-spectrum illnesses, substance use disorders, and personality disorders being most closely associated with violent behavior; however, violence may occur more commonly in those with mental illness (e.g., 8% of patients with schizophrenia commit violent acts as compared with 2% of individuals without mental illness). Among violent offenders, 47% of men and 21% of women have been diagnosed with an antisocial personality disorder. When substance abuse is a co-morbid condition, the risk of violent behavior rises by 70% in those with schizophrenia, and by 240% in individuals with a personality disorder.[16,17] A recent review analyzed the risk of violence in mental illness along four dimensions: Low impulse control and affective dysregulation increased the risk of violence (particularly in substance use disorders), whereas having a paranoid cognitive personality style or a narcissistic injury was likely to increase the risk of violence in those with schizophrenia-spectrum disorders and personality disorders.[20]

Data from twin and family studies suggest that aggression (particularly irritable and impulsive aggression) has significant heritability (44% to 72%).[21] Violent

TABLE 45–1 Risk Factors Associated with Violent Behavior

Past history: Past violent behavior, substance abuse, early victimization (e.g., physical abuse), juvenile detention, parental arrest record
Demographic: Male, young (age 15 to 24), poor, uneducated, unemployed, limited social supports, recently divorced
Diagnostic: Organic brain syndrome (e.g., delirium), personality disorder, psychosis, co-morbid substance abuse
Clinical features: Command auditory hallucinations, current substance abuse, paranoid delusions, poor impulse control, poor insight, low IQ score
Psychological: Low tolerance for frustration and interpersonal closeness, low self-esteem, tendency toward projection and externalization, anger

Adapted from Rocca P, Villari V, Bogetto F: Managing the aggressive and violent patient in the psychiatric emergency, *Prog Neuropsychopharmacol Biol Psychiatry* 30(4):586-598, 2006.

and aggressive behavior is greatly influenced by gene–environment interactions (including familial relationships and experiences, and the witnessing or experiencing of violence during childhood), as well as cultural and socioeconomic factors that encourage aggression. People who have a biological risk for aggression may be more vulnerable to environmental adversity and more likely to engage in violence later in life.[22]

NEUROBIOLOGY

Phenomenology

Violence and aggression have complex biological, environmental, and psychological determinants.[4,11] Furthermore, the susceptibility to aggression depends on the overall psychopathologic context. For example, emotional dysregulation in the context of a susceptibility to aggression may lead to aggressive acts only within interpersonal relationships—as with borderline personality disorder. For individuals with a posttraumatic stress disorder and a susceptibility to aggression, aggressive behavior may be triggered only by cues reminiscent of the original trauma. Alternatively, the cognitive distortions and disinhibition associated with substance abuse lead to unpredictable or purposeful aggressive behaviors.[11]

Brain Circuitry

In any of the examples just mentioned, impulsive aggression can be thought of as having a lower threshold for aggressive (motor) responses to stimuli without reflection on the consequences of their actions. In other words, there is too little input from the orbital frontal cortex and anterior cingulate cortex (which provide top-down control, interpretation of social cues, and prediction of reward and punishment) and too much input from the limbic regions (the repositories of aggressive drives).[11,23,24]

The limbic system (which includes the amygdala, hippocampus, septum, cingulate cortex, and fornix) has regulatory control of aggressive behaviors in humans and animals. The hypothalamus regulates neuroendocrine responses through output to the pituitary gland and the autonomic nervous system. In the hypothalamus, the anterior, lateral, ventromedial, and dorsomedial nuclei are often described as areas crucial to animal aggression; they are considered to be involved in the control of aggression in humans. In individuals with borderline personality disorder and in perpetrators of domestic violence, functional neuroimaging studies have demonstrated increased activity of the amygdala and the hypothalamus.[25,26]

The prefrontal cortex modulates input from both the limbic system and the hypothalamus. In particular, the orbital frontal cortex and anterior cingulate cortex have been strongly implicated in calibrating behavior to social cues, and modulating behavior based on expectations of negative consequences.[11,27,28] Functional neuroimaging has also demonstrated decreased glucose metabolism in the frontal cortices of individuals with a history of physical aggression (i.e., violent criminals and patients with borderline personality disorder). This suggests inefficient processing by the frontal regions in these individuals, which leads to ineffective suppression of limbic signals that occur in response to provocative stimuli. Furthermore, damage to the frontal lobe from a variety of causes (including anoxic injury, violent trauma, and closed head injury) results in increased impulsivity and reduced executive control of emotional reactivity.[11,29–31]

Neuromodulators and Other Neuroactive Substances

Low central serotonin (5-HT) function has been correlated with impulsive aggression. More specifically, serotonin facilitates prefrontal cortical lesions. Therefore, 5-HT innervation decreases in these regions can lead to increased aggression.[32,33] This is supported by studies showing that selective serotonin reuptake inhibitors reduce impulsive aggression.[34] Violent patients have also been found to have a low turnover of 5-HT, as measured by its major metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid (CSF). Furthermore, antagonists of the 5-HT_{2A} receptor reduce impulsivity in animal models, and atypical neuroleptics with 5-HT_{2A} antagonism reduce aggressive behavior in clinical populations.[11,35] More recent neuroimaging studies have demonstrated reduced serotonergic stimulation in the orbital and ventromedial prefrontal activation in patients with intermittent explosive disorder, in those with borderline personality disorder, and in depressed patients with a history of suicide attempts.[11,36–38]

Catecholamines (e.g., dopamine and norepinephrine) may facilitate aggression directed toward others. They are believed to be involved in the initiation of aggressive behavior by affecting frontal lobe circuits.[11,39] Acetylcholine in the limbic system stimulates aggression in animals; cholinergic pesticides have been cited as provoking violence in humans. Furthermore, imbalance in glutaminergic–gamma-aminobutyric acid (GABA) activity in the limbic regions may induce hyperactivity in these areas and lead to aggressive behavior. Reduced activity at GABA receptors may contribute to aggression, whereas increased activity at glutamate receptors is believed to inhibit aggression.[11,39]

Other proteins that act on the central nervous system (CNS) influence the likelihood of aggressive behavior. Above-normal concentrations of vasopressin in CSF

TABLE 45–2 Neurobiological Implications for Pharmacotherapy of Aggression

	ANATOMIC SUBSTRATES FOR AGGRESSIVE BEHAVIOR	
PHARMACOLOGIC CLASS	**SUBCORTICAL AREAS**	**FRONTAL AREAS**
Anticonvulsants	↓ Limbic irritability	—
Atypical neuroleptics	↓ Subcortical dopamine stimulation	↑ Frontal inhibition
Opiate antagonists	↓ Endogenous opiates	—
Serotonergic agents	—	↑ Frontal inhibition
Stimulants	—	↑ Frontal inhibition

Adapted from Siever LJ: Neurobiology of aggression and violence, *Am J Psychiatry* 165(4):429-442, 2008.

have been correlated with a life history of aggression in personality-disordered patients. Oxytocin has been shown to influence trust and affiliative behaviors; a deficit of oxytocin may contribute to hostility and mistrust, setting the stage for aggressive behavior.[40,41] Endogenous opioids have also been associated with aggressive behavior. Reduced CSF endogenous opioid concentrations have been associated with self-injurious behavior in those with a borderline personality disorder. Increased levels of testosterone and steroids induce aggression and enhance the brain circuitry related to social aggression[11,42] (Table 45–2).

Systemic hormones also influence the propensity for aggression. Cortisol concentrations are lower in individuals with high aggression (e.g., in antisocial criminals and perpetrators of domestic violence).[11,42] More recently, lower cholesterol levels in patients with personality disorder have been associated with aggressive and impulsive behavior.[43–45]

DIFFERENTIAL DIAGNOSIS

The multiaxial *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)[46] diagnostic system has five domains to categorize aggressive or violent behaviors. Because management of aggressive behaviors is predicated on an accurate diagnosis, the diagnosis of the underlying cause is crucial; it hinges on initial consideration of organic causes (including intoxication or drug withdrawal) and psychiatric etiologies. A wide range of psychopathology (from major mental illness to personality disorders to life circumstances, such as job stress or loss—situations that alter coping mechanisms) should be considered.

Medical Causes

When considering the differential diagnosis of violent and impulsive behavior, the psychiatrist should assume that a medical condition or substance abuse problem is at the root of the behavior before considering psychiatric illnesses.

A variety of primary CNS disorders can generate aggressive and violent behavior. These include traumatic brain injury, intracranial hypoxia or bleeding, an intracranial mass, and dementia of any type. Because of the protean nature of aggression, particular attention should also be paid to that caused by seizure disorders. Seizure-related aggression involves ictal aggression (typically nonpurposeful, stereotypical behavior during the seizure), postictal aggression (secondary to confusion or agitation), and interictal aggression (which may result from subthreshold electrical brain activity) that elicits violence.

Other medical causes of aggression include delirium (from a host of underlying medical conditions and hormonal and metabolic abnormalities). For a more exhaustive differential diagnosis of the underlying medical causes of delirium and dementias (Table 45–3), see Chapter 10.

Violence is more prevalent in patients with substance abuse and dependence than in those without.[18] In the acutely intoxicated state, behavior is often characterized by disinhibition, which places individuals at greater risk for violence. During withdrawal from alcohol and other sedative–hypnotics, delirium or agitation may also precipitate aggression. Chronic alcohol abuse with secondary brain damage or dementia may lead to aggressive behavior that persists beyond the state of acute intoxication or withdrawal. Acute intoxication or withdrawal from psychostimulants (e.g., cocaine, amphetamine) can lead to agitation, paranoia, psychosis, and violence. Hallucinogens (e.g., phencyclidine, lysergic acid diethylamide) may also precipitate psychosis and violence. Opiate intoxication and withdrawal, as well as behaviors required to obtain these drugs, may also increase the risk for violence.

Other prescription medications (e.g., anticholinergics, steroids) and over-the-counter preparations may induce aggression. In the fitness subculture, the use of various herbal and nutritional supplements and the abuse of hormone therapies may result in an altered mental status that could manifest as violence, aggression, and impulsivity.

When determining the likelihood of medical factors that play a role in an aggressive or impulsive episode, one should take a history, obtain corroborating information from family or friends, perform pertinent laboratory studies, and conduct a physical examination that will hone the differential diagnosis. The following three clinical examples illustrate how agitated behavior with a medical cause can be mistaken for a psychiatric diagnosis.

CASE 1

Mr. A, a 37-year-old man with chronic alcohol abuse, was brought by police to the emergency department (ED) after getting into an argument with staff at a local shelter. The argument escalated in an uncharacteristic manner for Mr. A: he pulled a knife on a staff member. Fortunately, Mr. A was subdued before being able to use it. He was uncooperative during the examination in the ED, and he shouted expletives at nursing and security staff. He was thought to be acutely intoxicated until his vital signs were checked: his temperature, pulse, and blood pressure were all elevated. Furthermore, Mr. A's doctors were surprised that laboratory studies revealed a negligible blood alcohol level and no other substances of abuse in his system. He was diagnosed with alcohol withdrawal and treated with benzodiazepines, which led to a resolution of his agitation and aggression.

CASE 2

Ms. B, a 45-year-old woman with chronic schizoaffective disorder, returned to the ED because of a decompensation of her illness. Her case manager found her roaming the streets of her neighborhood and picking fights with neighbors and strangers. Although she readily backed down before becoming violent, her persistent and impulsive temper continued to flare, and she required containment and further evaluation. In the ED, laboratory studies showed a sodium blood level of 115 mEq/L. She was admitted to the medical service for management of her hyponatremia caused by inappropriate antidiuretic hormone secretion.

CASE 3

Ms. C, a 26-year-old woman, was brought to the ED by her family after aggressively and uncharacteristically shoving her mother without provocation. Ms. C had been invited to a family dinner in honor of her recent job change. She was extremely irritable and accused her family of being part of a plot to prevent her from being successful in her new job. When they tried to dissuade her from thinking that, she became belligerent, aggressive, and threatening. The family brought her to the ED, worried that she was emotionally unstable. At triage, she was alert but shaking and irritated by any questions. She admitted to intentionally taking extra (i.e., an overdose of) isoniazid tablets (which had been prescribed for a positive purified protein derivative skin test during a preemployment medical screening) while overwhelmed by concerns about her new job. Within minutes of her arrival in the ED, she had a grand mal seizure and was admitted for further tests and treatment.

Psychiatric Causes

Violent and impulsive behaviors are nonspecific; they may be part of most major mental illnesses at some time during the course of the illness. When assessing whether a psychiatric illness contributed to violence, it is important to consider Axis I conditions, Axis II disorders, and organic causes on Axis III.

Diagnoses on Axis I

Schizophrenia or Psychosis, Not Otherwise Specified

The prevalence of violent behavior in individuals with schizophrenia is similar to that for those with major depression or bipolar disorder. Individuals who are paranoid (e.g., with delusions of persecution) may act violently toward a perceived threat. Command hallucinations associated with violent content (toward oneself or others) dramatically increase the potential for violence in individuals with schizophrenia. Disorganized thought and behavior may also lead to violence.

Affective Illness

Unipolar depression may be accompanied by an increase in hostility and by anger attacks (in nearly half of cases) that can lead to violent behavior.[47] Depression that is co-morbid with psychotic features may further increase the risk of violence. Patients with bipolar disorder (with a manic, hypomanic, or mixed presentation) often display irritability, anger outbursts, omnipotence, and paranoia, which may lead to impulsive aggression.

TABLE 45–3 Differential Diagnosis of Psychosis and Agitation

GENERAL CATEGORY	CAUSE/DIAGNOSIS
Organic mental disorders	Aphasia
	Catatonia
	Delirium
	Dementia
	Frontal lobe syndrome
	Organic hallucinosis
	Organic delusional disorder
	Organic mood disorder (secondary mania)
	Seizure disorders
Drugs	Substance abuse (e.g., cocaine and opiates)
	Steroids
	Procarbazine HCl
	Antibiotics
	Anticholinergics
Drug withdrawal	Alcohol and sedative–hypnotics (barbiturates and benzodiazepines)
	Clonidine
	Opiates
Psychotic disorders	Schizophrenia
	Delusional disorder
	Psychotic disorders not otherwise specified (NOS)
	Brief reactive psychosis
	Schizoaffective disorder
	Shared paranoid disorder *(folie à deux)*
Mood disorders	Bipolar disorder
	Major depression with psychotic/agitated features
	Catatonia
Anxiety/fear	Anxiety disorders
	Acute reaction to stress
Discomfort	Pain
	Hypoxia
	Akathisia
Personality disorder	Antisocial
	Borderline
	Paranoid
	Schizotypal
Disorders of infancy, childhood, and adolescence	Autism
	Mental retardation
	Attention deficit hyperactivity disorder
	Conduct disorder

Impulse-Control Disorders

Impulsive disorders, as classified by the DSM-IV, are a "residual" diagnostic category.[48] Diagnoses in this category include kleptomania, pyromania, pathologic gambling, trichotillomania, intermittent explosive disorder, and impulse-control disorder not otherwise specified (NOS).[49,50] Each of these conditions involves a drive or a temptation to perform an act that is harmful to the person or to others, or the failure to resist an impulse. Other associated features are the experience of increasing tension (e.g., dysphoria or arousal, often sexual) before committing the act that is followed by a release of tension, a sense of gratification,

or a sense of pleasure and relief during and after the act. There also may be a sense of guilt, regret, or self-reproach after the behavior.

Patients diagnosed with an impulse-control disorder have an increased risk of being diagnosed with a substance abuse disorder, with obsessive–compulsive disorder (OCD) or another anxiety disorder, with an eating disorder, or with a mood disorder. Moreover, there is an increased incidence of substance abuse disorders and mood disorders in family members of those with impulse-control disorders. Theories place impulse-control disorders on a spectrum of affective disorders, as a variant of OCD, or as a blend of mood, impulse, and compulsive disorders. Historically, these disorders were thought to result from psychodynamic conflicts; however, more biological hypotheses have been explored since improvement of impulsive symptoms has been accompanied by use of the serotonergic antidepressants.[50–52]

Intermittent explosive disorder is a diagnosis that characterizes individuals who have episodes of dyscontrol, assaultive acts, and extreme aggression that is out of proportion to the precipitating event and is not explained by another Axis I or an Axis II disorder. It is considered rare and a diagnosis of exclusion.[53,54] Intermittent explosive disorder and personality change that results from a general medical condition, aggressive type, are the current diagnoses available to patients with episodic violent behavior. Most violent behavior can be accounted for by a variety of psychiatric and medical conditions. The most common diagnosis associated with violence is personality change resulting from a general medical condition (e.g., seizures, head trauma, neurologic abnormality, dementia, or delirium), aggressive or disinhibited type. Personality disorders of the borderline or antisocial type must also be ruled out. Psychosis from schizophrenia or a manic episode may also cause episodic violence. Aggressive outbursts while intoxicated or while withdrawing from a substance of abuse would rule out the diagnosis of intermittent explosive disorder. Psychopharmacology is commonly used in the management of this chronic disorder. Anticonvulsants, lithium, β-blockers, anxiolytics, neuroleptics, antidepressants (both serotonergic and polycyclic agents), and psychostimulants have all been used with varying degrees of success. The acute management of aggressive and violent behavior may involve the use of physical restraints, parenteral neuroleptics, and benzodiazepines. Long-term outpatient management of intermittent explosive disorder requires attention to the therapeutic alliance between the clinician and the patient.

Impulse control disorder NOS is a category of disorders that do not meet diagnostic criteria for any of the previously discussed impulse-control disorders or for another mental disorder involving impulse control. Included in this category are diagnoses such as pathologic spending, pathologic shopping, repetitive self-mutilation, compulsive sexual behavior, and compulsive face picking. Most of the literature on this diagnostic category focuses on repetitive self-mutilation. It is more common in women than in men; however, it is considered endemic in male prisons. Two thirds of self-mutilators have a history of sexual and physical abuse during childhood. The disorder starts in adolescence and is characterized by severe psychosocial morbidity.[48]

Attention Deficit Disorders

Attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) begin in childhood and can persist into adulthood. The impulsivity, inattentiveness, and behavioral problems that accompany these conditions may lead to aggressive acts. Other childhood developmental disorders and learning disorders are also associated with aggressive and impulsive behaviors, including self-mutilation.[55]

Diagnoses on Axis II

Antisocial personality disorder is frequently associated with violent and impulsive behavior and criminality. Further complicating this is that sociopaths frequently have co-morbid substance abuse. Patients with borderline personality disorder may display aggression toward themselves or others as part of their impulsive behaviors. Those with a paranoid personality disorder often react to perceived threats with violent reactions toward that perceived threat. Those with mental retardation and other developmental disorders tend to have poor impulse control; depending on the underlying cause (e.g., head trauma), these states may lead to violence.[56–58]

Diagnoses on Axes IV and V

Environmental precipitants are as important as underlying psychiatric or medical diagnoses when determining how dangerous a patient might be. Axis IV parameters (e.g., occupational, social relationship, educational, housing, economic, and legal problems) can lead to aggression and to violence. A patient's current level of function (as measured on Axis V) can also aid the clinician in predicting the threat of violence. The more stressors one has (on Axis IV) and the lower the level of function (on Axis V), the higher is the possibility for violence in those prone to violence.

ASSESSMENT OF THE VIOLENT PATIENT

General Considerations

To ensure the safety of a patient and those around him or her, the evaluator must provide a timely diagnosis and an appropriate acute management plan.[59,60] In crisis situations, the ABCs of emergency evaluation of aggressive and impulsive behavior include safety, diagnosis, and management.[8] Safety is the first priority when confronted by a potentially violent patient. Control of the patient and of the environment must be obtained to prevent harm to the staff and to the individual being assessed. Without proper safety mechanisms, adequate evaluation is impossible. Diagnosis of underlying psychopathology, substance abuse, or medical conditions then guides specific treatment. If there is no medical or psychiatric diagnosis, then perhaps the legal authorities are more suitable for the management of the patient's behavior. Management, in the form of chemical sedation (with neuroleptics or benzodiazepines, or both), along with seclusion or restraint (or both) may be necessary to ensure the safety of patient and staff, as well as to allow the evaluator to perform an accurate assessment.[59,60]

Interview of the Potentially Violent Patient

Before the examiner can interview the potentially violent patient, a safe environment must be secured. All potentially dangerous materials should be removed from the patient

and from the interview room. The room should be scrutinized, before and during the interview, for objects that can be used as weapons (e.g., pens, needles, phones). Escape from the room should be possible, and all activity in the room should be highly visible (i.e., through a window or via a security camera). The ideal interview room would contain an emergency call button, and it should not be possible to lock the room from within. The consultant should pay careful attention to the patient's behavior for signs of imminent danger. Escalating behaviors include verbal threats or threatening gestures, physical agitation (e.g., rapid movements, pacing, knocking over furniture, slamming doors), muscle tension (e.g., clenching of the jaw or fists), and invasion of personal space. If an escalating behavior is seen, the examiner's interventions should direct the patient to regain the locus of control. If the examiner's attempts to redirect the behavior fail to calm the patient and merely increase his or her level of self-control, then tranquilization and application of restraints may be necessary to regain control and to ensure safety.

Once a safe environment is established, the assessment of a violent patient includes two distinct but interconnected steps: the diagnostic assessment and the violence risk assessment. Both require a thorough history, a directed physical examination, and (often) obtaining corroborating sources of information and laboratory data.[17]

History

The diagnostic history must be obtained in the initial phases of the interview process to ascertain and to treat any potentially life-threatening medical causes for the patient's agitation or aggressive behavior. The mnemonic WWHHHHIMPS can be used to quickly rule out life-threatening causes (see Table 10–3).

Once life-threatening medical causes of aggressive behavior have been ruled out, the clinician should evaluate the patient for other medical causes (e.g., previous head trauma, neurologic difficulties such as seizure disorders), for substance-related causes (e.g., intoxication or withdrawal), and for primary psychiatric diagnoses (e.g., mania or acute psychosis) that may increase the patient's risk for aggression and may guide treatment.

Given the assortment of patients who engage in violent behavior, a violence risk assessment is one of the most difficult tasks for the medical and psychiatric professional. The best indicator of future violence remains a history of violence.[17,18] Therefore, seeking a history of previous violence in a patient is an integral part of the interview. Unfortunately, it is often difficult to elicit an accurate account. The best approach involves direct questioning of violent behaviors (Table 45–4). Other factors associated with an increased risk of violent behavior are listed in Table 45–1.

TABLE 45–4 Assessment of Violence

1. Ask screening questions.
   a. Do you ever think of harming anyone else?
   b. Have you ever seriously injured another human being? (Tell me about the most violent thing that you have ever done.)
2. Determine the specifics of past violence.
   a. At what age did violent acts begin?
   b. How frequently did those acts occur?
   c. What was the most recent act?
   d. How severe were the actions?
   e. Has there been a recurring pattern of escalation preceding violence?
   f. Have there been common precipitants surrounding the acts?
   g. Have any violent actions resulted in legal recourse or incarceration?
   h. Has there been a history of recklessness, suicidal ideations, arrests, or impulsivity?
   i. Does the patient have a family history of violence, abuse, or gang involvement?
3. Ask about prior evaluations and treatments related to violent behavior, including medical work-ups, diagnostic tests, and old records.
4. Collect information from as many ancillary sources as possible, including family members, victims, court records, medical records, and previous professional caregivers.

Examination of the Violent Patient

The mental status examination of the potentially violent patient begins like a standard examination. However, careful consideration must be given to safety. If at any time during the examination, the examiner feels unsafe, he or she should stop the interview and resume it only after safety has been ensured. The initial assessment should focus on elements of the mental status (e.g., the sensorium, disordered thought, mood and affect, cognition, agitation, hallucinations, evidence of intoxication by drugs or alcohol). Mental status abnormalities or symptoms (as listed earlier) can increase the likelihood of aggressive action and alert the physician to medical conditions that require further work-up or immediate treatment. For example, affective disorders, either mania or depression, may impair a patient's judgment and lead to violence. The impulsivity accompanied by mania can lead to irrational thoughts and aggression. The hopelessness of a depressed individual, combined with psychotic thoughts, may lead a person to attempt suicide or murder. Thought disorders, psychosis with paranoid features, and command hallucinations create a situation that can produce dangerous and difficult-to-predict behavior. Just as in the evaluation of the suicidal patient, patients with violent thoughts toward others must be assessed in terms of their specific plan, the lethality of their plan, and the possibility that the plan can actually be carried out. Determination of the relative risk of violence in this manner helps in the development of a disposition plan (e.g., inpatient versus outpatient management). Documentation of agitation through standardized rating scales, such as the Overt Agitation Severity Scale (OASS), is useful in anticipating escalating behaviors and determining when to intervene.[1]

Physical examination, guided by findings from the history, should target medical causes of violence. Because violence is more likely in a patient with an organic brain

syndrome or acute intoxication/withdrawal, the clinician should tailor the examination toward identifying or ruling out these diagnoses. Based on physical findings and the patient's medical history, appropriate diagnostic tests should be performed. These can include laboratory tests (e.g., routine chemistry tests, blood counts, tests of serum and urine toxicology; and a pregnancy test should be considered for all women of childbearing age); an organic work-up for dementia; an electroencephalogram; neuroimaging and other radiologic tests as indicated; and neuropsychological and cognitive testing.

TREATMENT OF THE VIOLENT PATIENT

Management of the aggressive patient can be divided into acute management and chronic management. There are no medications that specifically target aggressive behavior; the psychiatrist must apply general principles to guide treatment. Treatment of the underlying psychiatric illness, if present, should be optimized; if that fails, it is best to use the most benign treatments in an empirical and systematic way. Target symptoms should be well defined and monitored in response to specific interventions. Efficacy should be defined by parameters that can be observed and measured. The symptom checklist in the OASS is useful for documenting progress in the management of agitation and aggressive behaviors.

Acute Management

In the acute setting, the goal in treatment of the violent patient is to reduce the risk of harm to both the staff and the patient and to facilitate the diagnostic process. Clinical intervention should strive for the least coercive and aggressive interventions available.[61] Noncoercive interventions (including verbal and behavioral techniques, such as talking in a soft, nonconfrontational tone, providing a quiet room with an easily accessible exit, and offering the patient a meal) aim to de-escalate the situation. All of these interventions seek to separate the emotional and behavioral aspects of the patient's condition. By using an approach that is as empathic as possible, the clinician attempts to ally with the patient so that the patient feels understood and has an opportunity to alter the aggressive behavior. However, if the patient is unable to de-escalate with noncoercive interventions, then coercive interventions (including a show of force, forced seclusion, physical restraint, and the involuntary use of sedating medications) should be used as appropriate to ensure patient and staff safety.[17,62]

These interventions should be used solely to limit patient dangerousness, and never as punishment or for staff convenience. A show of force is not actually a coercive intervention; it implies that force will be used as a last effort to stop violent behavior. It also gathers the necessary personnel in the event that physical restraint or the administration of involuntary medication is needed. Furthermore, it is important for the patient to understand that through the show of force, the staff is still there to help him or her, even if it is only to help contain dangerous behavior.[17,61]

Often, when noncoercive means are insufficient to help a patient calm down, combining a show of force with an offer of voluntary acceptance of a sedating medication (e.g., an antipsychotic or a benzodiazepine) can help achieve safety (see later).

Physical restraint (the direct application of physical force to a patient without the patient's permission, to restrict freedom of movement) and seclusion (the involuntary confinement of a person alone in a locked room) are often a necessity; although controversial, they ensure safety of patients and staff. Once the decision is made to apply physical restraints, it is important to gather the appropriate number of staff members (a minimum of five) so that the intervention can be done quickly and safely. The patient should be informed of what is going to happen and should be invited to cooperate with staff. Once the physical intervention is complete, documentation (including the ineffectiveness of less coercive means) should be completed. Finally, to preserve the patient's rights, dignity, and privacy, there should be specific institutional guidelines for how often the patient should be monitored while restrained, how long a patient can be in restraints, and what conditions need to be met before releasing the patient.[17,61]

Acute Medical Management

Use of sedating medications (e.g., neuroleptics and benzodiazepines) is a humane and effective means for managing agitated and impulsive patient behavior. Because they are less coercive, oral formulations should be the first-line means of medicating patients. However, in the setting of acute aggression and agitation, drugs that can be delivered intramuscularly and that have a rapid onset and a favorable side-effect profile should be used. Once the patient is calm, the psychiatrist can perform a more thorough assessment to determine the diagnosis, treatment, and disposition.

Benzodiazepines are rapid, safe, and easily administered agents for moderate to severe agitation and when the potential for escalating behavioral dyscontrol exists. However, benzodiazepines may cause a paradoxical reaction in certain character-disordered individuals and in elderly persons. In general, when given in the intramuscular or oral form, these medications are effective sedatives in the acute care setting[17,61–63] (Table 45–5).

Alprazolam acts rapidly, but it can only be administered orally. The initial dose is usually 0.5 mg, and the initial dosage should not exceed 4 mg/day. Diazepam (with an initial dose of 5 mg) has a rapid onset of action and can be administered intramuscularly, orally, or intravenously. It has a long half-life (30 to 100 hours), and therefore it should be used cautiously in elderly patients, who will metabolize it slowly. Lorazepam may be given sublingually, orally, intramuscularly, or intravenously. The usual starting dose is 1 mg; its intermediate half-life (10 to 20 hours) makes it an ideal medication for initial treatment. Because it has no active metabolites, there is little risk of drug accumulation if the patient requires more than one dose to manage agitation and to maintain behavioral calm. In addition, lorazepam is metabolized by glucuronidation in the liver and excreted by the kidneys, which makes it easier to use in those with organ system failure.[64] The following case is an example.

TABLE 45–5 Selected Medications for Use in the Setting of Acute Agitation

MEDICATION	STARTING DOSE	MODE OF ADMINISTRATION	COMMENTS
Benzodiazepines			
Alprazolam	0.5 mg	Oral only	Short half-life requires frequent dosing.
Lorazepam	0.5-1 mg	Sublingual, oral, IM, IV	No active metabolites Preferred in patients with liver disease
Diazepam	5-10 mg	Oral, IM, IV, rectal	Use with caution with elderly patients because of long half-life.
Typical Antipsychotics			
Haloperidol	2-10 mg	Oral, IM, IV	Monitor QTc interval. Monitor for extrapyramidal symptoms (EPS).
Chlorpromazine	25-50 mg	Oral, IM	Highly sedating Monitor for anticholinergic effects and orthostatic hypotension.
Atypical Antipsychotics			
Olanzapine	2.5-10 mg	Oral, sublingual, IM	Sublingual dose does not have faster onset of action than oral. Sedating Much lower incidence of EPS
Ziprasidone	10-20 mg	Oral, IM	Monitor QTc interval
Aripiprazole	5-10 mg (oral) 9.75 mg (IM)	Oral, IM	Monitor for extrapyramidal symptoms.

CASE 4

Mr. D, a 54-year-old married executive, was seen in the cardiac care unit (CCU) because he was unable to remain in bed or to cooperate with the nursing staff. He had been admitted earlier that day from the ED, where he was diagnosed with an acute myocardial infarction and was given IV tissue plasminogen activator. On arrival in the CCU, he was distractible: he made frequent attempts to get out of bed and to pace. He could be redirected only briefly before resuming his efforts to get out of bed. Before the consultant arrived in the CCU, Mr. D was given diazepam and morphine for sedation to allow a computed topography scan of the head to be completed. The neuroimaging study revealed a midline intraventricular bleed presumably associated with the anticoagulant treatment initiated in the ED. Although staff initially characterized him as a type A personality with restlessness in a structured and controlled environment, his agitated and impulsive behavior actually stemmed from CNS irritability due to the presence of blood in his ventricles. Because further use of benzodiazepines and opiates would very likely only worsen his mental status, his behavior was managed with a high-potency neuroleptic.

Antipsychotics, particularly high-potency agents, are often highly effective in reducing agitation and violence in both psychotic and nonpsychotic patients (see Table 45–5). Haloperidol is a high-potency neuroleptic that is frequently used in this setting because of its favorable side-effect profile and overall cardiopulmonary safety. It may be given orally, IM, or IV, and it is usually effective when one or two 5-mg doses are administered IM or IV. It is often administered along with an anticholinergic agent (e.g., diphenhydramine or benztropine mesylate) to minimize the risk of extrapyramidal symptoms. Given IV, it is less likely to precipitate extrapyramidal symptoms; however, regardless of route, one must attend to the risk for torsades de pointes.[17,61,65] Virtually any antipsychotic may diminish aggression, but careful consideration should be given to the potency of, history of response to, and side-effect profile of the particular medication, and to the psychiatric and medical history of the patient. Atypical antipsychotics (e.g., clozapine, olanzapine, aripiprazole, quetiapine, ziprasidone, risperidone) have been used more in recent years.[17,61,65,66] In general, atypical neuroleptics are better tolerated than conventional agents; they have fewer extrapyramidal side effects and are associated with better long-term compliance.[17,65,66] As with other agents, oral doses should be considered first to encourage patient cooperation; however, if they are refused or the aggressive behavior escalates, intramuscular (IM) use should be considered. Currently, olanzapine, aripiprazole, and ziprasidone are available for IM use in the acute care setting.[67–69]

CASE 5

Mr. E, a 32-year-old single Russian immigrant, was forcibly brought to the ED after calling 911 and seeking "help" by provocatively expressing passive suicidal ideation. He was agitated and angry and intoxicated with alcohol, so staff were unable to reason with him. He was placed in four-point restraints, and a psychiatry consult was called to assess his mental status and his risk for suicide. He would not engage in a meaningful exchange. Therefore, haloperidol 5 mg IM and diphenhydramine 50 mg IM were administered. He became more cooperative and was examined. It became apparent that his right arm hurt. He described how he was forcibly removed from his apartment and taken down four flights of stairs. Once he was controlled, his restraints were removed for a radiographic examination, which revealed a fractured elbow that was then placed into a cast.

Long-term Management

The long-term management of the violent patient poses a complex challenge for the treating psychiatrist. First, appropriate treatment of any underlying psychiatric disorder should be maximized, using both psychotherapy and pharmacotherapy (see Table 45–2). Selective serotonin reuptake inhibitors have been used with some efficacy in patients with personality disorders, dementia, and mental retardation. One should be cautious when using any antidepressant in patients with bipolar disorder, because this may exacerbate, rather than lessen, certain symptoms.[70] Lithium has been used to reduce aggression in patients with mental retardation, conduct disorder, and antisocial personality disorder and in prison inmates; the target lithium level should be between 0.6 and 0.9 mEq/L. Anticonvulsants (e.g., carbamazepine, valproic acid, phenytoin) have been used with some success in reducing impulsive aggression. Gabapentin also has significant mood-stabilizing benefits that may be used in the management of aggression in a wide range of patients. It has also been used for patients with substantial anxiety and character pathology.[71] Benzodiazepines may be used in chronic, as well as acute, settings. Buspirone, a 5-HT_{1A} partial agonist, is a nonbenzodiazepine anxiolytic that has been used as an adjunct treatment for agitation and aggression.[72] β-adrenergic blockers have been used in high dosages to treat aggression; their effects may not be seen for several months. All patients should be started at a low dosage and then titrated to effect and tolerance. Propranolol may be gradually increased up to 1 g/day; it has been used successfully in patients with dementia and organic brain disorders.[73] Nadolol 40 to 120 mg/day and metoprolol 200 to 300 mg/day may also be used in patients who are chronically aggressive. Psychostimulants may be effective in reducing impulsive aggression in children with ADD/ADHD and in adults with residual ADHD. Bupropion and desipramine have been efficacious in adults with residual ADHD.

The long-term use of atypical neuroleptics in the management of aggression may provide behavioral control while addressing the underlying psychotic and affective components of aggression. Clozapine, risperidone, quetiapine, olanzapine, ziprasidone, and aripiprazole broaden the options for the treatment of psychosis.[74] Their relatively benign side-effect profile improves compliance, and their ability to enhance mood increases the options for the types of patients that can be treated for aggressive and impulsive behaviors.

Psychotherapeutic approaches (e.g., behavioral techniques, cognitive-behavioral therapy, and group and family therapy) have also been used to treat aggression and violence.[75] Such techniques (e.g., limit-setting, contingent reinforcement, distraction and redirection, relaxation, biofeedback) have been used in the ongoing inpatient and outpatient management of aggressive and impulsive patients with mixed success. The combination of medication and psychotherapy is still the best approach to the chronic management of aggression and violence.

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Psychiatric Illness during Pregnancy and the Postpartum Period

Betty Wang, M.D.
Marlene P. Freeman, M.D.
Ruta Nonacs, M.D., Ph.D.
Adele C. Viguera, M.D., M.P.H.
Lee S. Cohen, M.D.

Psychiatric consultation to obstetric patients typically involves evaluating and treating an array of psychopathology. Once thought to be a time of emotional well-being for women,[1] studies now suggest that pregnancy does not protect women from the emergence or persistence of psychiatric disorders.[2–7] Because many psychiatric conditions are chronic or recurrent and have high prevalence rates in women during the reproductive years, many women will become pregnant while receiving psychiatric treatment. Because many pregnancies in the United States are unplanned, women of reproductive age should know the risks and benefits of their medications even if they are not planning to become pregnant. Optimally, a woman and her psychiatrist should plan ahead for a pregnancy and assess the risks and benefits of treatment before conception. Given the prevalence of mood and anxiety disorders in women during the childbearing years[8,9] and the number of women who receive treatment for these disorders, it is apparent that many women become pregnant either shortly after discontinuing psychotropic medications or following a decision to maintain treatment during efforts to conceive.

Because rapid discontinuation of medication appears to increase the risk of relapse of mood episodes,[10,11] women should be educated about the risks and benefits of medications during pregnancy so that medications are not abruptly stopped (out of fear of exposing the fetus to medication). Furthermore, medications with relatively benign reproductive safety profiles should be used as first-line agents in women of reproductive potential. With increasing evidence of high rates of relapse following discontinuation of psychotropic medications (e.g., antidepressants,[12] mood stabilizers,[13] antipsychotics,[14] benzodiazepines[15]) and other data that describe new-onset psychiatric illness during pregnancy,[2,6,16] the value of psychiatric consultation during pregnancy and after delivery is evident. The risks of untreated psychiatric disorders to the mother and the baby include preterm delivery, poor nutrition, inadequate weight gain, poor prenatal care, inability to care for oneself, substance use (such as cigarettes or alcohol), termination of the pregnancy, and postpartum depression,[17,18] and these also deserve attention. Depression during pregnancy is a strong predictor of postpartum depression, a condition that can have dire consequences for the mother, the baby, and the entire family. Therefore, it is critical to sustain maternal emotional well-being during pregnancy.

Psychiatric evaluation of pregnant women requires careful assessment of symptoms (such as anxiety or depression) and decisions about the nature of those symptoms, including normative or pathologic, manifestation of a new-onset psychiatric disorder, and exacerbation of a previously diagnosed or undiagnosed psychiatric disorder. Unfortunately, screening for psychiatric disorders during pregnancy or the puerperium is uncommon. Even when depressed pregnant women are identified, definitive treatment is often lacking[19] and patients are often untreated or incompletely treated.[20] Screening for depression during pregnancy followed by thoughtful treatment can minimize maternal morbidity as well as the potential impact of an untreated psychiatric disorder on infant development and family functioning. Pregnancy is an emotionally laden experience that evokes a spectrum of normal reactions, including heightened anxiety and increased mood reactivity.

Normative experience needs to be distinguished from the manifestations of psychiatric disorders. Treatment of psychiatric disorders during pregnancy involves a thoughtful weighing of the risks and benefits of proposed interventions (e.g., pharmacologic treatment) and the documented[21,22] and theoretical risks associated with untreated psychiatric disorders. In contrast to many other clinical conditions, treatment of psychiatric disorders during pregnancy is typically reserved for situations in which the disorder interferes in a significant fashion with maternal and fetal well-being; the threshold for treating psychiatric disorders during pregnancy tends to be higher than with other conditions. Moreover, women with similar illness histories often make very different decisions about their care in collaboration with their physicians during pregnancy.

DIAGNOSIS AND TREATMENT OF MOOD DISORDERS DURING PREGNANCY

Although some reports describe pregnancy as a time of emotional well-being[1,23–25] that confers "protection" against psychiatric disorders, at least one prospective study describes

equal rates of major and minor depression (approximating 10%) in gravid and nongravid women. Several other studies also note clinically significant depressive symptoms during pregnancy (prenatal depression).[2,6,26,27] Women with a history of major depression appear to be at high risk for recurrence of depression during pregnancy, particularly when antidepressants have been discontinued.[5,28]

Making the diagnosis of depression during pregnancy can be difficult because disturbances in sleep and appetite, symptoms of fatigue, and changes in libido do not always indicate an evolving affective disorder. Clinical features that can support the diagnosis of major depressive disorder (MDD) include anhedonia, feelings of guilt and hopelessness, poor self-esteem, and thoughts of suicide. In addition, symptoms that interfere with function signal a psychiatric condition that warrants treatment. Suicidal ideation is not uncommon[29–31]; however, risk of clear-cut, self-injurious or suicidal behavior appears to be relatively low in women who develop depression during pregnancy.[30,31]

Treatment for depression during pregnancy is determined by the severity of the underlying disorder, by a history of treatment responses, and by individual patient preferences. Nonetheless, neurovegetative symptoms that interfere with maternal well-being require treatment. Women with mild to moderate depressive symptoms might benefit from nonpharmacologic treatments that include supportive psychotherapy,[32] cognitive therapy,[33] or interpersonal therapy (IPT),[34] all of which can ameliorate depressive symptoms. Given the importance of interpersonal relationships in couples who are expecting a child and the significant role transitions that take place during pregnancy and after delivery, IPT is ideally suited for treating depressed pregnant women; preliminary but encouraging data support the efficacy of this intervention. [35]

Using Antidepressants During Pregnancy

Several reviews have been published [28,36–40] regarding the risks associated with fetal exposure to antidepressants. Although data accumulated over the last 30 years have suggested that some antidepressants have favorable risk-to-benefit profiles during pregnancy,[41–43] information regarding the full spectrum and relative severity of risks of prenatal exposure to psychotropic medications is still incomplete. Moreover, the risks of medication use must be balanced against the risks associated with untreated psychiatric disorders that might adversely affect the mother and the fetus.

As is the case with other medications, four types of risk are typically cited with respect to potential use of antidepressants during pregnancy: risk of pregnancy loss or miscarriage, risk of organ malformation or teratogenesis, risk of neonatal toxicity or withdrawal syndromes during the acute neonatal period, and risk of long-term neurobehavioral sequelae.[42] To inform physicians about the reproductive safety of various prescription medications, the U.S. Food and Drug Administration (FDA) has established a system that classifies medications into five risk categories—A, B, C, D, and X—based on data derived from human and animal studies. Medications in category A are designated safe for use during pregnancy, whereas category X drugs are contraindicated, because they are known to have risks to the fetus that outweigh any benefit to the patient. Most psychotropic medications are classified as category C agents, for which human studies are lacking and for which risk cannot be ruled out. No psychotropic drugs are classified as safe for use during pregnancy (category A).

Unfortunately, this system of classification has noteworthy limitations. First, categorization is often ambiguous and can lead to unwarranted conclusions. For example, certain tricyclic antidepressants (TCAs) have been labeled as category D agents, indicating "positive evidence of risk," although the pooled available data do not support this assertion and, in fact, suggest that these drugs are safe for use during pregnancy.[44,45] Second, the categorization is often assigned on the basis of only a small amount of animal data and when human data are sparse or absent. Third, when larger and more rigorous studies become available on the reproductive safety profile of a medication, the category is rarely altered. Fourth, the categorization system fails to take into account the risks of the untreated maternal psychiatric disorder for the woman and her fetus. Therefore, the physician must also rely on other sources of information when counseling patients about the potential use of psychotropic medications during pregnancy.

Randomized, placebo-controlled studies that examine the effects of medication use on pregnant populations are lacking and are considered unethical. Therefore, much of the data related to the profile of reproductive safety for a medication is derived from retrospective studies and case reports. Studies that have evaluated the reproductive safety of antidepressants have used a more-rigorous prospective design,[44–49] or they have relied on large administrative databases or multicenter birth-defect surveillance programs.[50,51] Given the lack of clarity of the FDA risk categories, there will likely be a modification with the classification system that incorporates a more individualized and sophisticated approach to the use of medications in pregnancy.[52] Studies have not yet demonstrated a statistically increased risk of spontaneous miscarriage following prenatal exposure to antidepressants.[53]

Cumulative reports that describe the reproductive safety of selective serotonin reuptake inhibitors (SSRIs) have been reviewed.[39,40] These reports provide some reassurance that as a group of medicines, SSRIs are not major teratogens. Initially, some[54–57] reports suggested that first-trimester exposure to paroxetine was associated with an increased risk of cardiac defects (including atrial and ventricular septal defects). These findings prompted the FDA to change the labeling of paroxetine from category C to D, but two independent, peer-reviewed, comprehensive meta-analyses of studies assessing paroxetine exposure during the first trimester[50,51,53,58] failed to demonstrate the increased teratogenicity of paroxetine. Therefore, although it is widely believed that paroxetine might increase the risk of congenital malformations with first-trimester exposure, the most comprehensive studies to date have not supported this; paroxetine should still be considered a first-line agent for women who have responded well to it before pregnancy.

At present the data about the risk of major malformations after first-trimester use of SSRIs remain inconsistent. A large body of literature has failed to demonstrate a risk of major malformations with first-trimester exposure, but one study suggested that first-trimester use of SSRIs was

associated with increased risk of omphalocele, craniosynostosis, and anencephaly[50] and another suggested that first-trimester SSRI use was not associated with significantly increased rates of craniosynostosis, omphalocele, or cardiac defects, but it did note an increase in malformations with particular SSRIs. Sertraline was associated with omphalocele and septal defects, and paroxetine exposure was associated with right ventricular outflow tract construction defects.[51]

Bupropion may be an attractive option for women who have not responded well to fluoxetine or TCAs. Data thus far have not indicated an increased risk of malformations associated with bupropion use during pregnancy.[59–61] Bupropion deserves special consideration if a woman is attempting to abstain from smoking during pregnancy, as it helps with smoking cessation, and cigarettes are teratogenic. Bupropion may be an attractive option for women with attention deficit disorder who are receiving stimulants, because the reproductive safety profile of stimulants is more concerning than that of bupropion, an antidepressant that has been used with benefit in some patients with attention-deficit/hyperactivity disorder (ADHD).[62,63]

Limited data are available on the use of the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine[49] during pregnancy. Nonetheless, given the frequency of use of these medicines and the frequency of unplanned pregnancy[64] the data supporting the safety of venlafaxine is increasingly reassuring. Unfortunately there is little information available on the use of duloxetine in pregnancy.

Mirtazapine is a novel piperazinoazepine antidepressant; the data regarding the use of this medication during pregnancy is sparse, but in one small study it did not appear to increase the rate of major malformations.[65] Small studies of medication exposures can provide reassuring preliminary information, but large definitive trials are necessary to assess risks that might be rare and thus only observable with adequate sample sizes. Despite the growing literature that supports the relative safety of fetal exposure to SSRIs, multiple reports[46,66,67] have described adverse perinatal outcomes including decreased gestational age, low birth weight, and poor neonatal adaptation. However, others [44,68,69] have failed to note these associations. Particular concern has been raised regarding the potential effects of late-pregnancy exposure to SSRIs; one report[70] noted jitteriness, tachypnea, and tremulousness. Importantly, these effects have been described as transient (limited to several days following delivery). In general, most reports characterize as mild a neonatal syndrome following maternal use of antidepressants.

Conflicting reports have also raised a question about whether SSRI use in later pregnancy is associated with a serious but rare developmental lung condition, persistent pulmonary hypertension of the newborn (PPHN). Chambers and co-workers sounded the alarm when they found an increased risk of PPHN with SSRI use in a nested case-controlled study. They reported the risk of PPHN with exposure to SSRIs after 20 weeks at about 1%.[71] However, more-recent research has been more reassuring. Kallen and colleagues[55] also found an association between late SSRI use in pregnancy and PPHN, albeit a substantially smaller risk than that found by Chambers and co-workers.[71] The most recent study, however, failed to demonstrate any association between SSRI use during pregnancy and PPHN.[72] Readers must be mindful that PPHN is correlated with multiple risk factors including cesarean section, race, body mass index, and other factors not associated with SSRI use.[73]

Further investigation is warranted to clarify the association between SSRI use and neonatal risks, because previous studies that investigated neonatal outcomes in infants exposed to antidepressants *in utero* have not described serious complications with significant morbidity; instead neonatal adaptation syndromes have generally been considered mild, transient, and not requiring specific medical interventions. Unfortunately, the vast majority of reports that have attempted to delineate the potential effects of peripartum exposure to SSRIs have been limited by small sample size, by nonsystematic assessment of infant outcome, and by frequent use of nonblinded raters. Moreover, these studies have typically failed to assess the impact of maternal depression, which has also been associated with compromised perinatal outcome and neonatal behavioral differences.[17,22]

A limited amount of data is available on the long-term implications of *in utero* antidepressant exposure, and fluoxetine and TCAs are the best-characterized agents. In children exposed to fluoxetine, TCAs, or no medication, no differences have been detected in behavioral or cognitive development (in terms of intelligence quotient [IQ], language, temperament, behavior, reactivity, mood, distractibility, and activity level[47,68] among groups when followed through early childhood. Although the emphasis of research regarding use of antidepressants in pregnancy has addressed the effect of antidepressant drugs on risk for congenital malformation, more research is needed to assess the long-term effects of prenatal antidepressant exposure. In addition, there does not appear to be any difference in the level of internalizing behavior in children exposed to SSRIs during pregnancy compared to children of nondepressed mothers not on medication during pregnancy.[74] Therefore, while the data available are reassuring, further investigation into the long-term neurobehavioral effects of prenatal exposure to antidepressants is warranted.

Pharmacologic Treatment of Depression during Pregnancy: Clinical Guidelines

Since the turn of the century, increased attention has been directed to the question of how to best manage women who suffer from depression throughout reproductive events. Clinical lore has suggested that women enjoyed positive mood during pregnancy, but more-recent data demonstrate that many women face substantial risk for recurrence or the new onset of depression during pregnancy. There is also a greater appreciation that depression poses risks for fetal and neonatal well-being that need to be taken into account during the risk-to-benefit decision-making process.[28,37,41,43,75,76]

The majority of women who suffer from depression during pregnancy do not receive adequate treatment, despite the prevalence and consequences of untreated illness.[19] Despite the growing number of reviews on the subject, management of prenatal depression is still largely guided by experience, with few definitive data and no

controlled treatment studies to inform treatment. The best treatment algorithms depend on the severity of the disorder, the patient's psychiatric history, her current symptoms, her attitude toward the use of psychiatric medications during pregnancy, and, ultimately, the patient's wishes. Clinicians must work collaboratively with the patient to arrive at the safest treatment plan based on currently available information.

In patients with less-severe depression, discontinuation of pharmacologic therapy during pregnancy should be considered. Though data on the use of IPT or cognitive-behavioral therapy (CBT) to facilitate antidepressant discontinuation before conception are not available, it makes sense to pursue such treatment for women on maintenance antidepressant therapy who are planning to become pregnant. These treatment modalities can reduce the risk of recurrent depressive symptoms during pregnancy; however, this has not been studied systematically. Close monitoring of affective status during pregnancy is essential throughout pregnancy for women with a history of a mood disorder, regardless of whether medication is continued or discontinued. Psychiatrically ill women are at high risk for relapse during pregnancy, and early detection and treatment of recurrent illness can significantly reduce the morbidity associated with having prenatal affective illness.

Many women who discontinue antidepressants during pregnancy experience recurrent depressive symptoms.[77,78] In one study, women who discontinued their medications were five times more likely to relapse (with a rate of relapse of 68%)[5] as compared to women who maintained their antidepressants across pregnancy. Thus, women with recurrent or refractory depressive illness may decide (in collaboration with their clinician) that the safest option is to continue pharmacologic treatment during pregnancy to minimize the risk of recurrent illness. In this setting, the clinician should attempt to select medications during pregnancy that have a well-characterized reproductive safety profile that might obviate switching to one with a better reproductive safety profile.

In an ideal world, switching would occur before pregnancy and allow time for stabilization on a new medication. For example, one might switch from duloxetine, a medication for which there are sparse data on reproductive safety, to an agent such as fluoxetine or citalopram. In other situations, one may decide to use a medication for which information regarding reproductive safety is sparse, for example, a woman with refractory depression who has responded only to one particular antidepressant for which specific data on reproductive safety are limited (e.g., venlafaxine). She may choose to continue this medication during pregnancy rather than risk potential relapse associated with discontinuing the antidepressant or switching to another antidepressant for which the patient has no history of response.

Even if a woman continues taking an antidepressant during pregnancy, relapse can occur. Cohen and colleagues[5] reported that 26% of women who continue antidepressants had a relapse of MDD during pregnancy. Therefore, careful monitoring is required even if maintenance medications are continued. Only a small amount of information is available on the pharmacokinetic profile of SSRIs and newer antidepressants across pregnancy,[79–82] and some women experience lower serum medication levels in late pregnancy. Therefore, some women can require higher doses of medication as pregnancy progresses to maintain therapeutic benefits; this supports a need for frequent assessment. Older reports demonstrated that women might also have lower serum levels of TCAs in the third trimester.[45,79,80,83]

Women might also experience the new onset of depressive symptoms during pregnancy. For women who present with minor depressive symptoms, nonpharmacologic treatment strategies should be explored first. IPT or CBT may be beneficial for reducing the severity of depressive symptoms and can limit or obviate the need for medications.[33–35] In general, pharmacologic treatment is pursued when nonpharmacologic strategies have failed or when it is felt that the risks associated with psychiatric illness during pregnancy outweigh the risks of fetal exposure to a particular medication.

In situations in which pharmacologic treatment is more clearly indicated, the clinician should select medications with the safest reproductive profile. Fluoxetine and citalopram, with extensive data that support their reproductive safety, can be considered as first-line choices. Among the SSRIs, paroxetine is the most controversial (given reports regarding cardiovascular malformations with first-trimester exposure). However, more-comprehensive studies did not support this risk. Nevertheless, many women and their obstetric health care providers might remain apprehensive about use of paroxetine in pregnancy. The TCAs and bupropion have also been relatively well characterized and can be considered reasonable treatment options during pregnancy. Among the TCAs, desipramine and nortriptyline are preferred because they are less anticholinergic and less likely to exacerbate orthostatic hypotension during pregnancy. The amount of literature on the reproductive safety of the newer SSRIs is growing, and these agents may be useful in certain settings, particularly if a woman has had a good response to one of them in conjunction with poorer responses with better-characterized antidepressants.[9,48,84]

When prescribing medications during pregnancy, an attempt should be made to simplify the medication regimen. For instance, one may select a more sedating antidepressant for a woman who presents with depression and a sleep disturbance instead of using a more activating antidepressant in combination with trazodone or a benzodiazepine.

In addition, the clinician must use an adequate dosage of medication. Often the dosage of a medication is reduced during pregnancy in an attempt to limit risk to the fetus. However, this type of modification in treatment might instead place the woman at greater risk for recurrent illness. During pregnancy, changes in plasma volume and increases in hepatic metabolism and renal clearance can significantly affect drug levels.[85,86] Several investigators have described a reduction (up to 65%) in serum levels of TCAs during pregnancy.[45,83] Subtherapeutic levels may be associated with depressive relapse[45]; therefore, an increase in daily TCA or SSRI dosage may be required to obtain remission.[80]

With multiple studies supporting the finding of transient jitteriness, tremulousness, and tachypnea associated with peripartum use of SSRIs[70,87] some physicians (as well as FDA-mandated labeling across the SSRIs) have suggested

discontinuing antidepressants just before delivery to minimize the risk of neonatal toxicity. Another potential rationale for discontinuing antidepressants before delivery is derived from the assumption this would attenuate the risk of PPHN that has been associated with third-trimester exposure to SSRIs.[71] However, the recommendation is not data-driven and such a practice can actually carry significant risk because it withdraws treatment from a patient precisely as she is about to enter the postpartum period, a time of heightened risk for affective illness. In consideration of the well-characterized risks to the baby and to siblings in the family of a woman with maternal depression, treatment goals should include having a woman approach the postpartum period in remission from depression. The strategy of discontinuing medication before delivery, however, can increase the risk of a woman's entering the postpartum period with depression, and recovery could require substantial time.

Severely depressed patients who are acutely suicidal or psychotic require hospitalization and treatment; electroconvulsive therapy (ECT) is often selected as the treatment of choice. Reviews of ECT during pregnancy note the efficacy and safety of this procedure.[88–90] In a review of the 339 cases of ECT during pregnancy published since 1941, only 11 of the 25 fetal or neonatal complications, including two deaths, were likely the result of ECT. Given its relative safety, ECT may also be considered an alternative to conventional pharmacotherapy for women who wish to avoid extended exposure to psychotropics during pregnancy or for women who fail to respond to standard antidepressants.

BIPOLAR DISORDER DURING PREGNANCY

Historically, women with bipolar disorder (BPD) have been counseled to defer pregnancy (given an apparent need for pharmacologic therapy with mood stabilizers) or to terminate pregnancies following prenatal exposure to drugs such as lithium or valproic acid. However, more-recent and comprehensive data suggest that women can select treatment strategies that allow pregnancy with both the mother's and baby's safety in mind.

The risk of lithium exposure during pregnancy has been reassessed and is considered far safer than it was decades ago. Concerns regarding fetal exposure to lithium, for example, have typically been based on early reports of higher rates of cardiovascular malformations (e.g., Ebstein's anomaly) following prenatal exposure to this drug.[91,92] More recent data suggest the risk of cardiovascular malformations following prenatal exposure to lithium is smaller than previous estimates (1/2000 versus 1/1000).[93] Prenatal screening with a high-resolution ultrasound and fetal echocardiography is recommended at about 16 to 18 weeks of gestation to screen for cardiac anomalies. Nonetheless, the woman with BPD is faced with a decision regarding use of lithium during pregnancy; it is appropriate to counsel such a patient about the very small risk of organ dysgenesis associated with prenatal exposure to this medicine.

Lamotrigine is another mood stabilizer that is an option for pregnant women who have BPD and who demonstrate a clear need for prophylaxis with mood stabilizer. Although previous reports failed to show an elevated risk of malformations associated with lamotrigine exposure,[94–97] data from the North American Antiepileptic Drug Pregnancy Registry indicates an increased risk of oral cleft in infants exposed to lamotrigine during the first trimester; the prevalence was approximately 9 per 1000 births.[98]

Compared with lithium and lamotrigine, prenatal exposure to some anticonvulsants is associated with a far greater risk of organ malformation. An association between prenatal exposure to mood stabilizers, including valproic acid and carbamazepine, and neural tube defects (3% to 8%) and spina bifida (1%) also has been observed.[99–102] Fetal exposure to anticonvulsants has been associated not only with relatively high rates of neural tube defects, such as spina bifida, but also with multiple other anomalies including mid-face hypoplasia (also known as the "anticonvulsant face"), congenital heart disease, cleft lip or palate (or both), growth retardation, and microcephaly. Factors that can increase the risk for teratogenesis include high maternal serum anticonvulsant levels and exposure to more than one anticonvulsant. This finding of dose-dependent risk for teratogenesis is at variance with that for some other psychotropics (e.g., antidepressants). Thus, when using anticonvulsants during pregnancy, the lowest effective dose should be used, anticonvulsant levels should be monitored closely, and the dosage should be adjusted appropriately. Ideally, women of reproductive age should avoid treatment with valproate, and it should not be considered a first-line therapy in women with reproductive potential.

Information about the reproductive safety of newer anticonvulsants sometimes used to treat BPD, including gabapentin, oxcarbazepine, and topiramate, remains sparse.[103] Other efforts are under way to accumulate data from prospective registries regarding teratogenic risks across a broad range of anticonvulsants. The North American Antiepileptic Drug Pregnancy Registry was established as a way of collecting such information rapidly and efficiently (http://www.aedpregnancyregistry.org).

Prenatal screening for congenital malformations following anticonvulsant exposure (including cardiac anomalies) with fetal ultrasound at 18 to 22 weeks of gestation is recommended. The possibility of fetal neural tube defects should be evaluated with maternal serum alpha-fetoprotein (MSAFP) and ultrasonography. In addition, 4 mg a day of folic acid before conception and in the first trimester for women receiving anticonvulsants is often recommended. However, the supplemental use of folic acid to attenuate the risk of neural tube defects in the setting of anticonvulsant exposure has not been systematically evaluated.

Whereas use of mood stabilizers (including lithium and some anticonvulsants) has become the mainstay of treatment for managing both acute mania and the maintenance phase of BPD, the majority of patients with BPD are not treated with monotherapy. Rather, use of adjunctive conventional and newer antipsychotics has become common clinical practice for many patients with BPD. With growing data supporting the use of atypical antipsychotics as monotherapy in the treatment of BPD, patients and clinicians will seek information regarding the reproductive safety of these newer agents.

To date, abundant data exist that support the reproductive safety of typical antipsychotics; these data have been reviewed extensively elsewhere.[41] However, despite

their growing use in psychiatry, available reproductive safety data regarding the atypical antipsychotics are limited but increasing. Some patients who benefit from treatment with antipsychotics may decide with their clinician to discontinue the atypical antipsychotic or to switch to a typical antipsychotic with a better-characterized safety profile. Atypical antipsychotics are best avoided if possible, although they are not absolutely contraindicated during pregnancy. Atypical antipsychotics should be reserved for use in more-challenging clinical situations where treatment with more-conventional agents has not been helpful. Given the limited data supporting the use of typical antipsychotics as monotherapy for BPD, that course of therapy should not be pursued.

Patients with a history of a single episode of mania and prompt full recovery, followed by sustained well-being, may tolerate discontinuation of a mood stabilizer before an attempt to conceive.[93,104] Unfortunately, even among women with a history of prolonged well-being and sustained euthymia, discontinuation of prophylaxis for mania may be associated with subsequent relapse. In one study, the risk of recurrence of a mood episode during pregnancy in women who discontinued their mood stabilizer during pregnancy was 71%.[11]

For women with BPD and a history of multiple and frequent recurrences of mania or bipolar depression, several options can be considered. Some patients may choose to discontinue a mood stabilizer before conception as outlined earlier. An alternative strategy for this high-risk group is to continue treatment until pregnancy is verified and then taper off the mood stabilizer. Because the uteroplacental circulation is not established until approximately 2 weeks following conception, the risk of fetal exposure is minimal. Home pregnancy tests are reliable and can document pregnancy as early as 10 days following conception, and with a home ovulation predictor kit, a patient may be able to time her treatment discontinuation accurately. This strategy minimizes fetal exposure to drugs and extends the protective treatment up to the time of conception, which may be particularly prudent for older patients because the time required for them to conceive may be longer than for younger patients. However, a potential problem with this strategy is that it can lead to relatively abrupt discontinuation of treatment, thereby potentially placing the patient at increased risk for relapse. With close clinical follow-up, however, patients can be monitored for early signs of relapse, and medications may be reintroduced as needed.

Another problem with the strategy of discontinuing mood stabilizers when the patient is being treated with valproic acid is that the teratogenic effect of valproic acid occurs early in gestation (between weeks 4 and 5), often before the patient even knows she is pregnant. In such a scenario, any potential teratogenic insult from valproic acid may have already occurred by the time the patient actually documents the pregnancy.

For women who tolerate discontinuation of maintenance treatment, the decision of when to resume treatment is a matter for clinical judgment. Some patients and clinicians prefer to await the initial appearance of symptoms before restarting medication; others prefer to limit their risk of a major recurrence by restarting treatment after the first trimester of pregnancy. Preliminary data suggest that pregnant women with BPD who remain well throughout pregnancy might have a lower risk for postpartum relapse than those who become ill during pregnancy.[104]

For women with particularly severe forms of BPD, such as with multiple severe episodes, and especially with psychosis and prominent thoughts of suicide, maintenance treatment with a mood stabilizer before and during pregnancy may be the safest option. If the patient decides to attempt conception, accepting the relatively small absolute increase in teratogenic risk with first-trimester exposure to lithium or lamotrigine with or without an antipsychotic, for example, may be justified because such patients are at highest risk for clinical deterioration if pharmacologic treatment is withdrawn. Many patients who are treated with sodium valproate or other newer anticonvulsants, such as gabapentin, for which there are particularly sparse reproductive safety data, never received a lithium trial before pregnancy. For such patients, a lithium trial before pregnancy may be a reasonable option.

Even if all psychotropics have been safely discontinued, pregnancy in a woman with BPD should be considered a high-risk pregnancy, because the risk of major psychiatric illness during pregnancy is increased in the absence of treatment with a mood-stabilizing medication, and it is even higher in the postpartum period. Extreme vigilance is required for early detection of an impending relapse of illness, and rapid intervention can significantly reduce morbidity and improve overall prognosis. Therefore, close monitoring with assessment of mood, sleep, and other symptoms is urged throughout pregnancy and the immediate postpartum period.

Although the impact of pregnancy on the natural course of BPD is not well described, studies suggest that any "protective" effects of pregnancy on risk for recurrence of mania or depression in women with BPD are limited,[104] and the risk for relapse and chronicity following discontinuation of mood stabilizers is high.[10,105–108] Given these data, clinicians and bipolar women who are either pregnant or who wish to conceive find themselves between a teratologic rock and a clinical hard place.[109]

PSYCHOTIC DISORDERS DURING PREGNANCY

Although anecdotal reports describe improvement of symptoms in some chronically mentally ill women during pregnancy, as a group these patients are at increased risk for having poor fetal outcome.[110,111] Acute psychosis during pregnancy is an obstetric and psychiatric emergency. Similar to other psychiatric symptoms of new onset, first onset of psychosis during pregnancy requires a systematic evaluation. Psychosis during pregnancy can inhibit a woman's ability to obtain appropriate and necessary prenatal care or to cooperate with caregivers during delivery. [110–112]

Treatment of psychosis during pregnancy may include use of high-potency neuroleptics, such as haloperidol or thiothixene, which have not been associated with an increased risk of congenital malformations when used in the first trimester of pregnancy.[113,114] Historically, lower-potency antipsychotics have been avoided because of data that support an increased risk of congenital malformations associated with prenatal exposure to these compounds.[115,116] However, their use is not absolutely contraindicated.

Psychiatric consultation may be requested to consider treatment options for mild or intermittent symptoms of psychosis or for pregnant women with chronic mental illness, such as schizophrenia, who have discontinued therapy with neuroleptics. Although as-needed high-potency neuroleptics are appropriate for treating milder symptoms of psychosis, introduction or reintroduction of maintenance high-potency antipsychotics should be considered in schizophrenic women who have new-onset illness or a recurrent disorder. This approach can potentially limit overall exposure to these drugs by reducing the need for treatment with higher doses of drug during relapse. Patients with florid psychosis during labor and delivery might benefit from intravenous haloperidol, which can facilitate the patient's cooperation with the obstetrician, thereby enhancing the overall safety of the delivery.[117,118]

Less reproductive safety information on the newer atypical antipsychotic medications is available as compared to data on the conventional antipsychotics. Thus far, most of the reproductive safety data on atypical agents have often been limited to manufacturers' accumulated case series, and some terato-vigilance data that reflect a small number of total drug exposures and spontaneous reports. Data on olanzapine, clozapine, quetiapine, and risperidone are increasing but remain sparse.[119,120] The largest prospective study to date included relatively small numbers of women using olanzapine, risperidone, ziprasidone, and clozapine, but it did not demonstrate a greater risk of malformations in comparison to women who were not using medications (although users of atypical agents were more likely to smoke and to use other medications and were less likely to take prenatal vitamins). Aripiprazole was not included in this study, and at this time there are no data to inform its use in pregnancy. Although these results are somewhat reassuring, significantly larger studies are necessary to inform the reproductive safety profiles of atypical antipsychotics. To increase safety data regarding the use of atypical antipsychotic medications and pregnancy, the National Pregnancy Registry for Atypical Antipsychotics[121] and the National Register of Antipsychotic Medication in Pregnancy[122] were established.

Decisions regarding the use of these agents and other psychotropics must be made on a case-by-case basis. Given the limited data regarding the reproductive safety of atypical agents, patients taking an antipsychotic drug may choose to discontinue their medication or switch to a better-characterized conventional antipsychotic, such as perphenazine or haloperidol. However, many women do not respond as well to the typical agents or have such severe illness that making any change in their regimen can place them at significant risk. Thus, women and their clinicians may choose to use an atypical agent during pregnancy to sustain function, while acknowledging that information regarding their reproductive safety remains incomplete.

ANXIETY DISORDERS DURING PREGNANCY

Although modest to moderate levels of anxiety during pregnancy are common, pathologic anxiety (including panic attacks) has been associated with a variety of poor obstetric outcomes, including increased rates of premature labor, low Apgar scores, and placental abruption.[123–126] The course of panic disorder (PD) in pregnancy is variable. Pregnancy can ameliorate symptoms of panic in some patients and can provide an opportunity to discontinue medication.[127–130] Other studies have noted the persistence or worsening of panic-related symptoms during pregnancy.[3–5,131]

Consultation requests regarding appropriate management of anxiety symptoms during pregnancy are common. The use of nonpharmacologic treatment, such as cognitive behavior and other types of psychotherapy, may be of great value in attenuating symptoms of anxiety, and for most patients it should be part of the treatment plan.[132,133] For some patients, psychotherapy may be sufficient to manage anxiety disorders during pregnancy.

For other patients, especially those who experience panic attacks associated with new-onset or recurrent PD or those with severe generalized anxiety, pharmacologic intervention may be necessary. Many patients respond well to antidepressants, whose risks and safety profiles are discussed earlier. Concerns regarding the potential association between first-trimester exposure to benzodiazepines, such as diazepam, and increased risk for oral clefts have been noted in some older studies,[134–136] although other studies do not support this association.[137,138] One meta-analysis that pooled data from multiple samples of patients exposed to different types and doses of benzodiazepines for variable durations supported an increased risk of oral clefts following first-trimester exposure to these drugs[41]; this risk for oral clefts was approximately 0.6% following first-trimester exposure. However, a more recent meta-analysis that evaluated this potential association did not support the increased risk.[139]

For patients with PD who wish to conceive, a slow taper of their anxiolytic medications is recommended. Adjunctive CBT can help patients discontinue anti-panic agents and can increase the time to a relapse.[133] Some patients conceive inadvertently on anxiolytics and present for emergent consultation. Abrupt discontinuation of anxiolytic maintenance medication is not recommended given the risk for rebound panic symptoms or a potentially serious withdrawal syndrome. However, a gradual taper of a benzodiazepine (over more than 2 weeks) with adjunctive CBT may be pursued in an effort to minimize fetal exposure to medication.

If the taper of a medication is unsuccessful or if symptoms recur during pregnancy, reinstitution of pharmacotherapy may be considered. For patients with severe PD, maintenance medication may be a clinical necessity. TCAs or SSRIs are reasonable options for managing PD during pregnancy.[41] If patients do not respond to these antidepressants, benzodiazepines may be considered.[140] Although some patients choose to avoid first-trimester exposure to benzodiazepines (given the data on the risk for cleft lip and palate), benzodiazepines may be used without significant risk during the second and third trimesters and can offer some advantage over antidepressant treatment because they may be used on an as-needed basis.

Pharmacotherapy of severe anxiety during pregnancy includes treatment with benzodiazepines, TCAs, SSRIs, or SNRIs. These classes of drugs have demonstrated efficacy in the management of either generalized anxiety disorder (GAD)[141,142] or PD.[143–145] Pharmacologic treatment

of severe anxiety during pregnancy includes the use of TCAs or SSRIs as a nonbenzodiazepine alternative for panic attacks. Nonetheless, patients treated with an antidepressant alone for anxiety symptoms might not respond optimally. For these patients, benzodiazepines represent a reasonable alternative.

With respect to the peripartum use of benzodiazepines, reports of hypotonia, neonatal apnea, neonatal withdrawal syndromes, and temperature dysregulation[146–152] have prompted recommendations to taper and discontinue benzodiazepines at the time of parturition. The rationale for this course is suspect for several reasons. First, given data that suggest a risk of puerperal worsening of anxiety disorders in women with a history of PD and obsessive–compulsive disorder (OCD),[153–155] discontinuation of a drug at, or about the time of, delivery places a woman at risk for postpartum worsening of these disorders. Second, data describe the use of clonazepam during labor and delivery at doses of 0.5 to 3.5 mg/day in a group of women with panic disorder without evidence of perinatal sequelae.[140]

ELECTROCONVULSIVE THERAPY DURING PREGNANCY

Consideration of the use of ECT during pregnancy typically generates anxiety among clinicians and patients. However, its safety record has been well documented since the 1940s,[156–158] particularly when instituted in collaboration with a multidisciplinary treatment team, including an anesthesiologist, a psychiatrist, and an obstetrician.[90,158–160] Requests for psychiatric consultation on pregnant patients who require ECT tend to be emergent and dramatic. For example, expeditious treatment is imperative in instances of mania during pregnancy or psychotic depression with suicidal thoughts and disorganized thinking. Such clinical situations are associated with a danger from impulsivity or self-harm. A limited course of treatment may be sufficient followed by institution of treatment with one or a combination of agents (such as antidepressants, neuroleptics, benzodiazepines, or mood stabilizers).

ECT during pregnancy tends to be underused because of concerns the treatment will harm the fetus. Despite one report of placental abruption associated with the use of ECT during pregnancy,[161] considerable experience supports its safe use in severely ill gravid women. Thus, it becomes the task of the psychiatric consultant to facilitate the most clinically appropriate intervention in the face of partially informed concerns or objections.

BREAST-FEEDING AND PSYCHOTROPIC DRUG USE

The emotional and medical benefits of breast-feeding to mother and infant are clear. However, for some women, establishing breast-feeding can be difficult and can contribute to extreme sleep deprivation that can worsen the postpartum course of illness. It is important to consider the benefits and risks of breast-feeding given each woman's situation.

Given the prevalence of psychiatric illness during the postpartum period, a significant number of women might require pharmacologic treatment while nursing. Appropriate concern is raised, however, regarding the safety of psychotropic drug use in women who choose to breast-feed while using these medications. Efforts to quantify psychotropic drugs and their metabolites in the breast milk of mothers have been reported. The serum of infants can also be assayed to assess more accurately actual neonatal exposure to medications. The data indicate that all psychotropic drugs, including antidepressants, antipsychotic agents, lithium carbonate, and benzodiazepines, are secreted into breast milk. However, concentrations of these agents in breast milk vary considerably.

The amount of medication to which an infant is exposed depends on several factors[162]: the maternal dosage of medication, the frequency of dosing, and the rate of maternal drug metabolism. Typically, peak concentrations in the breast milk are attained approximately 6 to 8 hours after the medication is ingested. Thus, the frequency of feedings and the timing of the feedings can influence the amount of drug to which the nursing infant is exposed. By restricting breast-feeding to times during which breast milk drug concentrations would be at their lowest (either shortly before or immediately after dosing medication) exposure may be reduced; however, this approach might not be practical for newborns, who typically feed every 2 to 3 hours.

The nursing infant's chances of experiencing toxicity depend not only on the amount of medication ingested but also on how well the ingested medication is metabolized. Most psychotropics are metabolized by the liver. During the first few weeks of a full-term infant's life, there is a lower capacity for hepatic drug metabolism, which is about one third to one fifth of the adult's capacity. Over the next few months, the capacity for hepatic metabolism increases significantly and by about 2 to 3 months of age, it surpasses that of adults. In premature infants or in infants with signs of compromised hepatic metabolism (e.g., hyperbilirubinemia), breast-feeding typically is deferred because these infants are less able to metabolize drugs and are thus more likely to experience toxicity.

Since 1998, data have accumulated regarding the use of various psychotropics during breast-feeding.[162–165] The available data, particularly on the TCAs, fluoxetine, paroxetine, and sertraline during breast-feeding, have been encouraging and suggest that the amounts of drug to which the nursing infant is exposed are low and that significant complications related to neonatal exposure to psychotropic drugs in breast milk appear to be rare.[166–173] Typically very low or nearly undetectable levels of drug have been detected in the infant's serum; one report indicated that exposure during nursing does not result in clinically significant blockade of serotonin (5-HT) reuptake in infants.[173] Although less information is available on other antidepressants, serious adverse events related to exposure to these medications have not been reported.[163,164]

Anxiety is prevalent during the postpartum period, and anxiolytics often are used in this setting. Data regarding the use of benzodiazepines have been limited; however, the amounts of medication to which the nursing infant is exposed are low.[166] Case reports of sedation, poor feeding, and respiratory distress in nursing infants exist[148,174]; however, the data, when pooled, suggest a relatively low incidence of adverse events. [163,166]

For women with BPD, breast-feeding can pose more significant challenges. First, on-demand breast-feeding can significantly disrupt the mother's sleep and thus can increase her vulnerability to relapse during the acute postpartum period. Second, there have been reports of toxicity in nursing infants related to exposure to various mood stabilizers, including lithium and carbamazepine, in breast milk. Lithium is excreted at high levels in the mother's milk, and infants' serum levels are relatively high, about one third to one half of the mother's serum levels,[175–177] thereby increasing the risk of neonatal toxicity (which includes cyanosis, hypotonia, and hypothermia).[178] Although breast-feeding typically is avoided in women taking lithium, the lowest possible effective dosage should be used and both maternal and infant serum lithium levels should be followed in mothers who breast-feed. In collaboration with the pediatrician, the child should be monitored closely for signs of lithium toxicity, and levels of lithium, thyroid-stimulating hormone (TSH), blood urea nitrogen (BUN), and creatinine should be monitored every 6 to 8 weeks while the child is nursing.

Several studies have suggested that lamotrigine reaches infants through breast milk in relatively high doses, ranging from 20% to 50% of the mother's serum concentrations[179,180]; this may be explained by poor neonatal metabolism of lamotrigine. In addition, maternal serum levels of lamotrigine increased significantly after delivery, contributing to the high levels found in nursing infants. However, none of these studies has reported any adverse events in breast-feeding newborns. One worry shared by clinicians and new mothers is the risk for Stevens–Johnson syndrome, a severe, potentially life-threatening rash, most commonly resulting from a hypersensitivity reaction to a medication, that occurs in about 0.1% of patients who have BPD and are treated with lamotrigine.[181] Thus far, there have been no reports of Stevens–Johnson syndrome in infants exposed to lamotrigine. In fact, it appears that cases of drug-induced Stevens–Johnson syndrome are extremely rare in newborns. A single case report described a neonate who developed the syndrome after exposure to phenobarbital.[182]

Similarly, concerns have arisen regarding the use of carbamazepine and valproic acid. Both of these mood stabilizers have been associated in adults with abnormalities in liver function and with fatal hepatotoxicity. Hepatic dysfunction associated with carbamazepine exposure in breast milk has been reported several times.[183,184] Most concerning is that the risk for hepatotoxicity appears to be greatest in children younger than 2 years; thus, nursing infants exposed to these agents may be particularly vulnerable to serious adverse events. Although the American Academy of Pediatrics has deemed carbamazepine and valproic acid to be appropriate for use in breast-feeding mothers, few studies have assessed the impact of these agents on fetal well-being, particularly in mothers who are not epileptic. In women who choose to use valproic acid or carbamazepine while nursing, monitoring of drug levels and liver function testing is recommended. In this setting, ongoing collaboration with the child's pediatrician is crucial.

Consultation about the safety of breast-feeding among women treated with psychotropics should include a discussion of the known benefits of breast-feeding to mother and infant and the possibility that exposure to medications in the breast milk can occur. Although routine assay of infants' serum drug levels was recommended in earlier treatment guidelines, this procedure is probably not warranted; in most instances, infants have low or nondetectable serum drug levels and, uncommonly, serious adverse side effects have been reported. This testing is indicated, however, if neonatal toxicity related to drug exposure is suspected. Infant serum monitoring is also indicated when the mother is nursing while taking lithium, valproic acid, or carbamazepine.

PSYCHIATRIC CONSULTATION AND POSTPARTUM PSYCHIATRIC ILLNESS

The postpartum period has typically been considered a time of risk for the development of affective illness.[24] Although several studies have suggested that rates of depression during the postpartum period are equal to those in nonpuerperal controls, other research has identified subgroups of women at particular risk for postpartum worsening of mood.[26,185–187] At highest risk are women with a history of postpartum psychosis; up to 70% of women who have had one episode of puerperal psychosis experience another episode following a subsequent pregnancy.[24,187] Similarly, women with a history of postpartum depression are at significant risk, with rates of postpartum recurrence as high as 50%.[188] Women with BPD also appear to be particularly vulnerable during the postpartum period, with rates of postpartum relapse ranging from 30% to 50%.[10,186,189] The extent to which a history of MDD influences the risk for postpartum illness is less clear. However, in all women (with or without a history of MDD) the emergence of depressive symptoms during pregnancy significantly increases the likelihood of postpartum depression.[26]

Postpartum Depression

Diagnosis

During the postpartum period, about 85% of women experience some mood disturbance. For most women the symptoms are mild; however, 10% to 15% of women experience clinically significant symptoms. Postpartum depressive disorders typically are divided into three categories: postpartum blues, nonpsychotic major depression, and puerperal psychosis. Because these three diagnostic subtypes overlap significantly, it is not clear if they actually represent three distinct disorders. It may be more useful to conceptualize these subtypes as existing along a continuum, where postpartum blues is the mildest and postpartum psychosis the most severe form of puerperal psychiatric illness.

Postpartum blues does not indicate psychopathology; it is common and occurs in approximately 50% to 85% of women following delivery.[190,191] Symptoms of reactivity of mood, tearfulness, and irritability are, by definition, time-limited and typically remit by the 10th postpartum day. Because postpartum blues is associated with no significant impairment of function and is time-limited, no specific treatment is indicated. Symptoms that persist beyond 2 weeks require further evaluation and suggest an evolving depressive disorder. In women with a history of recurrent mood disorder, the blues may herald the onset of postpartum MDD.[26,192]

Several studies describe a prevalence of postpartum MDD of between 10% and 15%.[27,190] The signs and symptoms of postpartum depression usually appear over the first 2 to 3 months following delivery and are indistinguishable from the characteristics of MDD that occur at other times in a woman's life. The presenting symptoms of postpartum depression include depressed mood, irritability, and loss of interest in usual activities. Insomnia, fatigue, and loss of appetite are often described. Postpartum depressive symptoms also co-mingle with anxiety and obsessional symptoms, and women might present with generalized anxiety, PD, or hypochondriasis.[193,194]

Although it is sometimes difficult to diagnose depression in the acute puerperium given the normal occurrence of symptoms suggestive of depression (e.g., sleep and appetite disturbance, low libido), it is an error to dismiss neurovegetative symptoms (such as severe decreased energy, profound anhedonia, and guilty ruminations) as normal features of the puerperium. In its most severe form, postpartum depression can result in profound dysfunction. Risk factors for postpartum depression include prenatal depression, prenatal anxiety, and a history of depression.

Treatment

A wealth of literature on this topic indicates that postpartum depression, especially when left untreated, may have a significant impact on the child's well-being and development.[195,196] In addition, the syndrome demands aggressive treatment to avoid the sequelae of an untreated mood disorder, such as chronic depression and recurrent disease. Treatment should be guided by the type and severity of the symptoms and by the degree of functional impairment. However, before initiating psychiatric treatment, medical causes for mood disturbances (e.g., thyroid dysfunction and anemia) must be excluded. Initial evaluation should include a thorough history, physical examination, and routine laboratory tests.

Although postpartum depression is relatively common, few studies have systematically assessed the efficacy of nonpharmacologic and pharmacologic therapies in the treatment of this disorder. Nonpharmacologic therapies are useful in the treatment of postpartum depression, and several preliminary studies have yielded encouraging results. Appleby and associates[197] have demonstrated in a randomized study that short-term CBT was as effective as treatment with fluoxetine in women with postpartum depression. IPT has also been shown to be effective for treating women with mild to moderate postpartum depression.[198]

These nonpharmacologic interventions may be particularly attractive to patients who are reluctant to use psychotropic medications (e.g., women who are breast-feeding) or for patients with milder forms of depressive illness. Further investigation is required to determine the efficacy of these treatments in women who suffer from more-severe forms of postpartum mood disturbances. Women with more-severe postpartum depression may choose to receive pharmacologic treatment, either in addition to or instead of nonpharmacologic therapies.

To date, only a few studies have systematically assessed the pharmacologic treatment of postpartum depression. Conventional antidepressants (e.g., fluoxetine, sertraline, and venlafaxine) have shown efficacy in the treatment of postpartum depression.[69,197,199–201] In all of these studies, standard antidepressant doses were effective and well tolerated. The choice of an antidepressant should be guided by the patient's prior response to antidepressants and a given medication's side-effect profile. SSRIs are ideal first-line agents because they are anxiolytic, nonsedating, and well tolerated; bupropion is also another good option. TCAs are often used, and because they tend to be more sedating, they may be more appropriate for women who have prominent sleep disturbances. Given the prevalence of anxiety in women with postpartum depression, adjunctive use of a benzodiazepine (e.g., clonazepam or lorazepam) may be very helpful.

Some investigators have also explored the role of hormone manipulation in women who suffer from postpartum depression. The postpartum period is associated with rapid shifts in the reproductive hormonal environment, most notably a dramatic fall in estrogen and progesterone levels, and postpartum mood disturbance has been attributed to a deficiency (or change in the levels) in these gonadal steroids. Although early reports suggested that progesterone may be helpful,[202] no systematically derived data exist to support its use in this setting. Two studies have described the benefit of exogenous estrogen therapy, either alone or in conjunction with an antidepressant in women with postpartum depression.[203–205] Although these studies suggest a role for estrogen in the treatment of women with postpartum depression, these treatments remain experimental. Estrogen delivered during the acute postpartum period is not without risk and has been associated with changes in breast-milk production and more significant thromboembolic events. Antidepressants are safe, well tolerated, and highly effective; they remain the first choice for women with postpartum depression.

In cases of severe postpartum depression, inpatient hospitalization may be required, particularly for patients who are at risk for suicide. In Great Britain, innovative treatment programs involving joint hospitalization of the mother and the baby have been successful; however, mother-and-infant units are much less common in the United States. Women with severe postpartum illness should be considered candidates for ECT. The option should be considered early in treatment because it is safe and highly effective. In choosing any treatment strategy, it is important to consider the impact of prolonged hospitalization or treatment of the mother on the infant's development and attachment.

Postpartum Panic Attacks and Obsessive–Compulsive Disorder

Symptoms of postpartum panic attacks and OCD symptoms are often included in the description of postpartum mood disturbance, but a growing literature supports the likelihood that postpartum anxiety disorders are discrete diagnostic entities.[153,194] Several investigators have described postpartum worsening of PD in women with pregravid histories of this anxiety disorder but with an absence of co-morbid depressive illness.[4] Postpartum OCD has also been described in the absence of co-morbid postpartum MDD. Symptoms often include intrusive obsessional thoughts to harm the newborn in the absence of psychosis. Treatment with anti-obsessional agents, such as fluoxetine or clomipramine, has been effective.[155]

Postpartum Psychosis

Postpartum psychosis is a psychiatric emergency. The clinical picture is most often consistent with mania or a mixed state consistent with an episode of BPD[24] and can include symptoms of restlessness, agitation, sleep disturbance, paranoia, delusions, disorganized thinking, impulsivity, and behaviors that place mother and infant at risk. The typical onset is within the first 2 weeks after delivery, and symptoms can appear as early as the first 72 hours after delivery.

Although investigators have debated whether postpartum psychosis is a discrete diagnostic entity or a manifestation of BPD, treatment should follow the same algorithm to treat acute manic psychosis, including hospitalization and potential use of mood stabilizers, antipsychotics, benzodiazepines, and ECT.

Prevention

It is difficult to reliably predict which women will experience a postpartum mood disturbance, but it is possible to identify certain subgroups of women (e.g., women with a history of mood disorder) who are more vulnerable to postpartum affective illness. Several investigators have explored the potential efficacy of prophylactic interventions in these women at risk.[206–209]

Several studies demonstrate that women with a history of BPD or puerperal psychosis benefit from prophylactic treatment with lithium, instituted either before delivery (at 36 weeks of gestation) or no later than the first 48 hours following delivery.[206–209] Prophylactic lithium appears to significantly reduce relapse rates and diminish the severity and duration of puerperal illness.

For women with a history of postpartum depression, Wisner and colleagues[210] have described a beneficial effect of a prophylactic antidepressant (either TCA or SSRI) administered after delivery. However, a subsequent randomized, placebo-controlled study from the same group did not demonstrate a positive effect in women treated prophylactically with nortriptyline.[211] The authors have suggested that nortriptyline may be less effective than SSRIs for the treatment of postpartum depression. The efficacy of prophylactic treatment with SSRIs in this population is under investigation.

In summary, postpartum depressive illness may be conceptualized along a continuum, where some women are at lower risk for puerperal illness and others are at higher risk. Although a less-aggressive, wait-and-see approach is appropriate for women with no history of postpartum psychiatric illness, women with BPD or a history of postpartum psychiatric illness deserve not only close monitoring but also specific prophylactic measures.

PERINATAL PSYCHIATRY: FROM SCREENING TO TREATMENT

Clinicians who manage the care of female psychiatric patients before, during, and after pregnancy may be called on to evaluate women who experience a broad spectrum of difficulties. Symptoms may be mild, although the consultant is typically requested when symptoms become severe. It is not uncommon for women to present weeks or even months after the onset of psychiatric symptoms. Many women and their health care providers mistakenly believe that even serious mood symptoms are normal postpartum reactions, and many women may be afraid or embarrassed to disclose that they are suffering from depression. Psychiatric disorders may emerge anew during pregnancy, although more often clinical presentations represent persistence or exacerbation of an existing illness. Physicians therefore should screen more aggressively for psychiatric disorders either before conception or during pregnancy, integrating questions about psychiatric symptoms and treatment into the obstetric history. Identification of at-risk women allows the most thoughtful, acute treatment before, during, and after pregnancy and signals the opportunity to institute prophylactic strategies that prevent psychiatric disturbances in women during the childbearing years.

One report has described the finding that even among women with identified psychiatric illness during pregnancy, definitive treatment is often lacking or incomplete.[19] The extent to which women suffering from postpartum psychiatric illness are undertreated as a group is also very well described. Perhaps one of the reasons for failure to treat women who have psychiatric disorders during pregnancy is the concern regarding fetal exposure to psychotropics. Many clinicians can conceptualize the need to weigh relative risks of fetal exposure on the one hand versus the risk of withholding treatment on the other. However, given the inability to absolutely quantify these risks, clinicians often defer treatment entirely and consequently put patients at risk for the sequelae of untreated maternal psychiatric illness. Clinicians should realize that the process of managing psychiatric illness during pregnancy and the puerperium is not a process like threading a needle; it is not clear-cut, and much treatment described in the literature is not evidence-based. However, thoughtful decisions can still be made with these patients as clinicians review available information with them and as clinician and patient realize that no decision is risk-free and no decision is perfect. Thoughtful treatment decisions can be made nonetheless, taking into account available information regarding relative risks of treatment and the patient's wishes.

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Culture and Psychiatry

David C. Henderson, M.D.
Dana Diem Nguyen, M.D.
Marketa M. Wills, M.D.
Gregory L. Fricchione, M.D.

Gender, race, ethnicity, and culture may all have a tremendous impact on the diagnosis, treatment, and outcome for many individuals with psychiatric and medical problems. Although understanding every culture is impossible, use of some basic principles will help minimize clashes of cultures and lessen the risk of providing compromised medical care. When evaluating and treating a patient from a different culture, the clinician must be careful when making observations or applying stereotypes. The clinician must be aware at all times of his or her own feelings, biases, and stereotypes. In addition, the consulting psychiatrist must assess the impact of the hospital environment, the attitudes of the medical and ancillary care team, and the patient's experience within the health care system. Mistrust of the health care system is common and may influence a patient's behavior, level of cooperation, and adherence with recommendations. On the other hand, disparities in health care delivery exist and are influenced by factors such as gender, race, ethnicity, and culture.[1] Understanding a patient's culture will aid in the delivery of high-quality medical and psychiatric care. However, a little knowledge may be a dangerous thing. Variability among individuals is common; a patient may not fit into preconceived notions of his or her culture. The clinician must probe for cultural clues while remaining flexible enough to recognize that a patient's patterns and behaviors do not necessarily match the clinician's expectations.

CULTURE

Culture comprises a pattern of beliefs, customs, and behaviors, which a group (or people) acquire socially and transmit from one generation to another through symbols, shared meanings, teachings, and life experiences. It provides the tools by which people of a given society adapt to their physical environment, their social environment, and one another. It organizes groups with ready-made solutions to the problems and challenges that a people often face. Culture (as exemplified by art, literature, architecture, tools, machines, food, clothing, and means of transportation) can be observed directly through the five senses and through items collected in a museum or recorded on film. Other aspects of culture must be observed indirectly, usually through the behavior of people. These include the beliefs and values of the people, the reasons for considering some things sacred and other things ordinary, the things and events of which they are proud or ashamed, and the sentiments that underlie patriotism or chauvinism.

Each society establishes its own criteria regarding which forms of behavior are acceptable or abnormal and which represent a medical problem. Understanding an individual's culture or working with bicultural and bilingual interpreters may help clarify normal and abnormal behaviors. It is also important to recognize that an individual may have multiple cultures or subcultures that influence his or her behaviors. The consulting psychiatrist must often employ the skills of a detective to verify whether a patient's statements or beliefs are appropriate to his or her environment, heritage, and culture.

Cultural Assessment

A cultural assessment related to diagnosis and treatment should be included in the clinician's formulation of patients and their problems. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[2] Appendix I, provides an outline for cultural formulations. The DSM-IV emphasizes that a clinician must take into account an individual's ethnic and cultural context in the evaluation of each of the DSM-IV axes. This process, called *cultural formulation*, contains the following components:

Determination of Cultural Identity

Ethnic or cultural references and the degree to which individuals are involved with their culture of origin and their host culture are important. It is crucial to listen for clues about culture and ask specific questions concerning a patient's cultural identity. For instance, an Asian-American man who grew up in the southern United States may exhibit patterns, behaviors, and views of the world that are more consistent with those of a Caucasian southerner. Attention to language abilities and preferences must also be addressed.

Determination of Cultural Explanations

How an individual understands distress or the need for support is often communicated through symptoms (e.g., nerves, possession by spirits, somatic complaints, misfortune); therefore, the meaning and severity of an illness in relation to one's culture, family, and community should be determined. This explanatory model may be helpful when developing an interpretation, a diagnosis, and a treatment plan.

Determination of Psychosocial Function

Cultural factors can have a significant impact on the psychosocial environment and on function. Cultural interpretations of social stress, support, and one's level of disability and function must also be addressed. It is the physician's responsibility to determine the level of disability and help the patient and his or her family adjust to role changes caused by illness.

Determination of the Relationship Between the Clinician and the Patient

Cultural aspects of the relationship between the individual and the clinician should be considered. Moreover, cultural differences and their impact on the treatment must not be ignored. Language difficulties, difficulties eliciting symptoms or understanding their cultural significance, difficulties negotiating the appropriate relationship, and difficulties determining whether a behavior is normal or pathologic are common barriers to care. In the hospital the consulting psychiatrist must also attend to the environment in which the patient is receiving treatment. An intervention of this nature may improve the comfort of patients and their health care providers and the quality of the care provided.

Impact of Ethnicity on Psychiatric Diagnosis

In the United States, race and ethnicity have a significant impact on psychiatric diagnosis and treatment.[3–5] The need to reduce disparities in the mental health care of racial and ethnic minorities was recently underscored by the United States Surgeon General.[6] African Americans are frequently misdiagnosed as having schizophrenia when instead they have bipolar disorder or a psychotic depression. Moreover, treatment approaches and responses often differ depending on the diagnosis. The reasons for misdiagnosis are complicated. They include the fact that individuals from some ethnic or cultural backgrounds may present to the medical system later in the course of their illness than do Caucasian individuals; this results in the perception of a more severe illness.[5] The late presentation may be related in part to mistrust of the health care system. Physician biases also play a major role in misdiagnosis. Psychiatric diagnoses are often established by eliciting symptoms from patients that are then interpreted by the psychiatric expert. Many disorders have overlapping symptoms and can be used to support one diagnosis or disregard another. In the case of African Americans, affective symptoms are frequently ignored and psychotic symptoms are emphasized. This pattern has also been seen in other ethnic populations, including Hispanics, some Asian populations, and the Amish in the United States. African American patients are also more likely to receive higher doses of antipsychotics and depot preparations and to have higher rates of involuntary psychiatric hospitalizations and significantly higher rates of seclusion and restraints while in psychiatric hospitals.[3,5,7] The tendency is to oversedate such patients to reduce their so-called risk of violence despite, in some cases, little evidence that the patient was ever violent. These biases in psychiatric treatment continue and must be addressed.

Differences in Presentation of Illness

Cultural differences in the presentation of psychiatric illnesses abound. For instance, a Cambodian woman may present with complaints of dizziness, fatigue, and back pain, while she ignores other neurovegetative symptoms and is unable to describe feelings of dysphoria. American mental health care providers are generally unfamiliar with various Indo-Chinese culture-bound syndromes and with the meaning attributed to those symptoms by various cultures.[8,9] For example, common American expressions such as "feeling blue" cannot be readily translated into Indo-Chinese languages. A Cambodian clinician will ask Cambodian patients if they "feel blue" by using Cambodian terms which literally translate as "'heavy, overcast, gloomy." The Laotian way of describing feeling "tense" is feeling "like a balloon blown up until it is about to burst." Westermeyer,[10] in a case-controlled study in Laos, documented the general inability of Western psychiatrists to recognize the Laotian symptoms of depression.

Psychiatrists and primary care physicians who search for biological and structural reasons for complaints (e.g., back pain, headaches, and dizziness) may miss depression. Afflicted patients are often treated with meclizine for dizziness and analgesics for pain when an antidepressant would have been most appropriate.

From a cross-cultural perspective, evaluating the meanings of bizarre delusions, hallucinations, and psychotic-like symptoms remains a clinical challenge. A nonpsychotic patient may admit to hearing the voices of her ancestors (a feature that is culturally appropriate in certain cultural groups). In many traditional, non-Western societies, spirits of the deceased are regarded as capable of interacting with and possessing those still alive. It is difficult to determine whether symptoms are bizarre enough to yield a diagnosis of schizophrenia without an adequate understanding of a patient's sociocultural and religious background. On the other hand, caution must be taken not to assume that bizarre symptoms are culturally appropriate when in fact they are a manifestation of psychosis. The use of bicultural and bilingual interpreters, along with the search for information from other sources (e.g., family, community leaders, religious officials), may help determine whether an individual's experience is culturally appropriate or acceptable.

Additionally, while a great deal of attention has been paid to the study of panic disorder in Caucasians, little empirical research within the United States has looked at the phenomenology of panic disorder among minority groups. Compared with their Caucasian peers, African Americans with panic disorder report more intense fears of dying or going crazy, higher levels of numbing and tingling in their extremities, and higher rates of co-morbid posttraumatic stress disorder (PTSD) and depression. African Americans also use somewhat different coping strategies (e.g., religious practice and counting one's blessings) and endorse less self-blame. The incidence of isolated sleep paralysis is also higher in African Americans.[11]

Acculturation and Immigration

Recent immigrants or refugees arrive in the United States with a host of difficulties and psychosocial problems. A physician must ask about, and make an effort to

understand, the circumstances surrounding immigration. An individual may have been a political prisoner or a victim of trauma and torture, or he or she may have been lost or separated from family members. Under these circumstances the level of depression and PTSD experienced may be high. Literature on the contribution of acculturative stresses to the emergence of mental disorder is abundant.[12] The impact of acculturation may also lead to symptoms of depression, anxiety, "culture shock," and even PTSD-like symptoms.

The trauma and torture experienced by many refugees are also unfamiliar to the majority of American practitioners.[8] In spite of the numerous reports of the concentration camp experiences in Cambodia; the sexual abuse of Vietnamese boat women; and the serious emotional distress associated with escape, refugee camps, and resettlement experiences, limited research exists on refugee trauma and trauma-related psychiatric disorders and social handicaps.

Culture-Bound Syndromes

A culture-bound syndrome is a collection of signs and symptoms that is restricted to a limited number of cultures by reason of certain psychosocial features. Culture-bound syndromes are usually restricted to a specific setting, and they have a special relationship to that setting. Because culture-bound syndromes are classified on the basis of common etiology (e.g., magic, evil spells, angry ancestors), clinical pictures may vary.

Projection is a common ego defense mechanism in many non-Western cultures. Guilt and shame are often projected into cultural beliefs and ceremonies. Guilt and shame are attributed to other individuals, groups, or objects and may involve acting out, blaming others, and needing to punish others. Projection is also seen in magic and supernatural perspectives of existence. This leads to projective ceremonies and may lead to illness when the ceremonies are not performed.

Cultural psychoses are difficult to define. In cultural syndromes hallucinations may be viewed as normal variants. Delusions and thought disorder must be re-evaluated within a particular cultural setting. A culture may interpret abnormal behavior as relating to some kind of voodoo or anger and may regard the symptoms as normal even though symptoms are consistent with schizophrenia. Table 47–1 lists a number of culture-bound syndromes and the countries or regions where they have been described.

In the past it was believed that culture-bound syndromes occurred only in the country or region of origin. However, with significant population movements and the tendency for immigrants to remain within their culture (despite having moved to a new country), culture-bound syndromes have been observed in other parts of the world. One common culture-bound syndrome is *ataque de nervios*, which is commonly known and observed in Hispanic populations. As with many culture-bound syndromes, there may be significant overlap with DSM-IV psychiatric diagnoses. In one study 36% of Dominican and Puerto Rican subjects[13] diagnosed with *ataque de nervios* also met the criteria for panic attacks, although the features did not necessarily present together during the *ataque* episode.[13]

TABLE 47–1 Culture-Bound Syndromes

SYNDROME	CULTURE
Sleep paralysis *(amafufanyane)*	Zulu population of southern Africa
Sudden mass assault *(amok/benz)*	Malaysia, Indonesia, Laos, Philippines, Polynesia (called *cafard* or *cathard*), Papua New Guinea, Puerto Rico (called *mal de pelea*), and the Navajo (*itch'aa*)
Ataque de nervios	Latin American and Latin Mediterranean groups
Boufée delirante	West Africa and Haiti
Genital retraction *(koro)*	China and Malaysia
Startle-matching *(Latah)*	Malaysia and Indonesia
Running *(piblokto)*	Eskimos
Falling-out or blacking-out	Southern United States and Caribbean groups
Fright illness (hexing, voodoo, ghost illness)	Africa, Brazil, and native West Indians in Haiti
Ghost sickness	Kiowa Apache Indians
Mal de ojo "evil eye"	Mediterranean cultures and elsewhere
Qi-gong psychotic reaction	China
Taijin kyofusho	Japan
Shenjing shuairo or neurasthenia	China
Susto (meaning fright or soul loss)[17]	Hispanics in the United States, Mexico, Central America, and South America

Working with Interpreters

Communication problems are common even between English-speaking doctors and patients from similar socioeconomic backgrounds. Therefore it is not difficult to imagine the challenges and obstacles that a physician faces when working with limited-English–speaking patients whose culture may be unfamiliar to the doctor. Misunderstandings or a lack of comprehension about a patient's physical or psychiatric complaints may lead to misdiagnosis and result in unnecessary or inappropriate treatment. Patients, in turn, may feel frustrated, discouraged, or dissatisfied with their health care; this may lead them to refuse treatment or terminate their visits altogether.[14] Fortunately, interpreters can help bridge the communication gap between doctors and non–English-speaking patients.

Many states now have laws that require federally funded medical facilities to provide interpreters for their non–English-speaking patients. Whereas many interpreters are trained and certified to work with medical providers, translating for a mental health professional is very different and potentially challenging. Both interpreters and clinicians need to be aware of issues that may arise when using

interpreters in psychiatric settings. Some of the issues that clinicians face when working with interpreters may include the following[15]:

- Clinicians may feel they have less control in their work because their direct contact with the patient is decreased by the presence of the interpreter.
- Clinicians may feel uncertain about their role when working with interpreters who are more active and involved in the treatment process.
- Clinicians may have transference issues toward the interpreter.
- Conflicts may arise when clinicians and interpreters hold opposing views on a patient's diagnosis and treatment plans.
- Interpreters may find it difficult to work with clinicians of a different gender than their own.
- Clinicians may feel frustrated when they cannot verify what is being said to the patient.
- Clinicians may feel left out if the patient appears to have more of a connection with the interpreter.
- Interpreters may feel uncomfortable when asked to translate certain issues (e.g., sexual history or childhood abuse).

Recommendations When Working with Interpreters

Clinicians need to know the qualifications of interpreters. Do the interpreters have experience working with psychiatrists and psychologists? How much do they know about mental illness and mental health services? What are their personal views about mental illness? Interpreters who come from cultures wherein mental illness is highly stigmatized may bring biases or beliefs into the therapeutic process. It is well known that patients from certain cultures have been advised by their interpreters not to seek mental health services because only "crazy" people see psychiatrists and psychologists.

Clinicians should avoid using family members, friends, or clerical staff as interpreters.[16] Patients may not be able to disclose certain information in front of spouses or children. At the same time, it may be too difficult or distressing for a young child to have to hear certain details about his or her parent. In addition, family members have been known to omit or alter information they feel is too embarrassing or inappropriate to reveal to the clinician. In the past janitors and clerical staff were used as interpreters. This, of course, is strongly discouraged because cleaning and clerical staff may not have adequate medical or mental health language skills to provide accurate translations for clinicians. Unless there are no other alternatives, clinicians should avoid using family members and clerical employees as interpreters.

Trained interpreters should be treated as professional colleagues by clinicians.[16,17] Most interpreters are now well trained and can offer important cultural knowledge that can help promote the doctor–patient relationship. Clinicians should use the interpreters' language skills as well as their cultural expertise to help increase the clinician's understanding of the patient's culture, religion, and worldview. For some clinicians, interpreters are used only as voices to communicate with patients. These clinicians prefer word-for-word translations and do not want the interpreter to filter or alter what the patients say. Although this allows the clinician to maintain his or her role as the primary caregiver and to a certain extent control for what is being said to the patient, using direct translations can often lead to misunderstandings and confusion for both the patient and the clinician.

Literal translations from one language to another can be inaccurate and inappropriate. For example, "feeling blue," when translated word-for-word into Vietnamese, does not make any sense to the patients because it literally translates to "*cam giac xanh*," which means "feeling color blue." Certain words or concepts, such as depression and mental health, may not exist in the patient's country of origin. Interpreters may have to explain or describe the concept of depression to the patient, which requires much more time than what the clinician might expect. Clinicians must be patient, keeping in mind that it may take 10 minutes to translate one word. In addition, certain issues may be culturally inappropriate to discuss with a patient. Most women from Asian and Hispanic backgrounds feel uncomfortable if asked directly about sensitive topics (e.g., sexual abuse, family discord). Interpreters can be used as cultural consultants to assist clinicians with these more complex cases. Allowing interpreters the freedom and flexibility to re-phrase or summarize what is being said can help prevent misunderstandings and improve the exchange between the clinician and the patient.

Clinicians should meet with the interpreter briefly before each session to discuss expectations and clarify any issues or points that the clinician would like to address during the session.[15,16] Patients do not get as much time with the clinicians when they have to go through interpreters. Because everything must be translated back and forth, clinicians may find that they do not get as much accomplished in their session as they do with English-speaking patients. Time is a crucial factor when interpreters are involved. Thus clinicians should protect the patient's time by deferring any discussions with the interpreters that can wait until after the session.

Clinicians should always remember to introduce the interpreter to the patient at the start of the session if they have not met. This is also a good time to reaffirm issues of confidentiality.[15,16] Many patients feel uneasy about revealing personal issues or conflicts to members of their own community. Because most ethnic communities are small and close-knit, patients may fear that the interpreter will divulge their private information to others in the community. Patients are more likely to open up if they feel reassured that what they share with the clinician and interpreter will be kept in strict confidence. If possible, clinicians should try to use the same interpreter to help build trust and ensure continuity of care for the patient.[18]

During sessions clinicians should face and speak directly to the patients rather than the interpreters.[15–17] Although the patient and clinician may not be able to communicate through language, they can communicate and connect through eye contact, gestures of acknowledgment, and other nonverbal behaviors. It is helpful for the interpreter if the clinician can speak slowly and avoid using long and complicated sentences. The clinician should eschew technical or psychological terminology that does not translate easily and pause often to allow the interpreter time to translate. It is important to ask for clarification if there is

any confusion.[17] Two-way conversations should be avoided. Just as clinicians and interpreters should not engage in lengthy discussions in front of the patient, clinicians should interrupt when the patient and interpreter are talking for too long a time. Tension may arise when someone in the group feels left out.

After each session the clinician should encourage the interpreter to give his or her impression of the session; the interpreter often can provide important observations and feedback.[15] The clinician should ask the interpreter to clarify any issues or points that were not clear during the session. Clinicians can use this time to learn more from the interpreter about the patient's culture. The clinician and interpreter can also provide feedback about each other's performances. Good communication and trust between the clinician and interpreter are essential to care for patients with little or limited English.

ETHNICITY AND PSYCHOPHARMACOLOGY

There is emerging research on transcultural psychopharmacology (i.e., ethnopsychopharmacology)[19,20] that may aid the clinician's effective treatment of diverse populations. An understanding of ethnicity and its psychopharmacology and psychobiology is necessary to ensure high-quality care for ethnic minorities. Biological and nonbiological issues have a significant impact on the use of psychotropic medications.

Culturally shaped beliefs play a major role in determining whether an explanation about an illness and a treatment plan will make sense to a patient (explanatory models); for example, Hispanics or Asians often expect rapid relief with treatment and are cautious about potential side effects associated with Western medicine. Concerns about addictive and toxic effects of medications also arise. Some populations continue to use a mixture of herbal medicines and typically believe that polypharmacy is more effective. The use of herbal medicines is of great concern because of the risk of drug interactions and medical or psychiatric side effects or toxicity. The Food and Drug Administration (FDA) has issued a number of warnings on herbal medicine products, including the most popular weight loss products containing *Ephedra sinica (ma huang)*, which is the main plant source of ephedrine and which has been reported to cause mania, psychosis, and sudden death.

Patient compliance may be affected by incorrect dosing, medication side effects, and polypharmacy. Other factors include a poor therapeutic alliance and a lack of community support, money, or transportation; in addition, substance abuse or concerns about the addictiveness of a medication may be crucial. Communication difficulties and divergence between a patient's and a clinician's explanatory model play important roles in why a patient from an ethnic minority is significantly more likely to drop out of treatment. Exploring these beliefs will improve communication, adherence, and outcome.

Examining each patient's social support systems is vital. The ways in which a family interacts and functions have a significant impact on psychiatric treatment. For example, some Hispanics have more interactions with relatives and may become increasingly demoralized when their relatives are not involved in their treatment. Hispanics and Asians typically have a "closed network," which consists of family members, kin, and intimate friends.

Biological Aspects of Psychopharmacology

Pharmacokinetics deal with metabolism, blood levels, absorption, distribution, and excretion of medications. However, other pharmacokinetic variables (e.g., conjugation, plasma protein–binding, and oxidation by the cytochrome [CYP] isoenzymes) also play a role. Pharmacokinetics may be influenced by genetics, age, gender, total body weight, environment, diet, toxins, drugs, and use of alcohol, as well as disease states. Environmental factors include medications, drugs, herbal medicines, steroids, dietary factors, sex hormones, and use of caffeine or tobacco.

The activity of CYP liver enzymes is controlled genetically, although environmental factors can alter their activity. Understanding how pharmacokinetics and environmental factors relate to different populations will help the clinician predict side effects, blood levels, and potential drug–drug interactions. For example, CYP 2D6 is the isoenzyme that metabolizes many antidepressants (including the tricyclic and heterocyclic antidepressants and the selective serotonin reuptake inhibitors [SSRIs]); SSRIs can inhibit this enzyme, leading to accumulations of other substrates. CYP 2D6 also plays a role in metabolizing antipsychotics such as clozapine, haloperidol, perphenazine, risperidone, thioridazine, and sertindole. Although much emphasis has been placed on the CYP 2D6 metabolism of psychotropics, it is a major enzyme for the metabolism of numerous nonpsychotropic medications as well. This fact, which is often ignored clinically, can have a significant effect on the tolerability or toxicity of medications.

The incidence of "poor metabolizers" (i.e., individuals with little enzyme activity) at the CYP 2D6 is roughly 0.5% to 2.4% in Asian populations, 3% to 7.3% in Caucasians, 3.1% in Mexican Americans, 3.6% in Nicaraguans, and 1.9% in Tanzanians. African Americans and blacks have now been found to have 2% to 8% poor metabolism.[21–25] CYP 2D6*4 (CYP 2D6B) appears to be responsible for poor metabolizers in Caucasians. CYP 2D6*17 and CYP 2D6*10 are found in individuals of African and Asian origin, respectively, and are responsible for lower enzyme (intermediate or slow metabolizers). Individuals from these backgrounds are at great risk for toxicity, even when medications are used at low doses. For instance, a woman who develops hypotension and a change in mental status several days after starting 20 mg of nortriptyline may be found to have toxic blood levels and require cardiac monitoring. Table 47–2 lists drugs that are metabolized through different CYP enzyme systems.

Recently, a genetic variation of the extensive metabolizer gene that decreases activity at the CYP 2D6 enzymes by approximately 50% ("slow metabolizer") was discovered. This group appears to have enzyme activity levels that are intermediate between poor and extensive metabolizers.[19,26–30] One study found CYP 2D6*17 in 33% of African Americans and a reduced capacity to metabolize dextromethorphan, a CYP 2D6 probe drug.[21–22] Additionally, approximately 33% to 37% of Asians are considered

TABLE 47–2 Cytochrome P450 Isoenzymes, Substrates, Inhibitors and, Inducers

CYP	CYP 1A2	CYP 2C9/10	CYP 2C19	CYP 2D6	CYP 2E1	CYP 3A3/4
Inhibitors						
	Fluvoxamine	Fluvoxamine	Fluoxetine	Bupropion	Diethylithio-carbamate (Disulfiram)	Fluoxetine
	Moclobemide	Disulfiram	Fluvoxamine	Fluoxetine		Fluvoxamine
	Cimetidine	Amiodarone	Imipramine	Fluvoxamine		Nefazodone
	Fluoroquinolones	Azapropazone	Moclobemide	Hydroxybupropion		Sertraline
	Ciprofloxacin/ norfloxacin	D-propoxyphene	Tranylcypromine	Paroxetine		Diltiazem
		Fluconazole	Diazepam	Sertraline		Verapamil
	Naringenin (grapefruit)	Fluvastatin	Felbamate	Moclobemide		Dexamethasone
		Miconazole	Phenytoin	Fluphenazine		Gestodene
	Ticlopidine	Phenylbutazone	Topiramate	Haloperidol		Clarithromycin
		Stiripentol	Cimetidine	Perphenazine		Erythromycin
		Sulfaphenazole	Omeprazole	Thioridazine		Troleandomycin
		Zafirlukast		Amiodarone		Fluconazole
				Cimetidine		Itraconazole
				Methadone		Ketoconazole
				Quinidine		Ritonavir
				Ritonavir		Indinavir
						Amiodarone
						Cimetidine
						Mibefradil
						Naringenin (grapefruit)
Inducers						
	Tobacco	Barbiturates	Rifampin		Ethanol	Carbamazepine
	Omeprazole	Phenytoin			Isoniazid	Barbiturates
		Rifampin				Phenobarbital
						Phenytoin
						Dexamethasone
						Rifampin
						Troglitazone

CYP	CYP 1A2	CYP 2C9/10	CYP 2C/19	CYP 2D6	CYP 2E1	CYP 3A3/4	
Substrates							
	Tertiary amine TCAs	THC	Citalopram	Fluoxetine	Ethanol	Carbamazepine	Amiodarone
	Clozapine	NSAIDs	Moclobemide	Mirtazapine	Acetaminophen	Alprazolam	Disopyramide
	Olanzapine	Phenytoin	Tertiary amine TCAs	Paroxetine	Chlorzoxazone	Diazepam	Lidocaine
	Caffeine	Tolbutamide	Diazepam	Venlafaxine	Halothane	Midazolam	Propafenone
	Methadone	Warfarin	Hexobarbital	Secondary & tertiary amine TCAs	Isoflurane	Triazolam	Quinidine
	Tacrine	Losartan	Mephobarbital	Trazodone	Methoxyflurane	Buspirone	Erythromycin
	Acetaminophen	Irbesartan	Omeprazole	Clozapine	Sevoflurane	Citalopram	Androgens
	Phenacetin		Lansoprazole	Haloperidol		Mirtazapine	Dexamethasone
	Propranolol		Phenytoin	Fluphenazine		Nefazodone	Estrogens
	Theophylline		S-Mephenytoin	Perphenazine		Reboxetine	Astemizole
	Warfarin		Nelfinavir	Risperidone		Sertraline	Loratadine
			Warfarin	Sertindole		Tertiary amine TCAs	Terfenadine
				Thioridazine		Sertindole	Lovastatin
				Codeine		Quetiapine	Simvastatin
				Dextromethorphan		Ziprasidone	Atorvastatin
				Hydrocodone		Diltiazem	Cerivastatin
				Oxycodone		Felodipine	Cyclophosphamide
				Mexiletine		Nimodipine	Tamoxifen
				Propafenone		Nifedipine	Vincristine
				(IC antiarrhythmics)		Nisoldipine	Vinblastine
				β-blockers		Nitrendipine	Ifosfamide
				Donepezil		Verapamil	Cyclosporine
				d-fenfluramine		Acetaminophen	Tacrolimus
						Alfentanil	Cisapride
						Codeine	Donepezil
						Fentanyl	Lovastatin
						Sufentanil	Protease inhibitors
						Ethosuximide	Sildenafil
						Tiagabine	Disopyramide
						Warfarin	Losartan

NSAID, Nonsteroidal antiinflammatory drug; *TCA*, tricyclic antidepressant; *THC*, tetrahydrocannabinol.

"slow metabolizers," whereas 34% of Nicaraguans and 18% of Mexican Americans were found to be slow metabolizers. [29,31] This may explain ethnic differences in the pharmacokinetics of neuroleptics and antidepressants. Although these individuals are not as likely to experience toxicity at extremely low doses (e.g., poor metabolizers), they are likely to experience significant side effects at lower doses. These individuals may quickly be classified as "difficult patients" because they complain of side effects at unexpectedly low doses. The preceding information is striking considering that numerous studies have shown that African Americans, for instance, receive higher doses of antipsychotics, are more frequently treated with depot neuroleptics, and have higher rates of involuntary commitments and seclusion and restraints than do Caucasians. Whereas data on pharmacokinetics of neuroleptics have been mixed in African Americans, Asians have been shown to have a higher "area under the curve" for haloperidol.[20,32] Korean Americans have also been found to have higher blood levels of clozapine and to respond to lower doses of clozapine compared with Caucasians. In fact, although sertindole, metabolized by CYP 2D6, did not make it to the U.S. market, the phase II clinical trials included a sufficient number of African Americans to determine that their sertindole blood levels were 50% higher than Caucasian subjects who took the same dose.

The CYP 2C9 isoenzyme is involved in the metabolism of ibuprofen, naproxen, phenytoin, warfarin, and tolbutamide. Approximately 18% to 22% of Asians and African Americans are poor metabolizers of these drugs. CYP 2C19 is involved in the metabolism of diazepam, clomipramine, imipramine, and propranolol; it is inhibited by fluoxetine and sertraline. The rates of poor metabolizers of this enzyme are approximately 3% to 6% in Caucasians, 4% to 18% in African Americans, and 18% to 23% in Asians.[19,20]

Although ethnic or racial differences in metabolism at the 3A enzyme system have not been fully evaluated,[33–34] numerous substances have been found to either inhibit or induce this enzyme. Inhibitors include medications such as fluoxetine, fluvoxamine, nefazodone, norfluoxetine, clozapine, haloperidol, diltiazem, verapamil, gestodene, erythromycin, itraconazole, ketoconazole, and ritanovir. Grapefruit juice and corn have also been found to inhibit this enzyme system. This is clinically relevant because there are populations (including some Asian groups and Mexicans and Mexican Americans) that consume corn as a regular part of their diet. Many years ago, the "grapefruit juice diet" led to many patients having side effects with medications that were previously well tolerated.

Additionally, there is a CYP 3A4 "G" variant that is more common in African American men than Caucasian men. Within African American men, the "GG" (odds ratio 11.9) and "AG" (odds ratio 9.3) genotypes were associated with a risk of aggressive prostate cancer.[35]

Finally, lithium appears to be a drug with significant differences in dosing and tolerability across populations. African Americans are more likely to experience lithium toxicity and delirium compared with Caucasians (likely related to a slower lithium–sodium pathway and connected to higher rates of hypertension). Some Asian populations respond to lower doses and have lower serum levels of lithium (0.4 to 0.8 mEq/L).[19]

Also, the choice of medications, particularly atypical antipsychotics, should be tempered by an understanding of individual and population risk factors for medical morbidities (e.g., obesity, hypertension, diabetes mellitus, cardiovascular disease). For instance, many of the reports of diabetic ketoacidosis secondary to atypical agents have been in African Americans who are at higher risk for diabetes.[36,37]

THE "MEDICAL OMBUDSMAN" ROLE

In 1988 Pasnau[38] enumerated six fundamental functions of the consultation–liaison psychiatrist, including the role of "medical ombudsman" for the patient. Although the use of this term did not catch on, it signified the sometimes important need of medical and surgical teams to be reminded of the unique human nature of each patient in their care. Racial, ethnic, and cultural factors are obviously important characteristics of individuals. Psychiatrists in the general hospital can present these factors in their consultations and, as a result, enrich patient care.

TECHNIQUES TO MINIMIZE CULTURAL CLASHES AND MISDIAGNOSIS

Certain techniques may be employed to avoid misdiagnosis, mistreatment, and cultural clashes. The first moments of an encounter are often crucial. A clinician must be respectful to all patients and address them formally (e.g., Mr., Ms., or Mrs.). In some cultures an informal introduction is considered disrespectful and may have a lasting impact on the physician–patient relationship.

The relationship will be more complex and require more time to develop trust and an alliance. It will also take time to assure patients about confidentiality and educate them about mental illness to counteract stigmas that may be influenced by culture. Also, if the diagnosis is unclear or affected by ethnicity or culture, the clinician should consider a structured diagnostic interview (e.g., the structured clinical interview for DSM disorders [SCID]) to reduce the possibility of misdiagnosis. Finally, it is important to acknowledge the need to spend more time with patients from different cultures. A clinician must have patience and should expect longer sessions when using an interpreter.

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Legal Aspects of Consultation

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Ronald Schouten, M.D., J.D.
Rebecca W. Brendel, M.D., J.D.

Legal issues are common and acknowledged, although not willingly accepted, aspects of modern medicine. Physicians respond to these issues in various ways, ranging from denial of their existence, to resentment at the perceived intrusion into patient care they create, to obsessive concern that can ultimately interfere with good clinical care.

Although it is true that legal issues are ever-present, and at times are the dominant concerns of patients and providers, for the most part they exist in the background of care. When specific legal issues do arise, medical and surgical physicians often turn to the consultation psychiatrist for assistance (perhaps because the most common legal issues that arise [competency and treatment refusal], have to do with mental functions and abnormalities of behavior). Whatever the reason, the psychiatric consultant may be drawn into a turbulent atmosphere when medical and surgical staff are confronted with a legal issue. The well-prepared consultant can be invaluable in these matters.

The first and perhaps most important service provided by the consultant is to remind the consultee that the physician's safest havens within the law are the principles of good faith, common sense, and good clinical care. To be of maximum assistance, consultants should be familiar with relevant legal concepts, and use this knowledge to diminish consultees' anxiety and help them perform their jobs. The challenge for the psychiatric consultant is to ease the burden of the consultee by providing clinical insights and legal information and to know when and how to use the input of the hospital attorney.

Medicine has advanced rapidly in the twentieth century, giving rise to an evolving array of medicolegal issues. These issues are reflected in questions asked by residents and staff alike. How do I determine whether a patient is incompetent? If the patient is competent and making an irrational decision, does that decision have to be honored? What is my liability exposure as a consultant? If a managed care company refuses to pay for continued hospitalization or for a patient's admission to a psychiatric facility, can the physician be held liable if the patient commits suicide? If the patient has expressed a desire to hurt someone else, what are my obligations to that third party? What obligations do I have if my patient is human immunodeficiency virus (HIV)-positive and refuses to inform his or her sexual partner?

This chapter cannot provide definitive answers to these and all the other medicolegal questions faced by general hospital psychiatrists. Rather, this chapter outlines general principles that apply in almost all jurisdictions. Because state statutes and case law vary considerably on these medicolegal matters, hospital counsel and legal representatives of medical organizations and insurers should be consulted. They are excellent sources of information about legal aspects of general hospital psychiatry.

PHYSICIANS' RIGHTS AND OBLIGATIONS

Malpractice Liability

Malpractice, *negligence*, and *liability* are three terms that engender great concern and are often misunderstood. Malpractice law is a type of personal injury or tort law that concerns itself with injuries allegedly caused by the treatment activities of professionals. To establish a claim of malpractice, a plaintiff (the complaining party) must prove four things. First, it must be proved that the defendant physician owed a duty to the injured party. Where the injured party is the patient, the duty is to perform up to the standards of the average physician in the community practicing in that specialty. Failure to practice in accordance with that standard, unless there is some justification, constitutes the second element: negligence. The third and fourth elements are closely tied to the first two: The negligent behavior has to be shown to have been the direct cause of actual damages. In the event that all four elements are proved, the defendant may be held liable (responsible for the damage) and ordered to pay compensation to the plaintiff, either directly or through his or her insurer.[1–5] The four elements of malpractice are often summarized as the four Ds: duty, dereliction of duty, direct causation, and damages.

The liability exposure of consultants can be a concern for psychiatric consultants and others. Treating clinicians have the primary duty of care for the patient. Consultants, who by definition are brought in to provide advice to the treating clinicians, do not have the same duty to the patient. The consultant's duty of reasonable care is owed to the consultee, not the patient. This rule does not hold, however, where the consultant steps out of the purely consultative role and assumes direct responsibility for some aspect of the treatment relationship. For example, the consultant who evaluates a patient and then advises the treating physician that a course of antidepressant treatment is appropriate is not liable for an adverse outcome from the treatment. If, however, the consultant writes the prescription and monitors the treatment course, he or she has assumed the status of treating physician and may be held responsible for any adverse outcomes. [6,7]

Liability and Managed Care

Managed care and liability for injury when coverage is denied have been important issues ever since managed care arrived in force on the health care scene. The basic problem can be seen in this hypothetical example.

CASE 1

Mr. A was admitted to the trauma unit after leaping off a bridge into the river. After open reduction and internal fixation of his bilateral femoral fractures, the psychiatric consultant saw him. Mr. A was found to be suffering from major depression as well as alcohol abuse. He was believed to be at a moderate to high risk for suicide, and suicide precautions were instituted on the floor. Mr. A was begun on a course of antidepressants, but these had not yet begun to work when he was deemed surgically ready for discharge. The consultant recommended transfer to an inpatient psychiatry unit where Mr. A could undergo treatment for both his depression and substance abuse. Mr. A's mental health coverage had been carved out from his medical–surgical coverage. The utilization reviewer for his medical–surgical coverage insisted that he be discharged from the hospital and scheduled for outpatient physical therapy with visiting nurse coverage. The mental health management company sent its own psychologist reviewer to evaluate Mr. A. The reviewer agreed that Mr. A was depressed but denied authorization for psychiatric hospitalization. The reviewer opined that Mr. A was not acutely suicidal, did not need inpatient substance abuse treatment, and could be managed as an outpatient. He was given the names of the three psychiatrists in his town who were authorized under his plan and was able to get an appointment scheduled for 2 weeks after discharge. Mr. A was discharged from the hospital, over the objections of the consultant. The consultant had found that the patient was still significantly depressed and at risk of drinking again but not committable because he was not imminently suicidal. Ten days later, the visiting nurse found him hanged in his apartment. The death was ruled a suicide. Mr. A's family brought a malpractice action against the hospital, the treating physicians, the consultant, and the managed care company.

What liability does the managed care company have in a case like this, in which the denial of care results in harm to the patient? Would the managed care company's liability supersede that of the physicians? The answers to these questions are still unclear. There have been a series of legal cases addressing these issues, and the law is still evolving. At present, there is a possibility that managed care companies may be held liable in these situations if the company exerted such control over the decision-making process that the physician's judgment was overridden. In other words, for the physician to avoid liability, he or she must protest the denial of care, appeal it to the highest level that the insurer provides, and take other reasonable steps to ensure the patient's safety. Depending on the facts, the liability may be assigned entirely to the managed care company, to the physician, or be shared.[8–11] At present, treating physicians are regarded as independent contractors and therefore bear separate and often sole responsibility. There are policy arguments against that model, which may lead to future changes.[12]

Whatever the policy arguments, under federal law, there are specific limits on managed care companies' liability for denial of care. Most often, decisions made by managed care organizations to limit care are subject only to limited legal remedies under the Employee Retirement Income Security Act (ERISA) of 1974. ERISA limits most employees of private companies to suing their health plans for the cost of the care denied by the managed care organization only, and not for recovery of losses that result from the denial of care or for punitive damages.[13] ERISA's protection of managed care plans from liability for the consequences of their decisions is increasingly seen as unfair given the level of control over treatment decisions exercised by some plans. As a result, several federal court cases have eroded the prohibition on damages under the law, but these cases represent only small gains, the trend in cases has appeared to have come to a halt, and it remains to be seen whether lawmakers will amend ERISA.[14,15] In addition, state law efforts to hold managed care companies liable for damages have been largely unsuccessful.[16] For the time being, in the face of bad outcomes, patients may try to shift liability to physicians and hospitals to recover losses.[17]

Confidentiality and Privacy

Confidentiality is the clinician's obligation to keep matters revealed by a patient from the ears of third parties.[2,4] It is usually demanded and protected by statute and custom. A variety of exceptions to confidentiality exist, usually where the courts or the legislature determine that maintenance of confidentiality will result in more harm than good from a societal standpoint. This rationale provided the basis for the California court's decision in *Tarasoff v. Board of Regents*,[18] in which the court held that psychotherapists have a duty to act to protect third parties where the therapist knows or should know that the patient poses a threat of serious risk of harm to the third party.[19,20] In looking at the public policy issue, the court stated,

> The Court recognizes the public interest in supporting effective treatment of mental illness and in protecting the rights of patients to privacy. But this interest must be weighed against the public interest in safety from violent assault.[18]

Although not all states have adopted this view, the majority have. A number of states have enacted statutes dealing with this fertile area of malpractice liability.[21] The consultant should be familiar with the relevant statutory and case law concerning this issue in his or her jurisdiction. The consultant should also be aware that liability can arise when medical or surgical colleagues fail to breach confidentiality and do not warn family members or other contacts about the potential for contagion from an infectious disease.[22] In fact, liability for such failure set the stage for the court's decision in *Tarasoff*.[18] Additionally, a small number of states, including Massachusetts, have held that a physician may be held liable for injuries to a third person that result from the failure to warn a patient about the side effects of medications, such as where a patient falls asleep at the wheel of a car and was not warned of the sedating effects of a medication.[23]

Although infectious disease has been the subject of duty to protect cases in the past, infection with the HIV has been treated somewhat differently than other infectious diseases. Controversy persists about the obligation of a physician to warn the partner of an HIV-positive patient when the patient refuses to do so. Many states have statutes that address this issue, with varied approaches, adding to the confusion and highlighting the controversial nature of the issue. The psychiatric consultant should learn the

requirements of the jurisdiction in which he or she practices. Several articles and book chapters have addressed this controversial issue, some of which are cited in this chapter.[24–29]

In addition to situations in which disclosure is mandated to protect a third party, such as in *Tarasoff*[18] and infectious disease situations, other breaches of confidentiality may be mandated by statute or case law to protect vulnerable third parties. For example, all 50 states in the United States have statutes that require specific individuals, including physicians, to report suspected child abuse or neglect to state social service agencies.[30,31]

Many states also require that known or suspected abuse or neglect of the elderly or the disabled be reported.[31] Failure to comply with these requirements can result in substantial penalties. More recently, some states have begun requiring physicians and others to report known or suspected cases of domestic violence to law enforcement or to designated agencies. Mandatory reporting statutes serve an important societal purpose, but they are not without controversy. Every clinician should become aware of the specific requirements in his or her jurisdiction.[32]

Patient health information is also subject to regulation under a federal law known as the Health Insurance Portability and Accountability Act (HIPAA) of 1996. As of mid-2003, institutions and individual providers are required to comply with HIPAA rules. HIPAA has affected hospital practice by requiring distribution, in writing, of the institution's privacy policy to all patients and by mandating physicians to undergo training on privacy and disclosure provisions. The rules are too complex to review in full; however, several salient points stand out for psychiatrists.

Among the most relevant provisions of HIPAA is the treatment of medical records and the distinction between general psychiatric records and psychotherapy notes. Patients are entitled to a copy of their medical records; they also have the explicit right to request changes in the record. Whether or not the applicable staff person amends the contested information, the involved correspondence becomes part of the record. Although HIPAA affords special status to psychotherapy notes and allows psychiatrists not to disclose these notes to patients, this exception is narrow. To qualify for protection under the psychotherapy notes provision, the notes must be kept separate from the patient's medical record. However, even if kept in a separate psychotherapy record, specific types of information are not subject to the psychotherapy notes exclusion; these include medications prescribed, test results, treatment plans, diagnoses, prognosis, and progress to date.[33–35] It should be noted, however, that these notes are considered to be part of the medical record in the event that a subpoena is received for medical records in the course of litigation.

The practical implication of HIPAA regarding psychiatric record-keeping is that psychiatric records, whether in an outpatient clinic or contained in a medical chart from a nonpsychiatric hospitalization, are broadly accessible to patients or anyone they authorize to access their records. Therefore consulting psychiatrists should consider documentation of sensitive therapy material carefully because it will be treated like the rest of the medical record unless the psychotherapy notes are kept in a separate file.

Like patients, health insurance companies' access to psychotherapy records is restricted. Health insurance companies cannot demand access to information contained in psychotherapy notes as a requirement of payment for care. If, in a particular circumstance, psychotherapy notes are released to an insurance company, written consent from the patient is required under HIPAA. This consent requirement is in sharp contrast to the disclosure rules for the general medical and general psychiatric record for insurance purposes; HIPAA does not require consent for disclosure of this information to insurance companies for the purpose of obtaining payment for treatment—medical or psychiatric. HIPAA also does not require specific consent for the release of information for treatment or health care operations purposes. Operations purposes, for example, include quality assurance, licensing, and accreditation. There are 11 additional circumstances in which disclosure is permitted without patient consent, including emergencies and mandated reporting situations, such as child abuse—which are generally considered to be a part of current medical practice. But other situations, including exceptions for law enforcement and attorney requests, may be more concerning.[33,35]

Refusal to Treat Patients

Refusal to treat patients, in or out of the hospital, is a right that is rarely invoked by physicians. The physician–patient relationship is, at heart, contractual in nature. Both parties have the same right to enter, or to refuse to enter, the relationship as they do with other contracts. Once the physician offers to treat and the patient accepts, the contract is established and the physician's right to refuse or withdraw is limited in certain ways. For example, maintaining a walk-in clinic or emergency department (ED) can be construed as an implicit offer to treat on an emergent basis. The patient's presentation at the clinic or ED is an acceptance of the offer, creating a contract. It does not necessarily create an obligation to provide ongoing care, so long as the walk-in or emergency nature of the services is clear and appropriate information is provided regarding ongoing care. In a situation in which a prospective patient discusses his or her history with a physician, it may be difficult to assert that no relationship has been established, particularly if the patient is under the impression that a treatment relationship exists. Physicians should clarify at the outset of the treatment encounter that they may or may not accept a case. It is usually helpful to explain at the first visit that this is an initial evaluation to determine whether or not it is appropriate for the physician to take this particular individual as a patient. Clearly, this principle does not include the emergent, or even urgent, medical problem. In the event that no physician–patient relationship has been created in the initial contact, referral of such a patient to a health care facility, such as a walk-in clinic, demonstrates concern for the patient without necessarily creating an obligation to treat.[24–28,36–38]

When the physician elects not to treat an individual, the physician should make every effort to provide an alternative course to avoid claims of abandonment.[1,2] Abandonment is the unilateral severance of the relationship by the physician, leaving the patient without needed medical care.

The optimal care of the patient is the first consideration. Whenever a physician desires to transfer the patient to another physician, the transferring physician must take steps to ensure continuity of care by specific arrangement with the physician who is going to treat the patient. The physician may terminate the treatment relationship with a patient for a variety of reasons, including nonpayment, repeated failure to keep appointments, or threatening behavior. In such cases, the patient should be notified of the decision, the available treatment options (including a specific referral, if possible), and available sources of emergency care. The course pursued and the reasons and indications for the transfer or termination should be documented in the medical record.[2,3]

The physician's right to refuse to provide care for patients may be restricted where the refusal is based on the patient's specific illness or inherent characteristics. The refusal to care for patients of certain races, religions, ethnic origins, or disease type (e.g., acquired immunodeficiency syndrome) raises significant ethical concerns as well as potential liability under Title VII of the Civil Rights Act of 1964 and the Americans with Disabilities Act. These are beyond the scope of this chapter. The general rule, however, is that physicians and other clinicians may be charged with unethical conduct and in some situations with violation of patients' civil rights, when treatment is refused on a discriminatory basis.[39,40]

The issue of terminating the physician–patient relationship usually arises when some conflict has developed between physician and patient over the course of treatment or as a result of noncompliance.[41] Knowing about the physician's right not to treat is important for consultants. Often the knowledge that a physician can stop treating a particular patient allows enough "give" in a confrontation so that the consultee's anxiety diminishes and negotiation can begin.

End-of-Life Care and Advance Directives

Care of the dying and hopelessly ill patient continues to generate difficult questions, staff conflicts, and requests for help from physicians who find themselves faced with these clinical, ethical, and legal dilemmas.[42,43] Controversy and turmoil are generated when the patient loses the capacity to participate in the decision-making process. The decision of a competent patient to refuse life-sustaining treatment yields similar results. The general rule is that every competent adult has the right to make his or her own decisions about medical care, based on personal preference, even if that choice conflicts with what a majority of others would choose under similar circumstances. An important distinction must be drawn between the competent patient's request that treatment be withheld or withdrawn and requests that the physician take some active, independent step to terminate the patient's life. The former are generally regarded as being within the realm of the patient's right to make treatment decisions. The original illness, rather than the withholding or withdrawal of treatment, is regarded as the cause of death in such situations. Active steps taken to end a patient's life are considered euthanasia; in many states, the complying physician could be subjected to criminal prosecution.[43–45] In fact, in two 1997 cases, the Supreme Court of the United States upheld two state laws prohibiting physician-assisted suicide after physicians challenged the constitutionality of the laws.[45–47] However, the Supreme Court of the United States has also limited the ability of the federal government to prevent states from allowing physician-assisted suicide. Specifically, in 2006, the Court ruled against the federal government when it attempted to use federal law to block the ability of Oregon physicians to prescribe controlled substances for the purpose of physician-assisted suicide.[48] For more than a decade, Oregon was the only state that legalized physician-assisted suicide. Shortly before the submission of this chapter, Washington passed a physician-assisted suicide law based largely on the Oregon statute.

The treatment requests of the dying patient have not always been taken seriously, especially when the patient's choice is to terminate care. Physicians struggle when faced with a patient who refuses further treatment, especially when there is some hope of improvement. Physicians often find it difficult to give up the fight even at the request of the patient. Consulting psychiatrists in such circumstances should be concerned with determining whether the patient's request to forgo heroic efforts stems from depression or pain and whether or not the patient is capable of understanding the nature of the request. In other words, is the patient's refusal of further treatment informed? If so, the next challenge is working with the treatment team so that they can accept the patient's decision.

When minor children suffer terminal conditions, in the absence of any overriding legal requirements, parents are generally permitted to make decisions regarding continuation of extraordinary efforts.[32,49,50] The consulting psychiatrist is urged to seek the advice of the hospital's general counsel when confronted with these issues. The maze of governmental regulations, statutes, and case law in this area combined with the emotionally charged nature of the situation demand expert legal input. Nevertheless, the larger challenge for the consultant and the treatment team lies in helping the child's parents with the turmoil at hand and the grief ahead.

The psychiatrist should do what he or she can to ensure the comfort of the patient, such as seeing that treatment of clinical depression and alleviation of tractable pain are not overlooked in the anxiety that surrounds the dying patient (see Chapter 41). Development and documentation of written guidelines for the management of these difficult situations can be helpful in ensuring rational constancy in approach. Such attention to the relief of suffering decreases conflict between patient, family, and staff. In turn, this helps avoid legal involvement in the situation.

The status of the patient's right to refuse life-sustaining treatment varies among the states. In 1990 the Supreme Court of the United States handed down its opinion in *Cruzan v. Director, Missouri Department of Public Health*.[51] The Court held that all competent individuals have a constitutionally protected right to refuse life-sustaining treatment. When a patient is incompetent, however, the court held that the state can assert its interest in preserving life and require clear and convincing evidence of the now-incompetent patient's preferences in such matters before a surrogate decision-maker will be allowed to refuse the treatment on the patient's behalf. In most jurisdictions, surrogate decision-makers, whether family members or

guardians, are allowed greater freedom in drawing conclusions about the patient's preference.

Many states have statutes that allow competent individuals to issue advance directives concerning future medical care in these situations. All states have statutes providing for durable powers of attorney, an instrument that can be used to delegate decision-making authority to another person in the event of incapacity. All physicians should be aware of what prior directives are valid in their jurisdictions and encourage their patients to explore these issues with them and with their legal representatives. Under the Patient Self-Determination Act of 1990, all health care facilities, nursing homes, and health maintenance organizations must inquire on admission or enrollment whether a patient has an advance directive. If not, the patient must be offered information on the subject and an opportunity to create a directive.[52–54] Notwithstanding nearly two decades of this legal requirement, it is estimated that only a minority of Americans (30% to less than 50%) have executed an advance directive.[29]

RIGHTS OF PATIENTS

It is no news that the relationship between physician and patient has changed considerably over the years. The pendulum has swung between the extremes of paternalism and total patient autonomy. More recently, the impact of restrictions on patient choice imposed by managed care has been added to the equation. Most physicians and their patients operate on some middle ground between the extremes of complete patient autonomy and medical paternalism. The fundamental principle is that it is the patient, not the physician, who makes the ultimate choice regarding treatment. This ethical concept has been operationalized by legal decisions and by legislation. Although some physicians still view these changes as dangerous to patient care and as intrusions into their domain of clinical judgment, they represent much-needed measures for protection of the rights of mentally and medically ill patients. Nevertheless, food and drug laws, restrictions on new and experimental treatments and procedures, and commitment and restraint laws—all modified in recent years—trigger anxiety for physicians who previously concerned themselves with only consent, competency, and refusal of treatment against medical advice (AMA).

Informed Consent and Evaluation of Competency

Informed consent issues and the evaluation of competency are major components of the medicolegal workload. Informed consent has been an essential feature of medical practice since the 1960s. It is a process by which the patient agrees to treatment, in which the consent is based on adequate information, and it is voluntarily given by a patient who is competent to do so.[55] The term *informed consent* is somewhat misleading; we are as concerned with informed refusal as we are with informed consent. Bowing to convention, the term informed consent is used with the understanding that the same standards apply to informed refusal.

Informed consent is required before the initiation of any medical treatment, but exceptions do exist. Informed consent need not be obtained in an emergency in which delay would seriously threaten the well-being of the patient. In such cases, the physician is under an obligation to use his or her best judgment and to act in good faith. Such behavior is unlikely to result in litigation, especially if the physician documents (immediately after the emergency passes) the events and the reasons for the steps taken. Other exceptions to informed consent have been found where the patient waives the right to receive information, where the patient is incompetent, or where providing the information needed for informed consent would cause the patient's physical or mental health to deteriorate (known as *therapeutic privilege*). The therapeutic privilege is problematic; it is mentioned here because it has been invoked in the past and was for many years a mainstay of medical paternalism (e.g., patients who were treated for carcinoma without being told the diagnosis for fear it "would just upset them" and worsen their overall condition). Situations in which the therapeutic privilege can be justifiably invoked are rare. The fact that providing the information might lead the patient to refuse treatment or would cause the patient considerable anxiety does not justify invoking therapeutic privilege. The situation must be one in which the informed consent process itself would cause risk of grave harm. The physician who forgoes the informed consent process under the name of therapeutic privilege does so at his or her own risk.[55–57]

An essential feature of modern consent is that it be informed. Simple consent, in which the patient gives the physician blanket permission to take care of medical problems, is not deemed adequate, unless the patient has made a specific decision to waive informed consent. The amount and type of information to be provided to the patient or the surrogate decision-maker vary somewhat among jurisdictions.[2] The two basic standards are the professional standard and the patient-oriented standard. In the former, the physician is required to give that amount of information that the average physician in that specialty would provide under the circumstances. In other words, it looks to the standard of care. In other states, the amount of information to be provided is determined by what the patient would require to make an informed decision. This is also known as the materiality standard. In some states, the materiality standard is applied on the basis of what the average patient would require to make a decision, whereas in other states it is assessed in terms of what the specific patient would require. In either case, the physician who covers the following information, taken from a leading Massachusetts case,[58] with the patient will generally be held to have provided adequate information:

- The diagnosis and condition to be treated
- The nature of the proposed treatment
- The nature and probability of the material risks of the treatment
- The benefits that may be expected from the treatment
- The inability of the physician to predict results
- The irreversibility of the procedure, if that is the case
- The likely results of forgoing treatment
- The likely results, risks, and benefits of alternative treatments

The second requirement for informed consent is that the consent be given voluntarily. Coercion is often in the eye of the beholder; the fact that coercion ostensibly occurs in the service of the best interests of the patient does not justify it from the ethical standpoint or qualify it as an element of informed consent. The line between persuasion and coercion often appears both narrow and vague. Generally speaking, if some negative contingency (including an exaggerated prediction of a poor prognosis) is attached to the patient's refusal of treatment, there is coercion, and any subsequent consent is technically invalid.

Competency is the threshold issue in the informed consent process. The term is familiar to all physicians; typically, it is used imprecisely. Competency is defined as the legal capacity of an individual to perform either a specific function or a wide range of functions; before such a determination by a judge, all adults are presumed to be competent. Only a judge can declare a person incompetent for specific functions or for all activities (global incompetence). The psychiatric consultant can only make a clinical assessment of the patient's capacity to function in certain areas. That assessment is usually, but not always, accepted by the court in its determination of incompetence.[2,55] What then of the numerous requests received by the consultation psychiatrist to determine the competency of medical and surgical patients? The use of competency as a shorthand term is justifiable so long as the consultant and the consultee are clear that the most the consultant can do is to assess the patient's capacity to engage in the decision-making process in question. The change in the patient's legal status must be left to a judge.

Competency is usually task-specific and defined in relation to a specified act: to make a will (testamentary capacity), to testify in court (testimonial capacity), to consent to or to refuse treatment (decision-making capacity), and the like. Being competent to perform one act does not mean that one is necessarily competent to perform another. Hence, the consultant called to evaluate a patient's competency must first determine the specific type of competency in question and be aware of the applicable judgment criteria. Once the consultant has determined the type of competency in question, the judgment hinges on how well the patient meets the criteria. For example, with regard to capacity to make treatment choices, we look to the patient's understanding of three things: the illness (that some thing is wrong and to some degree how wrong), the treatment (what is proposed and why it is relevant to what is wrong), and the consequences of the decision. Although a variety of means of assessing decision-making capacity have been proposed, Appelbaum and Grisso[59] have suggested the following four criteria that are particularly useful and straightforward:

1. Does the patient manifest a preference? A patient who is unable or unwilling to express a preference presumably lacks the capacity to make a choice. It does not necessarily follow, however, that a patient who expresses a choice is competent.
2. Is the patient capable of attaining a factual understanding of the situation (nature of the illness, treatment options, prognosis with and without treatment, risks and benefits of treatment, and so on)? The patient need not possess this level of understanding at the time of admission; he or she need only be able to receive the factual information and retain it in some reasonable form during the decision-making process.
3. Does the patient have an appreciation of the significance of the facts presented? Appreciation, in contrast to factual understanding, indicates a broader level of understanding related to the significance of the facts presented and the implications these facts hold for the patient's future.
4. Is the patient able to use the information presented in a rational fashion to reach a decision, that is, to weigh the facts presented in a logical manner? The focus here is not on the rationality of the ultimate decision, but on the rationality of the thought processes leading to the decision.

When a substitute decision-maker is deciding on behalf of an incompetent patient, the same elements of capacity to make a decision apply. The patient's health care agent has the responsibility to express the patient's choice, with an awareness of the facts and appreciation for their significance, thinking through the material in a logical fashion before making a decision.

Competency is not an all-or-nothing proposition, and the same level of competence is not required for all medical decisions. Most experts agree that the strictness of the competency test should vary as the risk/benefit ratio changes. In essence, there is a sliding scale for the level of competence needed before a person can be deemed competent to make medical decisions.[60–62] The more favorable the risk/benefit ratio, the lower the standard for competence to consent and the higher the standard for competence to refuse. For example, the patient who agrees to accept incision and drainage of an obvious wound abscess would not have his or her competence subjected to rigorous assessment. Refusal could not be taken so lightly; the more serious the abscess, the more intense the examination of competency would have to be. If the risk/benefit ratio were unfavorable to the patient (e.g., extensive surgery to remove a slow-growing brain tumor in a 94-year-old), refusal would not have to be challenged as meticulously as would consent. Although some criticize this approach as being too open to manipulation by a paternalistic physician, it accurately reflects professional obligations to ensure that patients make a truly informed decision based on a rational weighing of the risks and benefits involved. A similar approach was endorsed by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.[63,64]

Dementia, delirium, and psychosis are the conditions most often cited as causes of incompetence.[65–68] The consultant should always consider the possibility of a mood disorder as a basis for impaired competence to make medical decisions. The following example demonstrates some of the complexities of these evaluations.

CASE 2

A psychiatric consultant was asked to assess the competency of M. B., a 62-year-old man who presented to the ED with a massive subdural hematoma that he had suffered in repeated falls owing to bradycardia. He had a profound expressive aphasia; despite the size of the subdural hematoma, the patient was medically stable and intermittently lucid. Nevertheless,

neurosurgical staff were anxious to evacuate the subdural hematoma for fear of increased intracranial pressure. During his lucid intervals, the patient was verbally abusive to his physicians and to the consultant, stated clearly that he did not want surgery, and demanded to be discharged. The limited duration of his lucid intervals and his general irritability prevented the consultant from conducting a more complete mental status examination and determining the degree of his cognitive impairment, if any. An interview with his family members revealed that he had been drinking and becoming more depressed, with marked suicidal ideation, in the previous weeks. He had refused to see a physician about his bradycardia, stating that he would prefer to die. Based on this information, his mental status examination, and the risk/benefit ratio of the proposed treatment, the consultant determined that the patient lacked the capacity to give an informed refusal. An emergency court hearing was held with an "on-call" judge. The judge ruled that the patient was incompetent to refuse the planned procedure and appointed a family member to be his guardian. The guardian then consented to evacuation of the subdural. The patient tolerated the procedure well; on recovering from surgery and anesthesia, he informed the staff in a clear voice that he was going to sue all of them. The appointment of a guardian and receipt of informed consent by the guardian deprived the patient of any basis for a malpractice action.

Although depression must be considered as a possible cause of impaired judgment and incompetence, caution must be exercised. Just as a patient with schizophrenia is not automatically considered incompetent, a patient with major depression may also retain the ability to make rational decisions. Studies have found that medical decision-making capacity is altered by severe depression but not by depression of lesser severity.[69]

Patients may make decisions in one moment and change those decisions minutes or hours later. This can cause significant disruption of treatment for that patient and for others. Frequent shifts in patient choice can be the basis for questioning the patient's competence. Ideally the patient makes a competent choice before suffering a shift in mental status. Family members should be included in this process so they can assist the treatment team in the event of a subsequent change in the patient's decision.

The cause of incompetence may be treatable. Intense pain may lead a patient to refuse a needed procedure; treatment with adequate doses of analgesics may resolve the problem. Treatment of depression, when it is a factor, may be attempted with psychostimulants, which may act within 1 to 2 days. This can restore the patient's perspective so that the decision to refuse or accept is competently made. Delirium and agitation often interfere with treatment decisions and should be treated with a neuroleptic if no specific cause of the confusional state can be found. The consultant should not determine that the patient is permanently incompetent until these medications have been given an adequate trial, and other potential causes of the confusional state have been addressed. It must be remembered that even psychotic patients may have clear, rational reasons for refusing a treatment. Conversely, the refusal may be the result of voices telling the patient to leave the hospital, that they do not deserve treatment, or that the surgeon is a Federal Bureau of Investigation agent sent to spy on them.[70]

Occasionally, psychiatric consultants are asked to assess a patient's testamentary capacity, competency to execute a contract, financial competency, or the like. Such questions are unlikely to arise in the course of the usual medical consultation but instead are asked by an attorney or the courts, in anticipation, or as a result, of a challenge to the patient's competency to engage in these activities. In the case of testamentary capacity, for example, a psychiatrist may be asked to assess the mental status of a patient to determine whether he or she meets the legal standards for testamentary capacity and to provide documentation of this mental status in the event that the will is challenged after the patient's demise. To do so, the psychiatrist must possess both clinical skills and knowledge of the legal standards: The patient knows that he or she is executing a will, knows the extent of his or her estate, and knows the "natural objects of his or her bounty" (who would normally inherit). Because these assessments involve the application of specific legal requirements to clinical situations, the evaluation should be performed only after consultation with the referring attorney or court representative and with adequate knowledge of the legal standard. For this reason, many psychiatric consultants refer such consultations to colleagues who specialize in consultation to the legal system.[71]

To give consent, the patient must be able to make an informed judgment on the matter at hand. Patients with deficits in this area owing to communication difficulties (e.g., foreign language, deafness, or aphasia) or ignorance of important aspects of their care cannot technically give consent, whether or not they are competent. The physician who performs a procedure on a passive, confused, or fearfully mute patient who seems compliant or willing does so at his or her own peril; the physician risks a suit for battery. There is little protection in the ancient maxim *Qui tacet consentire videtur* ("silence gives assent").

The patient's capacity to give consent, understanding, and judgment should be documented in the chart or in office notes of the physician, along with the mental status examination and any specific questions asked about the proposed treatment. Impairment of intellect, memory, attention, or consciousness can limit the patient's understanding; impairment in reality testing, sense of reality, impulse control, and formal logic can influence judgment. The presence or absence of any or all of these should be documented clearly in the chart, along with their relationship to the illness and to the decision-making process.

The general rule in obtaining consent for treatment of minor children is that parents have both the obligation to provide care and the right to make treatment decisions. There are a number of complicating issues in this area, however. First, the age of majority varies by state. Second, minors' rights and the legal ability to consent vary according to the type of treatment being contemplated. Massachusetts, for example, permits minors to give consent for the treatment of drug addiction and sexually-transmitted diseases without seeking parental authorization. Virginia allows minors to consent to psychotherapy without parental consent. Third, the law is open to examination of the reason for the parents' denial of consent, rather than upholding it automatically. For example, denial of life-saving treatment because of the parents' religious beliefs will not be upheld.

Finally, the law recognizes the concept of the emancipated minor. This is a minor child who is free of parental control and dominance and is therefore deemed competent to consent in the eyes of the law, regardless of age. Informed consent by an emancipated minor, carefully documented in the record, usually protects the physician's action from criticism by the parent or guardian of that minor. Treating clinicians and consultants should learn the rules of their specific states concerning consent by minors.[49,50]

New drugs, treatments, and procedures should not be used without informed consent by patients (or the appropriate surrogate decision-maker) and proper authorization from hospital and government agencies. Although physicians have generally been given considerable freedom in prescribing medications and in doing procedures for off-label (not approved by Food and Drug Administration [FDA]) purposes, this freedom is constrained by federal and state regulations, the standard of care (enforced through malpractice actions), and the patient's right to be informed about the proposed treatment. Use of carbamazepine for treatment of bipolar disorder is a common example of this. As a matter of policy, patients should be informed that the medicine prescribed has not been given FDA-approval for that particular purpose and informed about the rationale for prescribing it.[36]

Civil Commitment and Restraint

Civil commitment and physical restraint are commonly encountered but poorly understood by patients and many nonpsychiatric physicians. Civil commitment is a process by which the power of the state is used to remove an individual from society and place him or her in an institutional setting. Originally the mentally ill were confined to institutions to protect the rest of society. As the approach toward the mentally ill became more enlightened, the goal of confinement was to provide treatment and protection. Under this approach, the state was fulfilling its role as protector of its citizens, much as a parent would act on behalf of a child. Hence, this is known as the state's *parens patriae* interest. With the blossoming of the civil liberties movement in the 1970s and the emphasis on individual autonomy, the individual's interest in personal freedom and privacy was given priority over the state's *parens patriae* interest. During the 1970s, the best interest or *parens patriae* approach to civil commitment was replaced by the dangerousness approach in most jurisdictions. This approach, based on the state's police powers, allows an individual to be involuntarily committed to a mental institution only if the individual poses a danger to himself or herself through direct injury, if there is a direct threat of physical harm to others, or if the individual is gravely disabled and unable to care for himself or herself in the community.[2,3,72]

In a general hospital, if a medical or surgical patient is psychiatrically committable but requires further medical or surgical treatment, the wisest course is to initiate commitment procedures and request that a local mental health facility accept the patient but allow the patient to remain in the general hospital for care. Budgetary concerns, insurance issues, and the general reluctance of both state and private psychiatric hospitals to take medically ill patients often make it difficult to place such patients. It behooves the consultation psychiatrist to learn how to anticipate the need for further psychiatric care and begin the search early. The need for commitment should be reassessed throughout this process and the process halted if appropriate.

This search for inpatient psychiatric placement increasingly requires negotiation with managed care companies to obtain permission for the hospitalization. Often, the interaction with health insurance companies occurs through the process of precertification, which requires the transferring hospital to gain approval for transfer and inpatient care from the insurer before the patient can be transferred and admitted to the receiving psychiatric facility. Because of frequent differences in general medical and psychiatric benefits within health plans, the same precertification process may be required even when a patient is transferred from a medical ward to a psychiatric unit in the same hospital. It is now commonplace for insurance plans to "carve out" or subcontract mental health benefits to a subsidiary or a different company with procedures and guidelines distinct from those of the parent company.

The psychiatric consultant often encounters questions regarding the restraint of patients on medical and surgical floors. Delirium, dementia, acute or chronic psychosis, or severe anxiety or panic can lead a patient to assault staff, to wander off the ward, or to fall. The suicidal patient being treated on an unlocked medical floor poses the risk of elopement and successful fulfillment of suicidal urges. Many hospitals have policies that allow the patient to be restrained before the psychiatric consultant is called. When this occurs, the role of the consultant is to provide management recommendations and approval for the restraint. Usually, the psychiatric consultant is asked to decide whether the restraints can be discontinued.

The legal aspects of restraint of patients on a medical or surgical ward vary among jurisdictions.[4,36] Generally speaking, a patient may be restrained for the purpose of protecting the patient or other patients and staff, for the purpose of allowing examination during an emergency, or for the purpose of treatment in situations in which the patient appears to lack the capacity to make treatment decisions and is refusing care. In this latter situation, no forced treatment should be initiated in the absence of an emergency unless surrogate consent has been obtained. In handling these situations, physician and staff are required to use the least restrictive alternative available. For example, where a sitter or observer is available for a potentially suicidal patient, that option is more appropriate than four-point restraints. Family members often ask whether they can substitute for a sitter. Although this may be possible in some situations, it requires careful clinical judgment that takes into account the type of pathology, the degree of impulsivity, the overall degree of risk, and the relative ability of the sitter to act objectively. Restraint is uncomfortable for the staff as well as for the patient and family, and there may be a tendency to avoid it whenever possible for some types of patients and a tendency to overuse it with others. Again, careful clinical assessment is essential so that protection is provided for those patients who need restraint without zealously overprotecting and restricting those who do not. The justification for restraint, including history and formal mental status examination, should be clearly documented in the

medical record, along with the psychiatric differential diagnosis, treatment, and management recommendations.

The restraint of patients gives rise to two potential sources of liability: battery and false imprisonment.[1] A battery is defined as the touching of another person without his or her consent (expressed or implied) or justification. False imprisonment may be charged where an individual is denied the right to move about freely by real or perceived methods of confinement. Failure to restrain a patient with a tendency to wander, who is subsequently injured, may result in a charge of professional negligence.

Malpractice claims based on battery or false imprisonment are rarely successful if the use of restraint is reasonable under the circumstances, the reasons for the measures are documented in the medical record, proper technique is used, and hospital policies are followed. Failure to restrain when indicated and improper restraining technique carry greater risks of harm to the patient and of malpractice claims.

Right to Refuse Treatment

The right to refuse a specific form of treatment or procedure has a long history and is firmly established in medicine. This right, based on the philosophical principle of autonomy, has been operationalized through the common law (case law), by legislation, and in state and the U.S. constitutions.[73–76] Although widely acknowledged, the right to refuse treatment is not absolute. It may be limited when it is in conflict with legitimate state interests of preserving life, preventing suicide, protecting the interests of third parties, or protecting the integrity of the medical profession.[77] Generally the decision of a competent patient to end treatment presents a difficult dilemma for the treatment team. If the issue ever reaches court, the competent patient's preference is rarely overridden. With the advent of advance directives (e.g., health care proxies and durable powers of attorney), the wishes of the patient, expressed when competent, can be honored after the onset of incompetence. The path to this conclusion is not as smooth as this might suggest. Consider the following example.

CASE 3

Ms. C, 22-year-old woman was admitted to the hospital after sustaining severe head injuries in a motor vehicle accident. After emergency evacuation of a subdural hematoma, her condition stabilized. She was unresponsive to verbal stimuli, did not track, but did withdraw to pain. She showed decorticate posturing. The treatment team urged aggressive measures, arguing that the injury was recent and the ability to predict ultimate outcome was limited. Tube feedings were begun and an early pneumonia treated with antibiotics. The patient's family told the treatment team that the patient would never want to be kept alive under such circumstances. The patient's mother explained that the patient's cousin had been in a motor vehicle accident 5 years earlier and had lingered in a persistent vegetative state for 3 years until her death. The family had to engage in a costly legal battle to get permission to terminate supportive care. When this occurred, the patient (who was a nursing student at the time) vowed that she would never allow this to happen to her or to her family. She told her family that she would want to be free of life-sustaining measures in the event of a serious injury if there were "no chance of recovery." In addition, she executed a health care proxy naming her mother as her agent for medical decision-making in the event of her incapacity. Her mother believed that the patient would have refused care if able to do so and insisted that the tube feedings be stopped. The treatment team resisted, arguing that there was hope for some recovery. After a series of meetings, the family acquiesced to the recommendations of the team and the patient was transferred to a rehabilitation facility, still posturing and not responding. Two weeks after transfer, she was returned to the hospital with septicemia. This time, the treatment team yielded to the family's preferences and the patient died peacefully.

As this example suggests, there are often no perfect answers to these problems. Both the treatment team and the family were well-meaning and tried to do what they believed was right for the patient. Meetings between the treatment team and the family, facilitated by the consultants to the unit, allowed a process to develop that gave the patient some chance at early recovery and for nature to take its course. Although difficult, the decision-making process was conducted with dignity, with the aim of maintaining the patient's autonomy and ensuring that the decision was informed and with concern for the ethical integrity of her caretakers. In a more contentious setting, the family could have charged the treatment team with battery. Under the law in that state, the agent appointed by the health care proxy (the mother in this case) had the same authority to make decisions as the patient would have if competent, including refusal of permission for further treatment. The treatment team could have raised legal challenges to the exercise of the proxy, arguing that it was not evident that there was "no chance of recovery." In some states, an argument would be made that shutting off the life support constituted murder or assisted suicide or that the state's interest in preserving life and preventing suicide outweighed the individual's expressed wish. The likelihood of such arguments being made or succeeding is much less in light of the Cruzan decision.[51] Finally, if the physicians or the institution had been ethically opposed to the termination of treatment, the request might have been denied and the patient transferred to the care of another physician or facility. The best solution to these challenging problems lies in the sharing of information and concerns between the family and the treaters. Immediate resort to legal posturing hardens positions and shuts off communications in most cases, to the detriment of all concerned.

The requirement of informed consent and the right to refuse treatment do not automatically apply in emergencies. In emergencies that appear to endanger the patient, or in acute situations that threaten the safety of the staff and other patients, the physician who acts in good faith while administering a treatment or procedure is generally not liable for failure to obtain informed consent. Good faith is in doubt, however, when the patient has made his or her preferences regarding treatment in the event of an emergency clearly known before the emergency and the physician chooses to disregard these preferences. For example, the physician who agrees to perform surgery on a Jehovah's Witness with the stipulation that there be no transfusions, even in an emergency, is hard pressed to plead good faith should he or

she violate that agreement in the event of a sudden hemorrhage. Some institutions have adopted policies specific to such situations. In the case of chronic medical conditions, ongoing situations, and prolonged heroic measures to sustain life, the emergency exception loses its applicability, and decisions regarding treatment must be returned to the competent patient or to an appropriate surrogate.

Leaving treatment AMA is the prerogative of any competent, nonconsenting patient.[78] The threat to leave AMA, similar to most other medicolegal conflicts, usually represents a clinical problem disguised as a legal dispute. The consultant called to evaluate the patient threatening to leave AMA must evaluate whether the patient is competent to make that decision. In the course of the evaluation, it is common to find that the patient is angry over a perceived lack of caring or dissatisfaction with the amount of information provided by the physician. The consultant who can restore communication between physician and patient may be successful in getting the patient to complete the course of treatment. If the patient does leave, the consultant may then have to calm the staff in preparation for the patient returning at a later date.

From a legal standpoint, if patients possess the capacity to make decisions and do not pose a risk of harm to themselves or others, they cannot be held against their will. A patient requesting to sign out AMA may be deemed to have the requisite capacity (competence) to do so if he or she understands the nature of the illness, the recommended treatment, the alternative treatments available, and the prognosis with or without treatment and is able to use this information in a rational manner to reach a decision. If the patient meets these criteria, he or she can leave against advice, whether or not the form is signed. In the event that the patient refuses to sign the form, the discussions before release and the fact that the patient refused to sign the form should be documented in the medical record.

CONCLUSION

This chapter began with a discussion of the role of the psychiatric consultant in helping consultees deal with medicolegal issues. It is appropriate to close it with a few cautionary words about the temptations present for those who undertake this task. Consultants are often tempted to meet the needs of their consultees by telling them what they want to hear. Nowhere is this more true than in the assessment of a patient's competency to consent to, or to refuse, treatment. This is compounded by the consultant's own inclinations, as a physician, to seek an outcome that is in the best clinical interests of the patient. In performing competency assessments and other consultations on medicolegal issues, such temptations must be strongly resisted. The assignment of the consultant is to be objective and focused on the issue at hand, rather than on what the consultant or consultee sees as the best overall clinical outcome. Such isolation of purpose is often difficult, but it is essential if the consultant is to serve the consultee and the patient. The consultant must also keep in mind that he or she is just that: a consultant whose job it is to advise, not to decide. The treating physician may choose to disregard the consultant's assessment that a patient is incompetent to make treatment decisions and proceed with treatment. The treating physician assumes both the legal and moral liability of his or her own actions. The consultant can serve only as a guidepost and only then by being both knowledgeable and objective. This task is made easier by taking the following approach to consultation on these highly charged medicolegal issues:

1. Know what you are being asked to do. That is, understand both the overt request and any covert agenda that may exist.
2. Know the clinical facts of the consultation.
3. Know, or find out, the salient legal requirements involved.
4. Determine the presence of any apparent conflict between good clinical care and the law.
5. Get to know the hospital attorney; share information and attempt to develop a multidisciplinary team approach to patient care.
6. Try to move all parties away from a crisis mentality to gain some time to resolve conflicts and to encourage compromise. Avoid ultimatums. Pushing back deadlines for procedures, treatment, leaving the hospital AMA, and the like decrease time pressures and allow people to think more clearly.
7. Understand the personalities of the physician and the patient.
8. Know the patient's next of kin, their understanding, fears, biases, personalities, and the probabilities of obtaining informed consent from them.
9. Act as a go-between so as to diminish anxiety and communication gaps among physician, patient, and family and try to find areas for compromise and agreement.
10. Search out covert disagreements and hidden fears in the physician and patient; try to find commonsense measures that would remedy these, and search for loopholes and areas in which conflicts can be mended or avoided.
11. Provide detailed documentation in the patient's medical record (or chart) of the patient's understanding, judgment, capacity to give consent, and clinical and psychiatric status as well as the course pursued.
12. Maintain an objective point of view while remaining mindful that the consultant's responsibility is to assess as accurately as possible the patient's capacity to give an informed consent and that truth is a higher goal than scheduling concerns of the consultee and ward staff.
13. Use such consultations to teach physicians that they have little to fear from the law and to teach patients that they have little to fear from their physicians.

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Collaborative Care: Psychiatry and Primary Care

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BJ Beck, M.S.N., M.D.

The convergence of several historic trends[1] in psychiatry, and more generally in the U.S. health care system,[2] has necessitated novel approaches to the psychiatric care of patients in the general medical setting. Such approaches, potentiated by advances in psychopharmacology, must contain cost, appropriately allocate limited health-care resources, and meet the mandates for safe, personalized, and high-quality care. Previously considered a hospital-based specialist, the psychiatric consultant must now be comfortable in the outpatient medical clinic, as shorter medical and surgical hospitalizations and more outpatient procedures, such as same-day surgery, have transitioned the locus of care for medically ill patients from inpatient to outpatient settings.[3] At the same time, primary care providers (PCPs) are seeing more seriously ill psychiatric patients in their outpatient practices, because shorter psychiatric hospitalizations have transitioned these patients back to their communities more quickly, without a concomitant increase in community mental health resources.[4] Consultation psychiatrists are well positioned to collaborate with their medical colleagues in the development and implementation of pragmatic and cost-effective outpatient models of care.

The burgeoning increase in medical expenses and the limited nature of our health care resources has moved the focus in the U.S. health care system from patient- to population-based care.[5] In a society that so highly values the individual, this painful transition has, nonetheless, exposed the tremendous fiscal burden of psychiatric morbidity. The psychiatrically disordered population experiences increased *physical* health care utilization, work absenteeism, unemployment, subjective disability,[6–8] and mortality. Although it is more difficult to demonstrate, there is also evidence of the cost-offset value of appropriate and timely psychiatric treatment.[9–11]

Changes in health care reimbursement have resulted in conflicted PCP incentives to recognize and treat psychiatric problems.[12] On the one hand, prepaid, provider-risk plans, such as health maintenance organizations (HMOs) and other capitated programs, have exposed the expensive use of general medical services by patients with untreated or poorly managed psychiatric illness. This statistic serves as an incentive for the PCP to initiate treatment for the more common psychiatric problems seen in primary care. On the other hand, the PCP gate-keeper system, which evolved to manage the expense of specialty care, can be a disincentive to the recognition of more serious mental illness or any mental condition the PCP is not comfortable treating. Managed care organizations (MCOs) often "carve out" behavioral health care and relegate it to managed behavioral health care organizations (MBHOs),[13] which may have limited referral networks that do not include the PCP's psychiatric colleagues. This situation makes the referral process a time-consuming disincentive and complicates future communication and collaboration between mental health and physical health providers.

Many of the MBHOs have spearheaded initiatives to promote treatment of common psychiatric problems in the primary care setting. However, because most do not have credentialed nonpsychiatric physicians, or have not contracted with them, this has essentially shifted the cost of the PCP's treatment of psychiatric problems to the (medical) MCOs. As managed care entities begin to see the value of promoting total health care, rather than focusing solely on cost containment, they also seek to "carve in" MBHO services (i.e., by co-locating behavioral health clinicians in their medical management units, for better collaboration and coordination of appropriate services). If another enlightened trend, the mixed services agreements (i.e., agreements between MCOs and MBHOs to reimburse providers for treating the patient in the most appropriate setting while negotiating their respective financial responsibilities based on the medical and psychiatric natures of the condition being treated) were to eventually migrate from the inpatient to the outpatient arena, negating the cost-shift issue, PCPs might have further incentive to treat their patients' common psychiatric problems in the primary care setting.

EPIDEMIOLOGY

In the early 1980s, the Epidemiologic Catchment Area (ECA) study attempted to quantify the prevalence of psychiatric problems in the general U.S. population. During a 6-month interval, the study found that roughly 7% of community residents sought help for a mental health problem. More than 60% of these individuals never saw a mental health professional but instead sought care in a medical setting (such as in the emergency department or from their PCP).[14] Even among those who met full criteria for a diagnosable psychiatric disorder, 75% were seen only in the general medical (rather than the mental health or psychiatric) setting.[15] Psychiatric distress, therefore, was exceedingly common among primary care populations. About half of general medical outpatients had some psychiatric symptoms. The use of structured diagnostic interviews detected a prevalence of 25% to 35% for diagnosable psychiatric conditions in this patient population. However, roughly 10% of primary care patients had significant psychiatric symptoms that did not meet criteria for a recognizable psychiatric disorder.[16] Of the full-criteria disorders, the vast majority were mood disorders (80%), with depression being the most

prevalent (60%) and anxiety a distant second (20%). The more severe disorders (e.g., psychotic disorders) were more likely to be treated by mental health professionals.[15]

The National Comorbidity Survey (NCS), conducted from 1990 to 1992, found a lifetime prevalence of one or more psychiatric disorders in U.S. adults of about 50%, with a 30% 1-year prevalence of at least one disorder.[17] Alcohol dependence and major depression were the most common disorders.

In 2001 to 2002, a rigorous replication of the NCS (NCS-R) was undertaken to incorporate measures of severity, clinical significance, overall disability, and role impairment.[18] The NCS-R revealed the risk of major depression to be relatively low until early adolescence, when it began to rise in a linear fashion. The slope of that line has become steeper for each successive birth cohort since World War II. The lifetime prevalence of significant depression is 16.2%; the 12-month prevalence is 6.6%.

Two findings, however, are of particular interest. One is that 55.1% of depressed community respondents seeking care now receive that care in the mental health sector. The other significant finding, attributable to advances in pharmacotherapy and educational efforts, is that 90% of respondents treated for depression in any medical setting now receive medication. Although this suggests improvement in the community treatment of depression, it is tempered by two further findings. One is that almost half (42.7%) of patients with depression still receive no treatment. The other significant finding is that only 21.6% of patients receive what recent, evidence-based guidelines (from the American Psychiatric Association and the Agency for Healthcare Research and Quality) would consider minimally adequate treatment (64.3% of those treated by mental health providers, and 41.3% of those treated by general medical providers).[18]

Much has been made of PCPs' failure to diagnose over half of the full-criteria mental disorders present in their patients,[19,20] but there is cause to reconsider the significance of the PCPs' failure to diagnose. Later studies have indicated that PCPs recognize disorders in their more seriously depressed[21] or anxious[22] patients, and that higher-functioning, less severely symptomatic primary care patients have relatively good outcomes, even with short courses of relatively low dosage medication. This spotlights the diagnostic ambiguity in primary care: these patients are different from those who seek specialty care (the population in whom most psychiatric research is done). Primary care patients tend to present earlier in the course of their illness, as they have an established relationship with their PCP that is not dependent on their having a psychiatric disorder. They frequently present with somatic complaints (the rightful domain of the PCP, after all), rather than psychiatric symptoms. Primary care patients also may have acute psychiatric symptoms that clear relatively quickly, even before medications have reached therapeutic levels (possibly because the condition being treated was an adjustment disorder). Such individuals might benefit as much from watchful waiting and from the empathic support of their PCP. There is a high noise-to-signal ratio in psychiatrically distressed primary care patients. That is, as many as one third of these significantly distressed patients have subsyndromal disorders that do not meet full *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria for a diagnosable mental disorder. This diagnostic ambiguity in the general medical setting is paralleled by the relatively good outcomes that primary care patients experience on what most psychiatrists would consider subtherapeutic dosages of psychotropics for inadequate durations.[19,23] Much of the angst of primary care patients resolves spontaneously, either with resolution of an initiating event, with the expressed concern of caregivers, or with the placebo effect of a few days' medication.

BARRIERS TO TREATMENT

Although symptom recognition is necessary, it is not sufficient to ensure treatment of psychiatric problems in the primary care setting.[24] Even when PCPs are informed of the results of standardized screening tests, they may not initiate treatment. PCP, patient, and systems factors collude to inhibit the discussion necessary to promote treatment ("don't ask, don't tell").[25]

Physician factors, the "don't ask" part of the equation, include the failure to take a social history or to perform a mental status examination.[26] This behavior has been attributed to deficits in training of medical students and residents,[27] to time and productivity pressures, and to personal defenses (such as identification, denial,[28] or isolation of affect). PCPs are experienced and more comfortable addressing their patients' physical complaints. Some PCPs fear their patients will leave their practice if asked about mental health issues. The PCP, like many patients, may not believe treatment will help. Not having a ready response or approach to a problem is a major deterrent to identification of a new problem in the context of a 15-minute primary care visit. Denial or avoidance may prevail when the time-pressured PCP feels unsure of how, or whether, to treat or to refer.

Stigma, which is prevalent among patients and providers, is a major patient deterrent to initiating a discussion of psychiatric symptoms. Often, patients "don't tell" because of shame or embarrassment. They may believe psychiatric problems are a personal weakness, and they may perceive that their PCP shares this belief. Patients may not know they have a diagnosable or treatable mental disorder.[29] These are among the reasons that primary care patients more frequently have physical complaints. Somatic complaints also increase the diagnostic complexity,[30] because medical disorders may simulate psychiatric disorders, psychiatric disorders may lead to physical symptoms, and psychiatric and medical disorders may co-exist.

Systems factors include the ever-changing health care finance and reimbursement climate. This encompasses managed care, carve-outs, provider risk, capitation, fee-for-service, free care, coding nuances, differential formularies, and prior authorization, all of which promote financial imperatives to contain cost and to increase efficiency. The systemic instability, confusion, and administrative time-creep easily overshadow the impulse to pursue the treatment of a possibly self-limited condition. Mental health carve-outs have either eliminated or greatly complicated the possibility of reimbursing PCP treatment of mental disorders. Prepaid plans, such as HMOs, significantly decrease incentives to offer anything "extra."[31] The

necessity to increase productivity has excessively shortened the routine visit, now often lasting less than 15 minutes, and the excessive burden of required documentation further erodes clinically available time. (The implementation in some practices of the electronic medical record [EMR] has standardized and improved screening, documentation, and follow-up[32] but has introduced further time-consumption issues.) The care-promoting advent of new, safer, more tolerable psychotropic medications has been offset by soaring pharmacy costs and by restrictive (possibly short-sighted[33]) formularies. The practice of primary care has reached a crisis point where the pressures are so overwhelming that few PCPs can sustain full-time clinical practice.

THE GOALS OF COLLABORATION

The four major goals of collaboration are to improve access, treatment, outcomes, and communication.

Access

Collaborative care in the primary care setting addresses physician and patient factors that limit the patient's access to appropriate assessment and treatment. Most patients are not new to the general medical setting and, therefore, feel relatively comfortable and unstigmatized in that setting. On the other hand, they may believe that the mental health clinic is for crazy people, and that they do not identify with the (perceived) clientele (it's not that they *believe* they don't identify, it's that they *don't* identify). A specified mental health wing or floor in the primary care setting may hold that same stigma and act as a disincentive for patients to access treatment. Most patients do not know of a psychiatrist or how to access care from one and may not feel certain that they need one. The unaided decision to foray into the mental health arena may be fraught with shame and anxiety, powerful deterrents to making that first call. Calling the PCP's office and making an appointment for fatigue, sleep problems, weight loss, or palpitations is infinitely less threatening.

An established relationship between the PCP and a trusted, accessible psychiatric consultant removes the onus of recognizing, treating, or referring patients with mental disorders. With this availability of expert opinion and backup, PCPs more readily identify psychiatric distress in their patients and are more likely to initiate treatment.

Treatment

In the past, PCPs often prescribed insufficient dosages of medications (e.g., amitriptyline 25 mg) for major depression.[34] Since the advent of safer, better-tolerated medications, such as selective serotonin reuptake inhibitors, the selection of medications by PCPs has improved,[35,36] although the dosage chosen often remains suboptimal. Benzodiazepines have been prescribed by PCPs more frequently than any other class of psychotropic medication, even for major depression,[37] although they now are appropriately surpassed by antidepressant prescriptions.[36] Collaboration with the consultation psychiatrist can improve the choice, dosage, and management of psychotropic medications. Collaboration is also helpful when the medication with which the PCP might be most familiar is off-formulary on a given patient's pharmacy plan. Such a treatment deterrent may instead become an opportunity for brief and pragmatic education.

Outcomes

Several studies have demonstrated better outcomes for seriously depressed primary care patients treated collaboratively by their PCP and a psychiatrist.[38–40] Cost offset, however, is difficult to demonstrate because of the hidden costs of psychiatric disability.[7,41,42] Nonetheless, there is some evidence for a decrease in total health care spending when mental health problems are adequately addressed.[11] Even if this were not so, the case for cost-effectiveness could be made.[9,43–45] That is, care for the patient's psychiatric problem is more cost-effective than spending the same amount of money addressing the often nonresponsive, somatic complaints of high-maintenance, high-cost medical patients.

Communication

Collaboration ends the PCP's justifiable complaint of the "black box" of psychiatry, because communication is implicit in these models of care. The flow of information is useful for the psychiatrist and for the PCP and must be bidirectional. PCPs' referrals provide pertinent information and state the clinical question. In addition to the target psychiatric symptoms, the PCP has important information about the medical history, allergies, treatments, and medications. The collaborating psychiatrist shares findings, diagnostic impressions, and treatment recommendations. Information about referrals and consultations should be written and, whenever possible, provided verbally. This protocol improves documentation and ensures an understanding between collaborating care providers. Secure e-mail environments may also provide a venue for almost immediate feedback and a focus on the pertinent details for the busy PCP.

Patients, of course, must be aware of the collaborative relationship between the PCP and the psychiatrist, and of their shared communication.

ROLES, RELATIONSHIPS, AND EXPECTATIONS

Successful collaboration requires a clear understanding of roles and their definitions. All parties, including the patient, should recognize the PCP's responsibility for the patient's overall care. The PCP is the broker and overseer of all specialty services. The psychiatrist is a consultant to the PCP and sometimes a co-treater, depending on the model employed. Collaboration does not breach patient confidentiality because the PCP and the psychiatrist are now within the circle of care, and the patient is informed of this relationship.

However, this free flow of communication and documentation has reasonable limitations. If a patient asks that particular details not be placed in the general medical record and these details do not directly affect medical care (e.g., a history of childhood incest), it is reasonable to respect this wish. The pertinent information (e.g., the

experience of childhood trauma) can be expressed in more general terms. However, information that affects medical treatment (e.g., current or past drug addiction) or safety (e.g., suicidal or homicidal intent, or previous suicide attempt) cannot be withheld from the PCP, and the patient should be so informed.

When the PCP refers the patient to the psychiatrist, the patient should understand what to expect from the visit. At the start of the visit, the psychiatric consultant should clearly and consistently state the parameters of the contact (e.g., whether it will be a one-time consultation, with or without the possibility of medication follow-up, or a referral for therapy). If the psychiatrist sees the patient more than once, the relationship between the PCP and psychiatrist may need to be restated. The clarity of the providers' roles and relationship serves to spare the patient a sense of abandonment, either by the PCP when the patient is referred to the psychiatrist, or by the psychiatrist when the patient is returned to the PCP for ongoing psychiatric management.

In collaborative models of care, it is common for the psychiatric notes to be placed in the general medical record, which may raise issues of confidentiality and privacy. Most states require a specific release for mental health or substance abuse treatment records. Psychiatric or mental health notes in the general medical record should be color-coded or otherwise flagged so that they can be removed when records are copied for general medical release of information. In practices with an EMR, some coding system must also be in place to avoid the inadvertent release of this information. (As mental health issues are increasingly treated by PCPs, the question of how PCPs document and protect such information is a growing concern in the era of the Health Insurance Portability and Accountability Act [HIPAA] of 1996, and it is hoped that they will be addressed in a way that does not further complicate and deter such treatment.)

MODELS OF COLLABORATION

Collaborative models differ in a number of ways, such as where the patient is seen, whether there is a single medical record, how providers communicate, whether the consultant recommends or initiates treatment, and whether the psychiatrist sees the patient (at all, once, more than once) or is an ongoing treater. Other differences include whether both providers are part of the same medical staff and how (physically, by telephone, or electronically) available the psychiatrist is to the PCP.

Outpatient Consultation Models

Consultation implies collaboration: the PCP refers the patient to the psychiatrist, or the PCP presents the patient to the psychiatrist to obtain expert advice or recommendations. Depending on the setting or the system, one medical record may be shared, or providers may maintain separate records and share pertinent information. Patients may be seen in either the psychiatric or the primary care setting.

Outpatient consultation differs from the practice of private psychiatrists who may have established referral sources in the primary care sector. Such psychiatrists generally do not develop truly collaborative relationships, with ongoing communication or shared records. They treat in parallel, not in collaboration.

Specialty Psychiatric Clinics

Specialty psychiatric clinics (such as an eating disorders clinic) generally maintain separate records, require the patient to be seen in the psychiatric clinic, and develop some means of ongoing, clinically relevant communication with the PCP. Patients typically need to have well-defined and recognized problems to get referred, and such clinics are usually located in teaching hospitals or tertiary care centers, as opposed to the PCP's practice setting. Although stigma may interfere with patient adherence to such a referral, one major advantage of such clinics is the expert, multidisciplinary approach they provide for patients with complex psychiatric and medical problems.

Consultation Psychiatrists

Consultation psychiatrists[46,47] may render a one-visit opinion in the primary care clinic, or the patient may be seen in the consultant psychiatrist's office, just as with other specialty consultations. This model is similar to the consultation model used in the inpatient medical setting. The consultation should be written or transcribed into the primary care record. Immediate communication, in person, whenever possible, or by phone or secure e-mail or voice mail, greatly enhances the usefulness of such consultations. The consultant generally does not initiate treatment but makes practical recommendations. The role of the PCP (especially when the consultation occurs in the primary care setting) enhances patient participation and decreases stigma. This model also promotes opportunities for ongoing informal education between the PCP and the consultant.

Psychiatric Teleconsultation

Psychiatric teleconsultation[48] is a service with full-time, experienced consultation psychiatrists available for immediate telephone consultation to PCPs. This service, which is not accessible to patients, can provide general psychiatric information, consultation about pharmacologic or behavioral management, or triage and referral functions. Computer technology is used to maintain a database, to promote timely referrals, and to generate follow-up letters to PCPs. There is currently no direct third-party reimbursement for the full-time teleconsultant's services. At one time, increased capitation was expected to provide a funding source because of the cost-offset of this timely service. That expectation, however, was never realized, which effectively terminated some of these services. (Some rural states are funding this option for psychiatric consultation in remote areas.)

The Three-Component Model

Supported by the MacArthur Initiative on Depression and Primary Care, a three-component model[49] (TCM) is a formalized system of consultative care that promotes the

primary care treatment of depression as a chronic disease, with regular measures of adherence and outcome to guide the evidence-based protocol of medication and other treatment adjustments. Educational modules exist for PCPs, consultant psychiatrists, phone-based care managers, and patients. The Patient Health Questionnaire-9 (PHQ-9) (a 10-item, one-page, self-administered tool that quantifies the patient's neurovegetative symptoms of depression[50]) is repeatedly used to track the patient's progress. Multiple measures of symptoms and treatment adherence are recorded on a standard form that facilitates consultation, communication, organized treatment review, planning, and adjustment.

Dissemination of the TCM model, and of its standardized materials, manuals, and educational modules, addresses the need to improve care for this large population (i.e., patients receiving depression treatment in the primary care setting) while also providing data to inform policy (and payment) decisions. Similar evidence-based endeavors underway include the Health Disparities Collaboratives (the combined effort of the Department of Health and Human Services, Health Resources and Services Administration, and the Bureau of Primary Health Care) and the IMPACT model[51] (initially funded by the John A Hartford, California HealthCare, Hogg, and Robert Wood Johnson Foundations).

Psychiatrist on the Primary Care Clinic Medical Staff

When the psychiatrist is a medical staff colleague of the PCP, there are enhanced possibilities for collaboration and shared care. This PCP–consultant proximity facilitates communication, formal and informal education, immediate access via "curbside" consultation, and heightened PCP awareness of psychiatric problems in their patients. This arrangement can also provide an excellent opportunity for training of both psychiatric and primary care residents. Patients appreciate being seen in the more familiar primary care setting, and they feel less stigmatized.

Several models of care have evolved or been developed to use the services of an in-house psychiatrist. The psychiatrist may consult as a member of the medical team, evaluate and treat patients in parallel with the PCP, alternate visits with the PCP while treatment is initiated,[9,40,51] or evaluate, stabilize, and return the patient to the PCP with recommendations for continued care, or facilitate referrals to outside mental health providers.[52]

Staff Consultant

Consultations, as mentioned earlier, are written in the regular medical record. The permanency of the psychiatrist allows a more finely tuned consultant–PCP relationship. For instance, with a previously established agreement, the consultant may initiate the recommended treatment. The consultation psychiatrist may offer clinically relevant suggestions during case conferences or discussions of more complex patients. The psychiatrist may also see the patient with the PCP during the primary care visit, capitalizing on the PCP's extensive knowledge of, and long-term relationship with, the patient to provide more timely treatment recommendations. In one such consultation model, a consultant and several clinicians travel to several primary care clinics in the larger health care system, and provide a variety of consultative, educational, and treatment services.[47]

Parallel Care

Some clinics keep separate mental health charts when the psychiatrist assumes the ongoing psychiatric care of patients in parallel with the PCP. This option requires some overt means of communication to keep all providers informed. In clinics with EMR, a single up-to-date medication list at least keeps both providers aware of current medications and medication changes.

Some primary care clinics incorporate a mental health unit or clinic. If this is an identifiable, special area within the clinic, it has the same stigma that it has when the clinics are truly separate. The larger the clinic and the more separate the clinical services, even when they are in the same circle of care, the greater is the diligence required on the part of each provider to meet the challenge of continued communication.

The psychiatric capacity of primary care clinics that offer these services is often inadequate to meet the needs of the total patient population. This situation can be challenging and can delay access because most patients would like to be treated in this setting. Uniform criteria facilitate the triage of patients for in-house treatment or outside referral. These criteria include justifiable considerations such as diagnosis, available community resources, language requirements, or payment source. Certain unstable or less common psychiatric problems may be better served in the mental health sector, either in community clinics with wrap-around services or in specific subspecialty clinics. In most communities, English-speaking patients have more options for treatment. Depending on the location and availability of appropriate, non–English-speaking services, patients may be preferentially kept in house or referred out. When otherwise appropriate, capitation favors treating the patient in-house. Patients with insurance generally have more options outside the primary care setting, and some insurance plans with mental health carve-outs may not cover psychiatric care in the same setting in which they cover medical services.

Collaborative Management

In collaborative management,[40,53] the patient alternates visits between the psychiatrist and the PCP in the primary care setting during initiation of treatment (i.e., in the first 4 to 6 weeks). The PCP then assumes responsibility for the patient's continued psychopharmacologic treatment. This model was developed as a research protocol for the treatment of depressed primary care patients (and it has been extended to the treatment of panic disorder[9] and patients with persistent depressive symptoms[53]). Patients are referred by the PCP, usually after an initial ineffective trial of medication. This intensive program of care has been cost effective for more severely depressed primary care patients.

Implicit to this model are certain underlying assumptions. Collaborative management assumes that PCPs can initiate appropriate treatment for depression, manage the

care of patients stabilized on antidepressant medications, and better care for more seriously depressed patients with the collaboration of in-house psychiatric consultation.[54] This model also assumes that such collaboration begins with PCP education and training. In addition, PCPs participate in regular teaching conferences. A psychoeducational module for patients is also an integral part of the treatment.

Primary Care–Driven Model

The primary care–driven model[52] evolved from the practical need to assist PCPs in the provision of quality psychiatric care for their own primary care patients with limited psychiatric resources. This model incorporates elements of consultation, teleconsultation, and collaborative management, with the goal of maximizing the treatment of appropriate primary care patients in the primary care setting. Established criteria are used for triage, with the appropriateness of PCP management being the first consideration. Photocopies or electronic copies of all psychiatric notes and evaluations are sent to the PCP and placed in the regular medical record. The clinic provides psychiatric training for both psychiatric and primary care residents. The underlying assumptions of this model (Table 49–1) include those of the collaborative management model, but they are more extensive, reflective of the broader diagnostic scope.

In this model, the written (or electronic) request for consultation or referral comes from the PCP. The referral includes the clinical question or problem to be addressed and any PCP-initiated medication trials. PCPs are also encouraged to call or stop by the psychiatrist's office, located in the primary care clinical area, for more general information about diagnoses, medications, or psychiatric and behavioral management.

Psychiatric services include formal evaluation, stabilization over several visits, and return of the patient to the PCP's care (with recommendations on how to take and how long to continue medications and when to re-refer). The psychiatrist also provides informal (curbside) consultation, brief consultation with the patient and the PCP during the patient's primary care visit, and behavioral treatment planning for the difficult-to-manage patient. Re-evaluation of patients previously seen occurs when there is a change, such as roughening (i.e., the recurrence of symptoms during the course of treatment), the development of new psychiatric symptoms or medication side effects, or a change in the medical condition or medications that affect psychiatric symptoms or medications. When a patient does not meet criteria for in-house treatment, the psychiatrist facilitates the referral to an outside psychiatrist or therapist (or both). Other mental health services include focused, short-term, and goal-oriented therapy, either individual or group (with master's degree–level clinicians located in the primary care clinical areas they serve). Collaborative care management is another service that helps broker and coordinate the care of patients with complicated medical, mental health, and addiction problems who use services in multiple settings.

TABLE 49–1 Underlying Assumptions of the Primary Care–Driven Model

Collaboration begins with education of primary care physicians (PCPs) *and* psychiatrists.
Patients' psychiatric needs should be met in the primary care setting when consistent with good care.
PCPs can manage the care of patients stabilized on psychiatric medications.
PCPs can initiate appropriate treatment for some psychiatric disorders.
PCPs can better care for the psychiatric needs of more patients with the collaboration of in-house psychiatric consultation.
Some patients and some disorders are unlikely to be stable enough for PCP management.
Responsibility for total care requires communication between the PCP and any other involved care provider or consultant.

A premise of the primary care–driven model is that not all patients are appropriate for PCP management. The psychiatrist should help the PCP recognize which patients need ongoing specialty care, and then assist with appropriate referral. Patients not recommended for PCP management include those with inherently unstable conditions, or with complicated medication regimens, or those who require close monitoring. Examples include patients with bipolar disorder, psychotic disorders, suicidal ideation, severe personality disorders, or primary substance abuse or dependence problems.

Collaborative care management is a program that bridges the needs for communication and coordination when patients must access services outside the primary care setting. It improves the care of patients with complex medical, psychiatric, and addiction problems that often require treatment spanning several community agencies. After a comprehensive diagnostic and functional assessment, necessary releases are signed so that the care manager can serve as a liaison between the PCP and all other care providers. The care manager involves the patient and all treaters in the development of a comprehensive treatment plan within a network of services, and tracks the patient from site to site throughout this plan. As a member of the discharge planning team, the care manager ensures that the patient returns to the appropriate network of services after care in a hospital, a detoxification program, or another residential or institutional setting. Like teleconsultation, the existence of this useful program has been severely limited by the lack of sustainable reimbursement sources. Some insurance plans and MBHOs are now trying to fill this gap with their own intensive case (or care) management programs for members who are frequent users of multiple services.

CHOOSING THE RIGHT MODEL

The choice of model for a given clinical setting depends on a variety of factors—patient population, payer mix, range of available community resources, and the location, type and size of the practice. Patients with higher educational or socioeconomic status may feel less stigmatized and be more able and willing to seek and pay for outside psychiatric services.[55] Some patients feel more comfortable in private practice settings that allow the greatest possible privacy. Mental health problems are less acceptable or even shameful in some cultures. These patient populations will favor a

more integrated and less visible system of care in the primary care setting. Capitation would most clearly demonstrate the cost offset and cost effectiveness of in-house collaborative models (and teleconsultation, if the market penetration is ever high enough). The primary care–driven model requires adequate community resources to refer patients not considered appropriate for primary care management. Suburban or rural areas that lack these resources are better served by parallel, or shared, care models. Small groups or solo practitioners may favor consultation models, either with a part-time but regularly scheduled consultant or through access to an outside consultant or teleconsultant as needed. Large practices, and especially training facilities, benefit most from the full range of in-house consultative and collaborative services that include formal education, case conferences, curbside consultation, and collaborative care management.

SUMMARY

Though mandated by changes in the health care system, collaborative models increase access and improve treatment for patients who would be unable or unlikely to receive psychiatric care outside the primary care setting. As states move to promote the concept of the "medical home" (i.e., bringing all specialties into the primary care realm and under the coordinating auspices of the PCP, especially for patients with complex medical, mental, and developmental conditions),[56] psychiatric services in the primary care setting may become not only more acceptable but also expected or even mandated. A number of considerations determine the best model for a given practice setting. Such factors include size, patient population, available community resources, payer mix, and other reimbursement sources. To remain viable, high-quality and cost-effective models need to adapt and evolve with the changing health care system. Psychiatrists and PCPs need to be flexible and innovative in their approaches to patient care, and to be diligent in the documentation of cost-offset to encourage payers to reimburse their services.[57,58] Medical,[59] psychiatric, and patient education services need to reflect these changes in caregiver roles and expectations.

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Coping with the Rigors of Psychiatric Practice

50

Abigail L. Donovan, M.D.
Edward Messner, M.D.
Theodore A. Stern, M.D.

The practice of medicine is focused on disease, not health, and on treatment, not primary prevention. Therefore, it should not be surprising that physicians have difficulty maintaining their own health, minimizing their stress, and preventing burnout in their own lives. Throughout medicine (and especially in psychiatry), clinicians confront suffering and despair more often than they see success and happiness. In addition, the very same character traits that make physicians successful (e.g., perfectionism, an exaggerated sense of responsibility, and selflessness) also make physicians vulnerable to stress.

Stress can be defined as the condition that occurs in response to adverse external influences; it is capable of affecting both physical and psychological health. The daily stress of practicing medicine, when left unaddressed or unmanaged, can progress over time to burnout. Burnout is a pathologic syndrome in which prolonged occupational stress leads to emotional and physical depletion and ultimately to the development of maladaptive behaviors (e.g., cynicism, depersonalization, hostility, detachment). Understanding the root causes of stress and burnout, exploring ways to reduce vulnerability to burnout, and learning skills to cope with the stresses inherent in psychiatric practice are important factors in building and maintaining a successful career and establishing a fulfilling life.

EPIDEMIOLOGY

Despite their academic, vocational, and societal success, physicians are immune to neither disease nor suffering. The practice of medicine is inherently stressful, and physicians are at high risk for burnout. Reported rates of burnout for practicing physicians range between 22%[1] and 60%[2]; these rates are even higher for residents (as high as 75% in one study[3]). In addition, physicians are also at risk for experiencing high levels of emotional distress, given the nature of their work; studies that have identified high rates of suicide among physicians support this idea. Whereas physicians, as a group, have lower mortality rates from several diseases (e.g., chronic obstructive pulmonary disease, liver disease), they have a higher rate of suicide than do other professionals and members of the general population[4] (Figure 50–1); for male physicians, the relative risk ranges from 1.1 to 3.4, and for female physicians, the relative risk ranges from 2.5 to 5.7.[5] In the general population, the suicide rate is four times higher for men than it is for women; in physicians, the rate of suicide for women is equal to that of men.[6] Up to 12% of physicians report an increased use of substances during residency[7]; psychiatrists have particularly high rates of substance abuse compared to those in other medical specialties.

ETIOLOGIES FOR STRESS AND BURNOUT

The practice of medicine in today's society is challenging and rewarding; however, it is also stressful and not without the potential for burnout. Several aspects of psychiatric practice leave the psychiatrist especially vulnerable to stress and, ultimately, to burnout (Figure 50–2).

Frequent Encounters with Distress

Psychiatrists encounter human suffering on a daily basis. The nature of psychiatric practice is that clinicians witness countless stories of sadness, anger, and betrayal. Although moments of joy and happiness can arise, they often seem few and far between. The chronic and devastating nature of many psychiatric diseases increases the emotional burden on the clinician. Because psychiatrists must remain emotionally available to their patients to experience and to express the empathy that is necessary for the formation of an alliance, this emotional availability makes psychiatrists particularly vulnerable to suffering alongside their patients (even though they must consistently maintain enough distance to remain objective). Therefore, a critical balance must be maintained and a precise emotional distance must be preserved.

Ethical Dilemmas

The patient's reliance on the psychiatrist for guidance can raise a host of ethical conflicts. Psychiatrists can find themselves in the position of watching their patients make unwise, and even dangerous, decisions and being unable to curtail this destructive behavior. Psychiatrists might have to enforce mandated treatment regimens, to hospitalize patients against their will, or even to physically or chemically restrain violent patients. There may even be times when a psychiatrist must intentionally break a patient's confidentiality for his or her safety or for the safety of another. None of these decisions is made lightly, and each requires a great deal of reflection and emotional energy.

Transference and Countertransference

The daily practice of psychiatry is filled by issues of transference and countertransference, which can lead to the development of intense emotions (e.g., hostility, aggression,

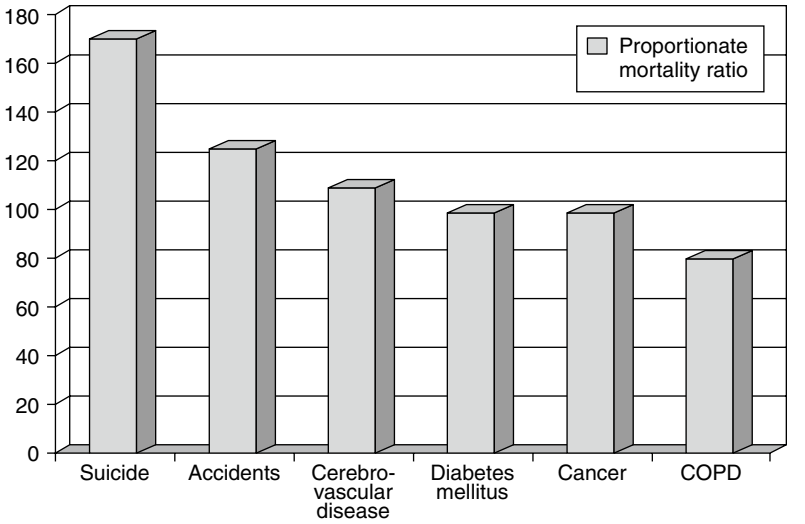

Figure 50–1. Proportionate Mortality Ratio for Causes of Death Among White Male Physicians. The Proportionate Mortality Ratio compares the proportion of deaths due to a specific cause in white male physicians with the proportion of that cause of death in all white male professionals. *(From Linzer M, Visser MR, Oort FJ et al: Predicting and preventing physician burnout: results from the United States and the Netherlands,* Am J Med *111(2):170–175, 2001.)*

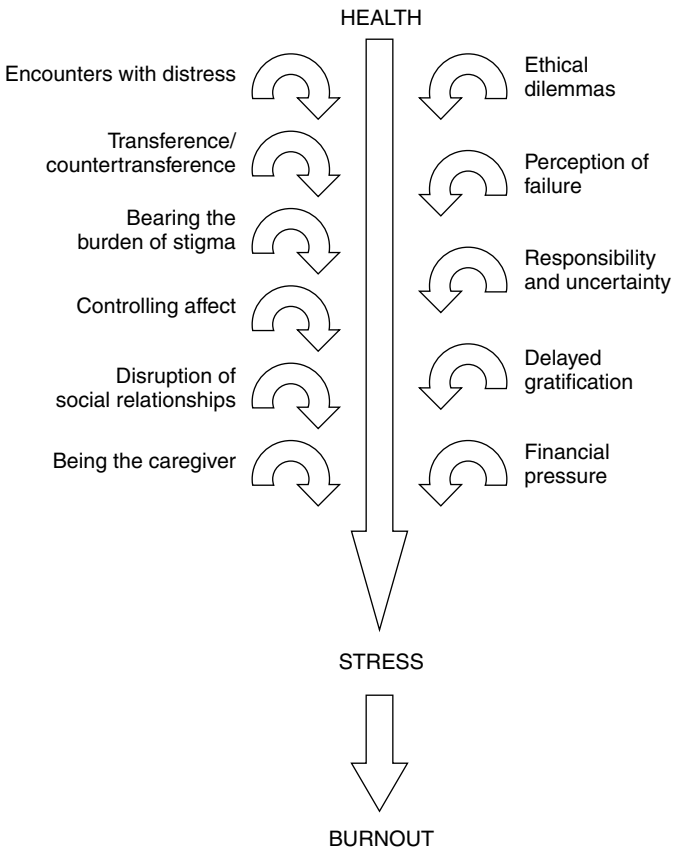

Figure 50–2. Etiologies of stress.

love) in the patient and in the clinician. Furthermore, several psychiatric illnesses have, as core symptoms, difficulty with interpersonal interactions. Afflicted patients, including those with borderline personality disorder and narcissistic personality disorder, can pose a special challenge to the psychiatrist. Coping with intense transference, while monitoring one's own countertransference, can be exhausting; it is a daily challenge for most psychiatrists.

The Perception of Failure

Psychiatrists treat chronic illnesses, which are subject to relapse and carry significant morbidity and mortality risks; thus, the very nature of psychiatric disease can lead the psychiatrist to experience feelings of failure as a doctor and as a healer. Despite knowledge of treatment-response rates, psychiatrists might ponder the notion that if they could

only find the right medication or say the right words, the patient would be healed. Failure to respond to treatment can be, and often is, viewed as a failure of both the medical intervention and the treater. The fact remains that due to the nature of psychiatric disease, not every patient will be healed; the psychiatrist then might experience feelings of failure.

BEARING THE BURDEN OF STIGMA

Psychiatry and its practitioners have come under intense public scrutiny. Psychiatric treatment, medications, and research have been called into question by the media, by the government, and by popular culture icons. Furthermore, whereas psychiatric successes take place behind closed doors, treatment failures have grown increasingly public and act as lightning rods for the stigma of mental illness. This public criticism can be disheartening and demoralizing; it can be difficult to maintain pride in one's work and accomplishments in the face of such challenges.

Controlling Affect

Despite the intensely emotional nature of psychiatric work, psychiatrists must consistently control their affect to do their jobs well. Although this control is necessary for the practice of psychiatry, it can ultimately lead to increased stress and vulnerability to burnout. Instead, informal debriefings with colleagues, or formal supervision, can encourage the necessary expression of what is controlled during patient encounters.

Responsibility and Uncertainty

The practice of psychiatry is multidimensional, and it incorporates interpersonal and individual dynamics, sociology, biology, and pharmacology. The complex nature of psychiatry also makes it an exhilarating, yet uncertain field. Although the breadth and depth of psychiatric research are growing exponentially, there is still a dearth of research to guide many clinical decisions; moreover, psychiatrists must often base clinical decisions on biased, incomplete, or ambiguous data. Challenges faced are further compounded by the added stress of answering to institutions, to insurers, to patients, and to their families. Health insurance organizations often establish standards of care without psychiatrist involvement; this can undermine the pride and self-determination of practitioners. Psychiatrists can find themselves in the difficult position of not being able to provide the treatment they believe is best; instead they may offer assistance based on the policies created by nonclinicians.

Disruption of Social Relationships

Psychiatrists often work in isolation; this leaves them alone to face the effect of psychopathology and disease. Furthermore, rules regarding confidentiality inhibit sharing the details of one's day with family and friends. Social engagements and family time can be interrupted (without warning) by emergencies. These factors can fracture social relationships, decrease social support, and increase the risk of burnout. Vocational burnout is, in turn, associated with low satisfaction in relationships (with patients and with clinical staff).

Delayed Gratification

The ability to delay gratification is an important developmental milestone. The practice of medicine raises it to an art form. But this skill, when taken to an extreme, can lead to burnout. Physicians may be tempted to put personal, non–work-related goals on hold, in the service of career success (e.g., "I can't get married, have children, or buy a house until I finish residency, have a stable practice, or have enough money in the bank."). Such rationalizations can be extended indefinitely and can lead to a life lacking balance and devoid of nonvocational success.

Being the Caregiver

Psychiatrists often have a strong need to be needed and to care for others. These traits are part of what initially draws individuals to the practice of psychiatry. At the same time, the dependence some patients develop on their psychiatrist can be overwhelming in its intensity. Focusing intently on the needs of others can lead to denial of one's own need to be cared for.

Financial Stress

Although the popular perception is that all doctors make copious amounts of money, the reality is quite different. The cost of medical education can be exorbitant, and it continues to rise each year; however, the salaries of many practitioners do not enjoy the same growth, and the increases in earnings over time might not match the rate of inflation. Many young doctors finish residency with enormous debt and with limited options for repayment and deferment of loans. Furthermore, the practical options for improving one's financial situation are limited to working longer hours or seeing more patients (for shorter periods of time). Either option is likely to increase, rather than to decrease, vocational stress; this pressure may be especially intense for physicians early in their careers.

SPECIAL SITUATIONS IN PSYCHIATRY

Coping with Patient Suicide

A Profound and Enduring Effect

Half of all psychiatrists have had one (or more) of their patients commit suicide[8,9]; approximately one third of those psychiatrists experienced such a loss while they were still in residency training.[8] One quarter of psychiatrists who had experienced patient suicide stated that it had "a profound and enduring effect" on them throughout their careers.[8] Although the practice of most medical specialties entails dealing with death, suicide in the practice of psychiatry takes on additional meaning. Because one of the primary tools in psychiatry is the individual, when the treatment fails, it can feel as if the treater has failed. Furthermore, whereas death from cancer can be seen as inevitable, death from suicide can be viewed as a choice.[10] When coping with a patient's suicide, it is important to remember that "a patient suicide is neither a unique event nor a personal failure."[11]

Reactions to Suicide

The reactions of a psychiatrist to a patient's suicide can be varied and intense. In addition, the psychiatrist must cope not only with his or her own reaction but also with the reactions of the patient's family and friends. The psychiatrist can experience grief, guilt, inadequacy, anxiety, depression, shock, shame, betrayal, and anger. The experience of anger and hostility toward the patient who committed suicide can further trigger guilt and self-blame. A sense of rejection can also be particularly poignant; although the psychiatrist was working to the best of his or her ability and trying all available therapies, the patient has said, through suicide, "You just weren't good enough." Younger clinicians may be especially vulnerable to this intense distress.

Coping

To cope effectively with a patient's suicide, the clinician must give himself or herself permission to experience a variety of emotions. While it may be extremely difficult, experiencing anger and hostility toward the patient is a necessary component of healing. Clinicians might also find themselves ruminating over treatment decisions, asking, "What if . . . ?" Although it is important to review the treatment course to learn from the unfortunate outcome, obsessive ruminations are likely to diminish one's confidence in decision-making and to impair coping with the tragedy. Shame and embarrassment, as well as a sense of personal failure, can prevent a psychiatrist from reaching out to colleagues. However, it is likely that several colleagues have had similar experiences and all may benefit from sharing their experiences.

Treating Dying Patients

In extreme situations, clinicians may find themselves refusing to care for suicidal (or for terminally ill) patients or wanting to leave the practice of psychiatry altogether. These wishes defend against the fear of future traumatic experiences with at-risk patients. Yet, as a seasoned therapist said about the treatment of suicidal patients, "If we do not treat dying patients, our patients will die alone."[12]

Coping with Boundary Crossings and Violations

Boundary Violations

The practice of psychiatry is filled with intense emotions (encouraged by regular, frequent, and lengthy patient contact). The intensity of these emotions, in combination with disruption in a clinician's personal and romantic relationships, can be a setup for boundary crossings and violations.[13] Boundary crossings are considered harmless deviations from clinical practice or from the therapeutic frame; however, boundary violations are deviations that are harmful and exploitive of the patient's emotional, financial, or sexual needs.

Decreasing Vulnerability

Of primary importance is the recognition by all clinicians that they are at risk for boundary violations; denial of this vulnerability prevents introspection and analysis of motives, as well as early consultation for difficult dilemmas. Other factors (including crises at work, at home, or in individual physical or psychological health) can make a psychiatrist particularly vulnerable to boundary violations. In such situations, the clinician may be tempted to confide his or her personal problems to the patient; such self-disclosure should serve as a warning that the clinician is on the precarious rim of the proverbial slippery slope. Other warning signs include idealizing the patient, and thus believing that he or she is deserving of special treatment; holding sessions at the end of the day or even "after hours"; allowing sessions to go on longer than the allotted time; allowing the patient to maintain a large, unpaid bill[14]; and, most important, a reluctance to discuss the case with colleagues or supervisors. Any of these signs should immediately prompt the clinician to seek objective consultation to examine these issues in depth.

Coping with Malpractice Litigation

Practicing medicine in today's society leads many doctors to fear litigation, regardless of actual negligence. This fear can be paralyzing and can lead to the desire to treat only "low-risk" patients. Unfortunately, there are no reliable methods to predict which patients are going to be litigious. Thus, it is the responsibility of the practitioner to cope effectively with the continuous risk of malpractice litigation.

Protecting Yourself

There are steps all practitioners can take to protect themselves against potential litigation. Appropriate documentation is critically important. The most common malpractice claim against psychiatrists occurs in cases where a patient has committed suicide; thus, documentation of both the risks and the protective factors, in addition to the rationalizations behind clinical decisions, is crucial.

Perhaps the most protective factor is a strong alliance with the patient. Maintaining and enhancing the therapeutic alliance can be accomplished in several ways. Clinicians might find it helpful to use language that speaks in terms of a joint effort with the patient, such as "Our problem is . . ." or "Our goal is . . . ." This language allows the clinician and the patient to speak of the therapy as a third entity in the room. It promotes a detachment from the illness and lets the patient know that he or she is not alone in the battle, but rather that he or she will fight right alongside the clinician.

Similarly, it may be beneficial for the clinician to maintain an alliance with the patient's family. This may be difficult to accomplish, because it is essential to maintain a patient's confidentiality. Even if the patient refuses contact, it may be helpful simply to convey one's desire to speak with the family, in the present or in the future. Building an allied and collaborative relationship with a patient is a key component of effective treatment and it might offer some protection against future litigation.

Coping with a Lawsuit

What if a clinician is actually faced with a lawsuit?[15] Unfortunately, the very same traits that constitute careful and competent doctors (e.g., responsibility, perfectionism, high standards) also subject them to self-doubt and to unearned guilt when confronted with a lawsuit. It may be of some solace to remember that only a small percentage of

malpractice lawsuits go to trial, and those that do usually find in favor of the physician. During the preparation, it may be helpful to work closely with your lawyer, restoring a sense of control and ownership over the future. It also is critically important to maintain personal interests and relationships outside of the workplace. Regardless of whether negligence actually occurred, it is normal to feel shame, guilt, and anger during (and even after) a lawsuit.

Coping with Residency Training

The rigors of a psychiatric practice can be demanding, and psychiatric residency training is often especially challenging (for example, a lack of control over daily schedules, sleep deprivation, a caseload filled with difficult-to-treat patients, responsibility without authority, and the need to balance autonomy and dependence). In training, there is also a desire to appear strong and competent to both colleagues and supervisors, leading some residents to view asking for help as a sign of weakness. These factors and multiple role conflicts conspire to make residents especially vulnerable to burnout.[16]

WHEN THE COBBLER'S CHILDREN HAVE NO SHOES

The cobbler was so busy making shoes for everyone else that he neglected to make them for his own children. Similarly, it is easy, in days filled with caring for the needs of others, to neglect one's own needs. Yet, to be good doctors, physicians must care for themselves. Several factors contribute to this type of self-neglect and burnout (Figure 50–3).

Denial of Vulnerability

Many doctors treat themselves as if they were superhuman. Although it is necessary for others to sleep, eat regular meals, and take vacations, physicians often deny their own basic needs. Moreover, psychiatrists wish to see themselves as consummate copers, immune to emotional impairment. When placed under stress, it is common for them to work harder and longer, which ends up compounding the initial problem.

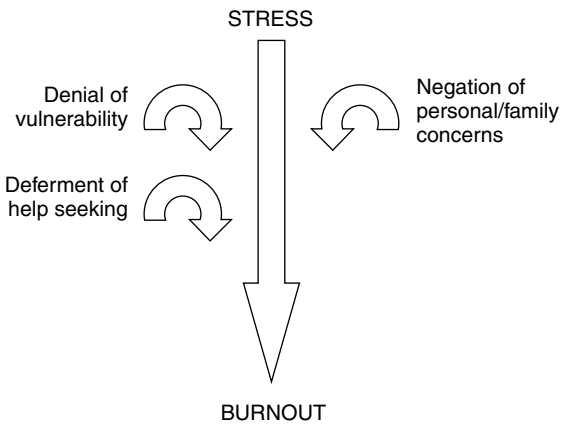

Figure 50–3. Factors contributing to self-neglect.

Negation of Personal and Familial Concerns

Personal and family concerns can be misjudged as being not as critical as is the relieving of pain and suffering. It can seem easy, if not important, to spend 1 more hour at work to see a patient in crisis; however, this can quickly become a practice that rapidly expands and soon becomes a pattern of working longer and sacrificing personal time. After long and stressful days, clinicians may be too emotionally exhausted for empathic listening, even-handed conversation, or recreation. As a result, clinicians can turn inward, internalizing their concerns and cutting themselves off from family and friends. This behavior compromises the strength of family relationships and decreases the support available for the clinician.

Deferment of Seeking Help

It is common to view seeking help for personal or family problems as a sign of frailty or personal failure. Some physicians are reluctant to seek help because of the stigma of mental illness. In general, although psychiatrists may be more open to psychotherapy for themselves, the possibility of a formal diagnosis and breaches of confidentiality, or having to report a problem to a licensing board, can make seeking help difficult. The intense pressure of a doctor's work can foster the creation of unachievable expectations. However, the physician's well-being is only undermined by this intolerance for human vulnerability.

How to Recognize Stress in Oneself

Psychiatrists are good at recognizing stress in others; however, recognizing stress in oneself requires a different skill set. Unrecognized and unmanaged stress can lead to anxiety or to depression, and it can have long-lasting effects for clinicians, patients, and families. Signs of stress include exhaustion, apathy, anhedonia, and despair, as well as somatic manifestations (including headaches and gastrointestinal disturbances). Further warning signs include disrupted sleep, conflict in family relationships, and changes in memory, concentration, and problem-solving ability. Perhaps the most important warning sign is the suggestion from friends, family, and colleagues that help is needed.

Stress can also affect attitudes toward patients. Clinicians may develop reactive misanthropy when they frequently encounter patients' pain and suffering, especially when expressed by the patient as hostility or devaluation. Clinicians might then find that warmth and concern are replaced with apathy, or even defensiveness and contempt. This emotional detachment can progress and carry over to all patients, so that the clinician is no longer able to appreciate fulfilling relationships with patients.

Stress, when prolonged or unmanaged, can progress to burnout. Signs of burnout include detachment from the meaning of one's work, open hostility, cynicism, and overwhelming occupational dissatisfaction. In addition, reactive misanthropy can progress to malignant misanthropy in the burned-out clinician. In this malignant form, the misanthropy one can develop toward a patient extends to other relationships, including those with staff, colleagues, other health professionals, and even friends or family. The unfortunate result is then a conflict with one's social values and intentions, leading to feelings of self-punishment and guilt.

HEALING THE WOUNDED HEALER

Be Your Own Most Important Patient

Maintaining a caring and empathic attitude toward one's patients requires treating oneself with kindness and concern. Whereas all doctors have strong coping skills (how else could physicians make it through training?), these skills can always be expanded and refined. Anticipating and preparing for difficulty, rather than relying on denial, can prevent emotional overload. Some useful coping strategies are outlined here and in Figure 50–4.

Process Experiences Regularly

One should talk with colleagues and supervisors regularly about difficult interactions, even when it means revealing personal vulnerability. Residents, in particular, may be tempted to use supervision as a time to discuss only therapeutic successes or positive interactions, in order to impress their supervisors or to project a sense of competence; however, supervision can be even more valuable when used to discuss difficult patient encounters or conflicted reactions to a patient. It is also possible to process experiences on one's own, perhaps reserving the commute home as a time for reviewing the day's events. Coping with stress on a daily basis, and processing emotions before one arrives home, can make it less likely for one to take the strain of the day out on family or friends. Furthermore, learning important lessons from difficult events can mitigate some of the distress that they cause.

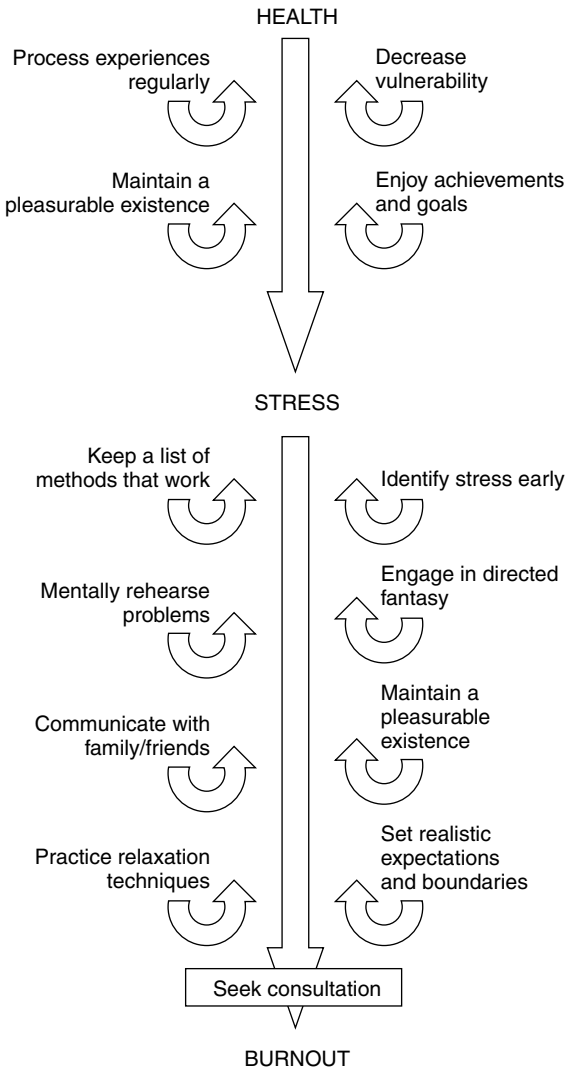

Figure 50–4. Coping with stress and preventing burnout.

Set Realistic Expectations and Boundaries

It can be gratifying and personally pleasing when a patient professes the need to communicate with their physician between sessions, or when a patient forgets an appointment but states he or she cannot possibly wait until the following week to see the treater. Being needed in this way can seem like an affirmation of why one became a doctor: to help those who cannot help themselves. However, speaking with patients frequently between encounters, or for extended periods, not only dilutes the therapeutic process but also adds a time-consuming burden for the physician. Rescheduling appointments again and again when a patient has forgotten the original appointment simply reinforces poor planning and adds additional stress to the physician's already crowded schedule. Although emergencies should be treated as such, physicians who maintain boundaries around phone calls and missed appointments for nonemergency issues protect the therapeutic frame and their own need for a manageable schedule, including time free from responsibilities of patient care.

Review Your Own History

Psychiatrists can identify useful coping strategies from the past and eliminate maladaptive ones. It can also be helpful to identify prior manifestations of stress, so that one can recognize them early and intervene before they reach a caustic level.

Keep a List of Methods That Work

One should make a list of coping strategies that have previously helped. During moments of extreme distress or crisis, it can be difficult to recall adaptive strategies. In addition, one can consider using constructive activities (such as athletics), as a means of discharging anger. Stretching or performing yoga can relieve muscle tension. Even an emotional release through tears can restore a psychic balance.

Decrease Vulnerability to Stress

There are many aspects of clinical practice (such as long hours and copious amounts of paperwork) over which clinicians have no control, but there are factors (e.g., treating physical illness, eating a balanced diet, exercising, getting enough sleep) that the individual can control that can reduce vulnerability to emotional stress.

Doctors are often poor patients. Despite access to health care, many physicians rarely visit their primary care physician, even when they are ill. Unfortunately, untreated illness only compounds stress.

Hectic schedules sometimes dictate meals on-the-go, or no meals at all, but proper nutrition is crucial for a healthy body and a healthy mind.

Exercise releases endorphins, and it can improve mood and energy. Enjoying exercise is an excellent way to relieve stress. Regular physical exercise contributes to physical health and to an overall sense of well-being.

Sleeping at least 8 hours every night has benefits; fatigue can leave one vulnerable to emotional stress and to dysregulation.

Mentally Rehearse Potential Problems

When a potentially difficult meeting or conversation is anticipated, it is helpful to rehearse statements and responses to questions. Having responses in mind before a crisis makes it more likely that one will stay calm in a tense situation. This technique also fosters a sense of control over the unexpected. One can also imagine expressing intense feelings (such as anger, sadness, or fear) as a means of decompression. Fantasizing in this way is most useful when one recognizes that the fantasy is distinct from real action; fantasies need not be enacted.

Engage in Directed Fantasy

One can imagine scenarios that are affectively intense (e.g., hitting a frustrating patient with a fire axe or duct-taping his mouth closed). The more outrageous the fantasies are, the more effective they will be at discharging emotion. The more unrealistic and outlandish, the easier it will be to distinguish between fantasy and a corresponding reality.

Communicate with Family and Friends about Anticipated Unavailability

Communication about one's unavailability will help others prepare and thereby lessen the likelihood that they will respond with anger and withdrawal. As one communicates about future work commitments, one can also make future social commitments. This action allows family and friends to know they are still held in high regard and it sets a framework for ongoing relationships. Above all else, open communication and a sense of togetherness should be maintained; hardship experienced as a team can deepen intimacy and mutual respect.

Enjoy Your Achievements and Your Goals

Previous triumphs should be pondered and joyful moments recalled. Original goals should be remembered, the progress made toward achieving them noted, and new goals for the future set. Being mindful of the progress toward life goals can instil a sense of pride and mastery. The strength gathered from memories of the high points of one's life can facilitate coping with everyday stresses.

Learn and Practice Relaxation Techniques

Tension and overstimulation can make sleep difficult, and the fear of returning to work without rejuvenation can only compound this difficulty. In the midst of this pressure, one may be tempted to resort to the use of alcohol or sedatives. However, one can learn deep-breathing techniques and progressive muscle relaxation to promote tranquillity and sleep. These exercises can also be used in the middle of a hectic day or during a stressful night on call to rejuvenate an exhausted mind and body. Clinicians can also learn self-hypnosis and use it to maximize relaxation during a busy day or to induce sleep reliably and quickly.

Maintain a Pleasurable Existence

It is often helpful to make a commitment to yourself to have one pleasurable experience each day. A pleasurable event can be something as simple as having a cup of tea, taking a short walk outside, reading a favorite poem, or speaking with a friend on the telephone. Even taking a few minutes between patients to stretch, to chat with a colleague, or to have a favorite snack can be rejuvenating. Keeping balance between stress and pleasure on a daily basis prevents burnout and promotes a positive mindset.

WHEN TO SEEK CONSULTATION

Consultation offers an objective point of view; it can be the first step in seeking help for the overwhelmed clinician. Consultation is not a sign of weakness; rather, it is the sign of a wise physician who recognizes that to help patients, one must first help oneself. Consultation should be considered for a variety of problems: symptoms of depression, disabling anxiety, self-prescription, escalating use or abuse of alcohol, inappropriate expressions of anger, impulsive behavior, or impaired clinical judgment. Other signals that should prompt consultation include working longer hours, having trouble in significant relationships, and becoming socially isolated.

TYPES OF PROFESSIONAL HELP

It might not be easy for a clinician to acknowledge that he or she needs professional help. It can be extremely difficult to surrender control when one is used to being in complete control. But it can also be a wise decision, especially to halt a downward spiral.

Psychotherapy

Psychotherapy provides the psychiatrist the valuable opportunity to experience the other side of the therapeutic relationship. Psychotherapy can be a rich, life-enhancing experience, it can improve coping skills, and it provides much-needed support for the overwhelmed clinician.

Psychopharmacology

Many physicians, and many psychiatrists, might see the need for medication as a sign of weakness or failure. However, doctors would rarely fail to use chemotherapy to treat a patient with cancer or insulin to treat a patient with diabetes. So too should medication be used to treat a biologically based psychiatric illness.

Couples Therapy

Strong family relationships are crucial for stress resilience. Unfortunately, family relationships are often among the first victims of vocational burnout. Couples therapy or family therapy can heal wounded relationships and restore lines of open communication, ultimately building protection against future stresses.

Group Therapy

Group therapy allows individuals to recognize that they are not alone in their suffering. Professional support groups can facilitate the sharing of common experiences and emotions and can promote connections between people who have similar strengths and difficulties. More general groups promote understanding of the difficulties inherent to all lifestyles.

Autognosis Rounds

Attendance at *autognosis* (literally "self-knowledge") rounds allow psychiatrists to share common experiences and to identify individual reactions to clinical situations. This knowledge can then be used to inform diagnoses and to minimize potentially harmful reactions to patients (e.g., managing hostility toward a patient so that it will not interfere with treatment). Autognosis rounds have proved valuable for psychiatric resident groups at the Massachusetts General Hospital for the past 4 decades.

CONCLUSION

The practice of psychiatry, with all its inherent stresses, is an honor and a fulfilling calling. "When we find ways to cope . . . ., we move toward the equanimity that can enable us to serve our patients with greater effectiveness and compassion. We also progress toward greater satisfaction in this noble profession of medicine and in our personal lives."[17]

Acknowledgment

This chapter is dedicated to [†]Dr. Messner, whose commitment to resident well-being was unparalleled. He taught us not only how to heal our patients but also how to heal ourselves.

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[†]Deceased.

51 Billing, Documentation, and Cost-Effectiveness of Consultation

Nicholas Kontos, M.D.
Robert M. Stern, M.D.
Theodore A. Stern, M.D.

The purpose of this chapter is to give psychiatric providers of consultation–liaison (C-L) services an understanding of the complex business aspects of their work. Understanding and appropriately adhering to the often-confusing guidelines for reimbursement can be stressful to clinicians and expose them to painful audits and substantial penalties, both personally and for their institutions. In this atmosphere providing ethical, legal, and appropriate services can be a daunting task. A fuller understanding of coding and billing will also help psychiatrists, C-L hospital-based programs, and hospital administrators to collect the appropriate reimbursement for services rendered. In this chapter we will address principles of coding, billing, and documentation that will improve medical documentation for C-L clinicians, as well as address improvements in clinical outcome and economic benefits accrued to the general hospital by operating a C-L service. Adherence to the following principles should facilitate capture of appropriate revenue for the services delivered while keeping the work of the C-L psychiatrist clinically focused. Pitfalls of "routine care" will also be explored.

DOCUMENTATION SHOULD REFLECT THE SERVICE ACTUALLY PERFORMED

Successful C-L services rely on the establishment of cooperative and collaborative relationships with medical colleagues. Hospital-based physicians are exposed to psychiatric co-morbidity on a daily basis. Their need for consultation may range from an opportunity to review their approach to a patient to a request for a comprehensive assessment. The needs of a physician do not always mirror the severity of the patient's medical condition. *Billing, however, is always geared to the patient's illness*. The insurance company or other third-party payer is paying for a service for an individual patient rather than purchasing the expertise of the clinician.

BILL ONLY FOR SERVICES DOCUMENTED IN THE MEDICAL RECORD

The overriding principle for third-party reimbursement is to bill for only those services documented in the medical record. The charge for service and the reimbursement available for the service are guided by definitions established by Current Procedure Terminology (CPT) codes. A brilliant, life-saving consultation that goes undocumented is not billable. The effectiveness and expertise of the consultant is not an issue for the collection of a reasonable fee. Moreover, significant pressure may be placed on clinicians to "maximize revenue" for the services they provide. This is especially true during difficult financial times. Efforts to "game" the system, by "up-coding" (i.e., charging for a more intensive service than delivered), are illegal and unethical. On the other hand, inadvertent "down-coding" on account of the sometimes-Kafkaesque documentation and billing rules is also unfair and ultimately damages the ability of hospitals and providers to care for patients. This chapter seeks to highlight the path that keeps consultations as clinically focused as possible while following the requisite rules for documentation.

FOLLOW THE MEDICARE GUIDELINES FOR ALL ENTRIES IN THE MEDICAL RECORD

Medicare is the predominant insurance coverage in the general hospital. This is especially true for a psychiatric consultation service for elderly or disabled patients. CPT codes were developed by the American Medical Association (AMA) and adopted by the Health Care Financing Administration (HCFA) in the early 1990s. The guidelines were established as mandatory for Medicare and Medicaid billing but are essentially universal in that they apply to most insurance plans. More important, Medicare guidelines for reimbursement are the strictest among insurance plans. *Adhering to the Medicare guidelines ensures that the provider will be in compliance with all insurance plans for appropriate coding for reimbursement purposes.*

For many psychiatrists, documentation requirements for inpatient psychiatric and consultation services are different in form and content from the documentation that might be employed in outpatient practices. Codes for billing inpatients reflect the need for the consultant to be aware of the physical status of the patient as well as the patient's psychiatric state. A premium is paid for thoroughness and attention to "process of care." Thus *documentation for inpatient consultative psychiatric services requires documentation of co-morbid medical problems*. An extensive psychiatric

examination, including recommendations for treatment and medication without the inclusion of elements of the review of systems, for example, can be billed only for the lowest consultation service code. Billing is otherwise considered "up-coding" and is prohibited by law. The critical ingredients of an appropriate note congruent with an appropriate billing code will be addressed in the section on documentation and coding.

OBTAIN PREAUTHORIZATION FOR SERVICES WHENEVER NECESSARY*

Health insurance companies vary in their requirements for precertification (i.e., permission for providing a consultation before the delivery of the service to enable payment for that service). Medicare, for example, does not require precertification, whereas most Behavioral Health Organizations (BHOs) require such precertification. Precertification is the rule for carve-out BHOs that are subcontracted to manage the mental health and substance abuse benefit for the larger medical insurance plan. A patient may be authorized by the primary insurance carrier for the medical admission, authorizing payment for all physicians performing medical consultations save the psychiatrist who requires specific and separate authorization from the carve-out company for payment for the psychiatric consultation.

Critical to the financial viability of C-L services is the management and monitoring of the billing and collection of third-party claims. Consultation services are often not billed for,[1] and the tracking of payments goes unmonitored. Each phase of the process between the provision of service and the receipt of payment for services presents its own dilemmas.

IDENTIFYING THE PAYER

During the admission process, most hospitals will have identified the primary, secondary, and supplementary insurance coverage.

It is critical for the managers of a C-L service to understand how each type of insurance adjudicates claims for professional services. Health insurance claims for hospital services are separated into two components: the technical or hospital charge and the professional or physician charges. For some insurers these charges are billed together, whereas for others they are billed separately.

Medicare, nonmanaged Medicaid, Blue Cross, and commercial indemnity plans will each pay both the technical (hospital) and professional (physician) components. Payments for each component are based on a previously negotiated fee schedule or percentage of charges submitted. Managed care plans will typically negotiate an all-inclusive fee for services rendered and will not pay for the professional (physician) charges separately unless they are specifically contracted for, apart from the day-rate for the hospital charge.

When a patient is insured by a managed care plan, C-L services must be contracted for separately to be reimbursed beyond the all-inclusive rate the hospital receives through the day-rate. If the insurer carves out the management of its mental health and substance abuse benefit to a behavioral health subcontractor, separate professional bills must be submitted to the carve-out behavioral health subcontractor. A common error for C-L services is the sending of the C-L consultation claim to the primary insurance carrier rather than the behavioral health subcontractor and receiving rejection for "service not covered" or "bill to carve-out." Too often these rejected claims are written off, which engenders increased irritation with the primary carrier or blaming of the C-L service for not obtaining prior authorization. The best method for ensuring that the correct payer is billed is to confirm with the medical insurer, usually by telephone, in advance of the treatment to determine whether the mental health benefit is carved out and, if so, to what organization. Then, one should contact the carve-out company to obtain prior authorization for the service. The critical request should be for both the initial consultation and follow-up visits, if necessary. Ideally, a systematic method for navigating this system should be built into the consultation process through departmental or hospital-level billing/reimbursement staff with at least initial guidance, and periodic review, by the C-L service administrator.

DEVELOP A STANDARD FORMAT FOR WRITING THE CONSULTATION NOTE

Several standards and guidelines collide when writing an efficient and effective consultation note. Standards established by the American Psychiatric Association (APA) Practice Guidelines for Psychiatric Evaluation of Adults[2] address the content of an appropriate psychiatric examination; these standards then must be adapted to the special conditions of the consultative examination. As noted by the Academy of Psychosomatic Medicine (APM) Practice Guidelines for Psychiatric Consultation in the General Medicine Setting,[3] the psychiatric consultation should also address the consultee-stated versus the consultant-assessed reason for referral, the extent to which the patient's psychiatric disturbance was caused by the medical or surgical illness, the adequacy of pain management, the extent of the psychiatric disturbance caused by medications or substance abuse, disturbances in cognition, the patient's character style, thoughts of dying, and psychiatric symptomatology. At the same time, those same APM Guidelines state that the "note is best if brief and focused on the referring physician's concerns."[3]

The consultation note should include the chief complaint, history of the present illness, medical and psychiatric history, social and family history, review of systems, mental status examination, and an impression and treatment plan (Table 51–1). It should also include data to support the billing code for reimbursement; documentation should reflect the appropriate level of care provided. Given this level of complexity, even the most competent and organized physicians may find it difficult to keep these guidelines in mind when they are writing a note.

*As this edition of the *Handbook* goes to press, mental health parity legislation has been passed (embedded in the President's economic stimulus package) in both congressional bodies. Consultation–liaison (C-L) service administrators and providers are strongly encouraged to monitor the effect that this and future legislation might have on such matters as carve-outs, prior authorization, and the like.

TABLE 51–1 Key Elements of the Initial Consultation Note

1. Document the date and time of the visit; write "psychiatry" at the top of the note.
2. Document the name of the doctor who requested the consultation and the reason for the consultation request.
3. Provide a chief complaint.
4. Provide a summary of the patient's medical history relevant to the current psychiatric situation; do not just duplicate information in the medical record and the problem list (provide at least four of seven categories of information [e.g., timing, severity, duration of symptoms, associated features]).
5. Provide a description of current psychiatric symptoms (or events leading up to the psychiatric consultation).
6. Document the psychiatric history; be specific about medication and other treatment effects and adverse reactions.
7. Document the family psychiatric history (include drug and alcohol use), including medication and other treatment responses.
8. Document the social history—work and school history, sexual history, drug and alcohol use history, legal history, social supports, and current living arrangements.
9. Provide the past medical history.
10. Document that a review of systems has been performed.
11. Provide a complete mental status examination, with at least nine fields of the following—appearance, behavior, speech, affect/mood, thought content (suicidal, homicidal, delusions, hallucinations), orientation, memory, attention, other cognitive tests, language, fund of knowledge, insight, and judgment.
12. List the current medications—review hospital medication records as well as doctor's orders.
13. Document recent and pertinent tests and procedures performed (e.g., laboratory studies, roentgenography [computed tomography, magnetic resonance imaging], electrocardiography, electroencephalography).
14. Document pertinent aspects of the physical examination (e.g., vital signs, neurologic examination findings, abnormal movements).
15. Provide your impression; use *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) diagnoses and readily understandable terminology (avoiding psychiatric jargon) as well as a formulation.
16. Provide your recommendations; be clear and concise; list medications exactly how you wish them given (including suicide precautions, recommendations for restraints or other consultations, and so on). Please note that all notes from consultations and follow-up visits should be written with discretion; keep in mind that medical–surgical charts frequently are read by hospital staff and sometimes by patients and their families.
17. Document the date of next follow-up visit and the planned frequency of visits.
18. Sign and print your (i.e., the consultant's) name, along with a telephone and/or pager number.

One of the authors (T.A.S.) has developed a working template for documentation that facilitates compliance with HCFA and Medicare guidelines (Figure 51–1). Templates must be considered works in progress, given shifting standards with respect to required content; the format presented is intended as a guide to a flexible document that can be amended as needed (see Figure 51–1). Other consultation forms have been developed by Worley and co-workers.[4]

We believe that the use of such a template minimizes the intrusiveness of billing requirements that would otherwise not be clinically necessary or might alter the level of complexity of the consultation performed. In addition, a template can facilitate more complete consultations, serve as a teaching tool for trainees, and catalyze research or internal review projects. Templates also lend themselves to inclusion in computerized medical records, prevent loss of critical observations and recommendations resulting from illegible notes, and decrease medical errors. Furthermore, from a time-management perspective, such templates can make clinicians more efficient with regard to documentation of relevant information. With the developing capacity to import computerized (observational and laboratory) results, vital signs, recent laboratory values, medication orders, and drug administration, data can be more easily included in the consultation note. At the same time, care must be taken to keep computerized notes focused and helpful.[5] The ability, conferred by technology, to import information easily or cut and paste text can be more a hindrance than a help if not coupled with actual human attention to what is pertinent and accurate.

BILL THE APPROPRIATE CODE

As of 2010, and despite protests from the Academy of Psychosomatic Medicine and the American Psychiatric Association, CPT Evaluation and Management (E&M) codes for inpatient consultation (99251-99255) are no longer reimbursable by Medicare. Other insurers are expected to follow suit. Consultations remain reimbursable under other codes, but, at present, imperfect 1:1 translation of the old codes onto the available ones has impeded arrival at a consensus on which codes are optimal. Table 51–2 attempts loose connections based on the Inpatient Hospital Care (IHC) codes (99221-99223), which MGH and many other institutions are currently using. The Psychiatric Diagnostic Interview Examination code (90801) remains usable and, in some cases, the Psychotherapy Codes (90810-90847). Follow-up codes (99261-99263) are also unchanged. Clearly, this is a situation to be monitored closely.

To use consultation codes properly, it must be clear that the consultation is a service requested by another physician or another provider rather than by the patient or the patient's family. The requesting physician must enter a written or digital request for psychiatric consultation; a statement in a progress note indicating the desire for psychiatric input is insufficient for reimbursement purposes.

Text continued on p.678.

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

Psychiatric Consultation Note

Date:_____/____/_____Time:_____ am pm

Consult Log #: _____
☐Inpt ☐ED ☐OPD
Request Type: Urgent ☐ w/in 24hrs. ☐ Convenience ☐

Asked to see this ___y/old ☐M ☐F for eval of:

☐ ΔMS ☐depress. ☐capacity to... ☐agitation ☐anxiety
☐PTSD ☐dementia ☐suicidality ☐Etoh/subs. ☐psychosis
☐coping ☐pharm eval. ☐eating dis. ☐grief ☐school probs.
☐obs./comp. ☐sex disfunct. ☐ relationship probs. ☐transpl. eval.
☐sleep disturb. ☐homicidal ideation ☐inadequate self care
☐Attention/impulse dis. ☐psychol. components ☐aggress. behavior
☐Other / describe _____

by:
(Dr./Service) _____

PCP: _____ Tele: _____
Pt's Tele: (h) _____ Pharmacy Tele: _____
(w) _____ Contact Person: _____

Use superscripts to indicate source of information. (1 = MD 2 = RN 3 = Pt 4 = Family 5 = Other)

HPI:
(please check off and include descriptions of at least 4 of the following features)

☐Timing
☐Severity
☐Duration
☐Quality
☐Context
☐Modifying Facts
☐Assoc. Signs/sx

(check if abnormal and indicate direction)

Depression:			Mania:		Risk factors for stress:		
☐Sleep -	☐Concentration -		☐Distractibility	☐Ideas that race	☐Chronic disease	☐Irritability	☐Learning Disab.
☐Interest -	☐Appetite -		☐Talkativeness	☐Grandiosity	☐Poor peer relat.	☐Perceives threat	☐Insecure attach.
☐Guilt +	☐Psychomotor -		☐Recklessness	☐Hypersexuality	☐Poverty	☐Unstable/safe envir.	☐Hyperactivity
☐Energy -	☐Suicidal +		☐Hyposomnia		☐Impulsivity	☐Inattentiveness	☐School failure

Psychiatric History: *(check if present and inidcate pertinent details) -or check-* ☐UNREMARKABLE

☐ Care by physician of same group practice w/in 3 years.

	HP (√)	Admissions (√)(Date)	Details / Medication trials
Depression			
Anxiety			
Psychosis			
Bipolar			
Personality Dis.			
Subs. Abuse			
DTs			
W/D sz			
Other: (specify)			

Abuse:
(check: ☐= current ◯= past) ☐◯Physical Abuse ☐◯Sexual Abuse

Psychiatric Treaters: Name tel. #
1. _____ _____

USE REVERSE SIDE PLEASE DO NOT WASTE SPACE

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Figure 51–1. MGH Psychiatric Consultation Note template.

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

*** Review of Systems: (○ = normal □ = abnormal)

○ Constitutional
□ △ appetite
□ fever
□ △ weight
□ △ energy

○ ENT
□ hearing

○ Cardiac
□ Chest pain

○ Resp
□ Cough
□ SOB

○ GU
□ urinary freq.

○ Lymph
□ lymph nodes

○ Musculo
□ weakness
□ pain

○ Eyes
□ △vision

□ Psych

○ Skin
□ rash

○ Neuro
□ numbness/tingle
□ speech diff.
□ personality△
□ lethargy
□ H/A
□ dizziness
□ syncope
□ confusion
□ imp. memory
□ diff. swallowing
□ incontinence
□ diff. w/ coord.
□ gait disturb.

○ Immune
□ freq. infections

○ GI
□ abdom. pain

Allergies: _____

Details of above:

or: ◯ Refer to note/worksheet of _____ (date)____/____/____ □ changes as above □ unchanged
(check)

Medical History *(check if present and indicate pertinent details) -or check-* □ *UNREMARKABLE*

Constitutional	Eyes	GI	Endocrine	Skin	Respiratory	Mus./Skel.	Immune	Reproductive:
□ Fatigue	□ Cataracts	□ PUD	□ Diabetes	□ Burns	□ Pneumonia	□ Fractures	□ HIV	□ Ammenoria
□ CFS	□ Glaucoma	□ Hepatitis	□ Hypothyroidism	□ Psoriasis	□ Asthma	□ Fibromyalgia	□ S/P Transplant	□ Pregnancies
□ Sleep dist.	□ Blindness	□ Crohn's	□ Hyperthyroidism	□ Other:	□ COPD	□ Other:	□ Other:	□ Prior births
□ Dizziness	□ Other:	□ Bowel dysf.	□ Other:		□ Other:			□ Currently preg.
		□ Other:						□ LMP

ENT	Hem./Onc.	GU	Cardiac	Neuro:		Immunizations	List others:
□ ⁻ Hearing	□ XRT	□ Bladder dysf.	□ CHF	□ Dementia	□ H/A	□ Polio	
□ Vertigo	□ Chemotx	□ UTI	□ AFIB	□ CVA	□ Gait dist.	□ DPT	
□ Other:	□ Multmyeloma	□ BPH	□ VT	□ MS	□ Syncope	□ Chicken Pox	
	□ CA colon	□ CRF	□ MI	□ Parkinsons	□ Neuro/musc. dis.	□ M/M/R	
	□ CA prostate	□ ARF	□ HTN	□ Meningitis	□ Disc disease	□ Hepatitis	
	□ CA breast	□ Other:	□ CAD	□ Head Trauma	□ Neuropathy	□ Influenza	
	□ CA Other:		□ Other:	□ Sz Disord.			
	□ Anemia			□ Other:			
	□ CNS tumor						

□ Prior Hospitalizations

Surgical History: *(provide dates of surgery where relevant)*

Cardio/vasc.
□ CABG
□ MVR
□ AVR
□ Pacemaker
□ AICD
□ AAA
□ CEA
□ Peripheral bypass

Ortho:
□ AKA
□ BKA
□ THR
□ Laminectomy

General:
□ Colon resection
□ Colostomy
□ Splenectomy
□ Appendectomy
□ Cholecystectomy
□ Gastrectomy
□ Nephrectomy
□ Portocaval shunt
□ TAH
□ BSO
□ Thyroidectomy
□ Laryngectomy
□ Skin grafting

□ Trach
□ G-Tube
□ T&A

Transplant:
□ Heart
□ Kidney
□ Liver
□ Lung
□ Bone marrow

Neuro:
□ Craniotomy

Others:
_____
_____
_____
_____

Medical Pharmacology: (Check: □ = current use) □ *NONE*

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Figure 51–1, cont'd

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

Date: _____ Psychiatric Consultation Note

Psychiatric Pharmacology: (check: ☐ = current use ○ = past use) △ = *NONE*

Neuroleptics:
☐ ○ Haloperidol
☐ ○ Olanzapine
☐ ○ Clozapine
☐ ○ Resperidol
☐ ○ Perphenazine
☐ ○ Other:

TCAs:
☐ ○ Amitriptyline
☐ ○ Desipramine
☐ ○ Nortriptyline
☐ ○ Other:

SSRIs:
☐ ○ Fluoxetine
☐ ○ Sertraline
☐ ○ Paroxetine
☐ ○ Fluvoxamine
☐ ○ Other:

Mood Stab./Anti-Conv:
☐ ○ Carbamazepine
☐ ○ Valproic acid
☐ ○ Phenytoin
☐ ○ Gabapentin
☐ ○ Phenobarbitel
☐ ○ Other:

☐ ○ Tacrine
☐ ○ Pemoline
☐ ○ Clonidine
☐ ○ Disulfiram
☐ ○ Zolpidem
☐ ○ Propofol

MAOIs:
☐ ○ Phenelzine
☐ ○ Tranylcypramine
☐ ○ Other:

Other Antidepressants:
☐ ○ Trazodone
☐ ○ Bupropion
☐ ○ Nefazodone
☐ ○ Other:

Bzs:
☐ ○ Alprazolam
☐ ○ Clonazepam
☐ ○ Diazepam
☐ ○ Lorazepam
☐ ○ Other:

Others:
☐ ○ Buspirone
☐ ○ Lithium
☐ ○ Methylphenidate
☐ ○ Dextroamphetamine

Social & Developmental History:

Employment/Education:	(check)	description
current:		
past:		

Marital Status:
☐S ☐M ☐D
☐W ☐Sep.

Education Level: ☐ < High School ☐ High School Grad ☐ College

Legal Problems: ☐ Current ○ Past
Details:

	yes	/	no
Advanced Directive	☐		○
Power of Attorney	☐		○
Developmentally Disabled	☐		○

Etoh/Subs. Abuse: (check: ☐= current use ○= past use; give dates of use on line)
☐ ○ Alcohol _____ ☐ ○ Narcotics _____
☐ ○ Benzos _____ ☐ ○ Hallucinogens _____
☐ ○ Stimulants/Cocaine _____ ☐ ○ IVDA _____
☐ ○ Other: _____
Details:

Family Medical History: (check appropriate box)	CAD	HTN	DM	Sz Dis.	CVD	Others
Father:						
Mother:						
Sibs:						
Children:						
Grandparents:						
Other:						

Family Psychiatric History: (check appropriate box)

	Deceased	Suicide	Depres.	Anxiety	Bipolar	Psychotic	Personality Dis.	Other
Father								
Mother								
Sibs (#)								
Children (#)								
Other:								

Family of Origin: ☐ Stable ☐ Chaotic

Relevant Details:

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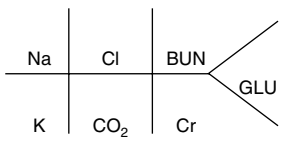
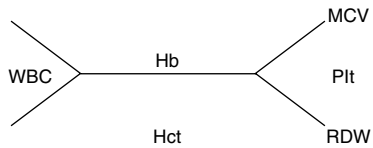
Figure 51–1, cont'd

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

Labs and Records: (Insert values in appropriate areas)





		Reviewed	Results Gathered by Review *(summarize)*
Labs:			
	U/A		
	ABGs		
	LFTs		
	TFTs		
	B12		
	Folate		
	Other:		
X-Rays:	CXR		
	Other:		
LP:			
EKG:			
EEG:			
CT: (type)			
MRI: (type)			
Other:			
Old Records:			

Tox Screen: *drugs:* _____ _____ _____ _____

levels: _____ _____ _____ _____

*** Vital signs:

☐ Temp_____ ☐ HR_____ ☐ BP_____ ☐ Resp. Rate_____ ☐ HT_____ ☐ WT_____

◯ (check) Refer to note/worksheet of _____ (date)___/___/___

Physical exam:
relevant features:

Corotid bruits — Pupils:
Hearing: — EOMS:
Cranial nerves: — Reflexes:
Coordination/gait:
Motor tone:
Visual acuity: — If date of last physical > 6 months, has pt been referred? ☐

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Figure 51–1, cont'd

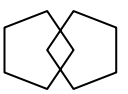
MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

Mini-Mental State Examination

(Add points for each correct response)

			Score	Points
Orientation				
1.	What is the	Year?	_____	1
		Season?	_____	1
		Date?	_____	1
		Day?	_____	1
		Month?	_____	1
2.	Where are we?	State?	_____	1
		Country?	_____	1
		Town or city?	_____	1
		Hospital	_____	1
		Floor	_____	1
Registration				
3.	Name three objects, taking one second to say each. Then ask the patient all three after you have said them. Give one point for each correct answer. Repeat the answers until the patient learns all three.		_____	3
Attention and calculation				
4.	Serial sevens. Give one point for each correct answer. Stop after five answers. *Alternate*: Spell WORLD backwards.		_____	5
Recall				
5.	Ask for names of three objects learned in Q.3. Give one point for each correct answer.		_____	3
Language				
6.	Point to a pencil and a watch. Have the patient name them as you point.		_____	2
7.	Have the patient repeat "No ifs, ands or buts."		_____	1
8.	Have the patient follow a three-stage command: 'Take a paper in your right hand. Fold the paper in half. Put the paper on the floor.'		_____	3
9.	Have the patient read and obey the following: 'CLOSE YOUR EYES.' (Write it in large letters.)		_____	1
10.	Have the patient write a sentence of his or her choice. (The sentence should contain a subject and an object, and should make sense. Ignore spelling errors when scoring).		_____	1
11.	Enlarge the design printed below to 1.5 cm per side, and have the patient copy it. (Give one point if all sides and angles are preserved and if the intersecting sides form a quadrangle.)		_____	1
			_____	= Total 30



References:

1. Folstein MF, Folstein SE, McHugh PR: "Mini-Mental State" A practical method for grading the cognitive state of patients for the clinician. J Psychiat Res. 1975; 12: 89-198.

2. Tombaugh T. McIntyre NJ: The Mini-Mental State examination: A comprehensive review. J Am Geriatr Soc. 1992; 40:922–935.

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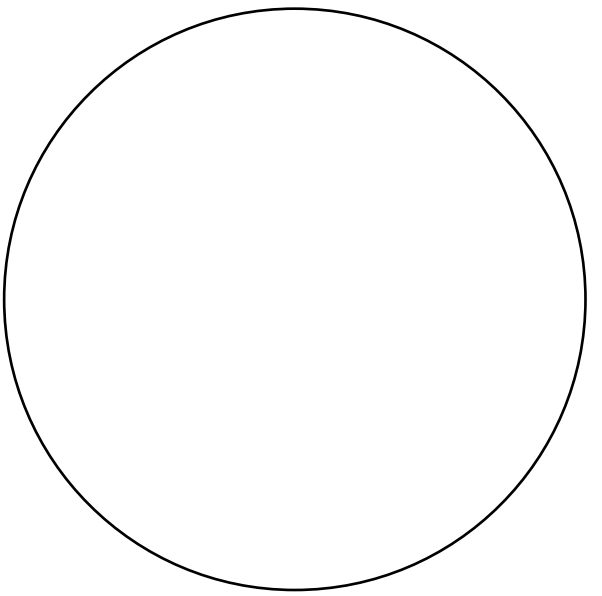
Figure 51–1, cont'd

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

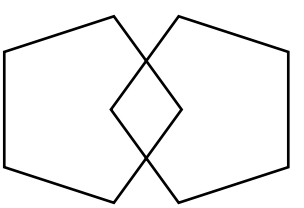
CLOSE YOUR EYES



Write a sentence below

MGH 81560 REV 11/95

Copy design below



USE REVERSE SIDE PLEASE DO NOT WASTE SPACE

Figure 51–1, cont'd

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

Date: _____ Psychiatric Consultation Note

General Appearance:
○ *Normal* Abnormal
☐ agitated
☐ unkempt
☐ psychomotor ret.
☐ SOB
☐ uncomfortable
☐ bruised
☐ hyperactive
☐ slumped
☐ fidgeting
☐ other:

HEENT:
○ *Normal* Abnormal
☐ oral thrush
☐ neck stiffness
☐ staring
☐ averts gaze
☐ other:

Musculo./Skel:
○ *Normal* Abnormal
☐ rigid
☐ cogwheeling
☐ flaccid
☐ myoclonus
☐ oral-buccal movements
☐ tremor
☐ tics
☐ other:

Gait:
○ *Normal*
☐ Abnormal

Speech:
○ *Normal* Impaired
☐ non-verbal
☐ slurring
☐ paraphasic errors
☐ rapid
☐ pressured
☐ monotonous
☐ non-fluent
☐ sparse
☐ non spontaneous
☐ verbose
☐ loud
☐ soft
☐ other:

Language:
○ *Normal* Impaired Ability
☐ naming objects
☐ repeating phases
☐ writing sentences
☐ other:

Level of Vocabulary:
○ *Normal*
☐ Impaired

Mood/Affect:
○ *Normal* Abnormal
☐ anxious
☐ depressed
☐ angry
☐ flat
☐ labile
☐ sad
☐ fearful
☐ constricted
☐ tearful

Mental Status
(Check ○ if category is normal, otherwise check abnormality ☐)
☐ belligerent/hostile
☐ uncooperative
☐ evasive
☐ guarded
☐ impulsive
☐ passive
☐ withdrawn
☐ laughs
☐ smiles
☐ other:

Thought process:
○ *Normal* Abnormal

Hallucinations:
☐ Vis ☐ Aud ☐ Tact
☐ Gust ☐ Sens ☐ other:

☐ impaired abstraction
☐ assoc. loose
☐ tangential
☐ perseverative
☐ delusional
☐ obsessed
☐ circumstantial

Calculation Ability:
○ *Normal*
☐ Impaired

Thought content:
○ *Normal*
☐ delusions
☐ ideas of ref.
☐ SI
☐ HI
☐ obsessions

Suicidal Ideation:
○ *No* Yes
☐ ideation
☐ plan
☐ attempts

Judgement & Insight:
○ *Normal* Abnormal
☐ poor
☐ confused
☐ other:

Memory:
○ *Normal* Abnormal
☐ short-term
☐ long-term
☐ other:

Attention Span:
○ *Normal*
☐ Impaired

Sensorium / Orientation:
○ *Normal* Disoriented
☐ Time
☐ Place
☐ Person

Homicidal Ideation:
○ *No* Yes
☐ ideation
☐ plan
☐ attempts

Diagnostic Impressions: Please detail all abnormal findings:

Axis I:
☐ Delirium (293.0) due to _____
☐ Delrium (780.09)
☐ Dementia (290.xx)
Early Alzheimer's:
☐ uncomplicated (.10)
☐ w/ delirium (.11)
☐ w/ delusions (.12)
☐ w/ depression (.13)
Late onset Alzheimer's:
☐ uncomplicated (.10)
☐ w/ delirium (.3)
☐ w/ delusions (.20)
☐ w/ depression (.21)

Vascular:
☐ uncomplicated (.40)
☐ w/ delirium (.41)
☐ w/ delusions (.42)
☐ w/ depression (.43)
☐ Dementia NOS (294.80)
☐ Demntia from HIV (294.9)
☐ Dementia from head trauma (294.1)
☐ Dementia from Parkinson's (294.1)
☐ Personality change (310.1) from _____
☐ Catatonia (293.89)

Etoh:
☐ dependence (303.90)
☐ abuse (305.00)
☐ intox (303.00)
☐ w/d (291.8)
Opioid:
☐ dependence (304.00)
☐ abuse (305.0)
Sed-hyp:
☐ dependence (304.10)
☐ w/d (292.0)
☐ Polysubs depend (304.80)
☐ Psychosis NOS (298.9)
☐ Psychosis med. condt. _____ (293.xx)

☐ Schizophrenia paranoid (295.30)
☐ Schizophrenia undiff. (295.90)
☐ Scz-affective (295.70)

☐ Major Depression
☐ single episode (296.2)
☐ recurrent (296.3)
☐ Depres. disor. NOS (311)
☐ Dysthymia (300.4)
☐ Bipolar I (296.xx)
☐ Bipolar II (296.89)
☐ Panic disorder w/ agoraphobia (300.21)

☐ Panic disorder w/o agoraphobia (300.01)
☐ Anxiety NOS (300.00)
☐ PTSD acute (309.81)
☐ PTSD chronic (309.81)
☐
☐ Somatization disorder (300.81)
☐ Conversion (300.11)
☐ Pain disorder (307.xx)
☐ Hypochondriasis (300.7)
☐ Breathing rel. sleep dis. (780.59)

☐ Psych. fators affecting Physical Illness (316.00)

Adjustment disorder:
☐ w/ depressed mood (309.0)
☐ w/ anxiety (309.24)
☐ w/ mixed features (309.28)
☐ Neuroleptic-induced Parkins. (332.1)
☐ NMS (333.99)
☐ Med-induced movement disorder (333.90)

Others:
☐ ADHD (314.01)
☐ Conduct Disorder (312.20)
☐ Anorexia Nervosa (307.10)
☐ Bulimia Nervosa (307.51)

Other Axis I:
Axis II: ☐ Borderline (301.83) ☐ Antisocial (301.7) ☐ Personality disorder NOS (301.9) Others: _____
Axis III: (see pages 1 & 2)
Axis IV:
☐ Problems w/ primary support group ☐ Problems related to social environment ☐ Educational problems ☐ Occupational problems ☐ Housing problems
☐ Economic problems ☐ Problems w/ access to health care services ☐ Problems related w/ legal system/crime ☐ Other psych. social & environmental problems
Axis V: GAF Score: [ ]

☐ *100–91* ☐ *90–81* ☐ *80–71* ☐ *70–61* ☐ *60–51* ☐ *50–41* ☐ *40–31* ☐ *30–21* ☐ *20–11* ☐ *10–0* ☐ *0*
Superior function | Mild sx | Serious sx/ impaired fx | Seriously impaired | Danger to self/others | Inadequate information

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USE REVERSE SIDE PLEASE DO NOT WASTE SPACE

Figure 51–1, cont'd

MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

Enter name and unit number on both sides of EVERY sheet. Name and unit number to be written distinctly when plate is not available.

Psychiatric Consultation Note

Date: _____

Impression: _____

Plan: (Dx'tic w/u; lab tests; pharm Tx; psychological Tx; mgmt. strategies;)

1. _____
2. _____
3. _____
4. _____
5. _____

Currently lacks capacity to:
☐ Make Tx decisions re: _____
☐ make disposition decisions
☐ leave AMA

suicide precautions: ☐ recommended ☐ ordered
sitter: ☐ recommended ☐ ordered
restraints: ☐ recommended ☐ ordered

Goals & Objectives	Tx Plan (Modality & Freq.)	Risks discussed	Side Effects Experienced
☐ Tx anxiety ☐ Tx Depression ☐ Tx Psychosis ☐ Provide support ☐ Improve function ☐ Improve relatshps. ☐ Return to work ☐ other:	☐ Psychotherapy Psychopharm: ☐ continue w/o ☐ dose: ☐ ¯ dose: ☐ Add: ☐ D/C: Check labs ☐ BUN/Cr ☐ LFTs ☐ TFTs ☐ CBC ☐ Levels ☐ Lytes ☐ other:	☐ Bleeding tendency ☐ H/A ☐ EPS ☐ ¯ WBC ☐ anemia ☐ LFTs ☐ rash/allergy ☐ ataxia ☐ hypotension/dizziness ☐ sex. dysf. ☐ GI distress ☐ insomnia ☐ sedation ☐ wt gain ☐ hypohtyroidism ☐ polyuria ☐ drug-drug inter. ☐ other:	☐ sedation ☐ dry mouth ☐ sex. dysf. ☐ palp ☐ GI upset ☐ rash ☐ other:

Consultant Name: _____ Signature: _____

Beeper #: _____ Date: ___/___/___ ☐ Attending ☐ Fellow ☐ Resident ☐ Med. Student

USE REVERSE SIDE PLEASE DO NOT WASTE SPACE

Figure 51–1, cont'd

TABLE 51–2 Inpatient Initial Psychiatric Consultation Codes—Comparison of E&M codes to IHC codes

UNUSABLE E&M CODE	TIME (MINUTES)	HISTORY	EXAMINATION	DECISION-MAKING
99251	20	Problem-focused	Problem-focused	Straightforward
99252	40	Expanded	Expanded	Straightforward
99221*	**30**	**Detailed**	**Detailed**	**Straightforward or low complexity**
99253	55	Detailed	Detailed	Low complexity
99222	**50**	**Comprehensive**	**Comprehensive**	**Moderate complexity**
99254	80	Comprehensive	Comprehensive	Moderate complexity
99223	**70**	**Comprehensive**	**Comprehensive**	**High complexity**
99255	110	Comprehensive	Comprehensive	High complexity
Definitions of Terms				
	HPI	ROS	Psych/FHx/SHx	MSE
Problem-focused	1-3 items	None	None	1-5 elements
Expanded problem-focused	1-3 items	1 system	None	6-8 elements
Detailed	4 or more items	2-9 systems	1 field	9-13 elements
Comprehensive	4 or more items	10 + systems	3 fields	14-15 elements

*IHC codes are set in bold type.
HPI, History of Present Illness; *MSE,* Mental Status Examination; *Psych/FHx/SHx,* Psychiatric/Family History/Social History; *ROS,* Review of Systems.

The content of the history, comprehensiveness of the examination, complexity of medical decision-making, and average time required to complete the consultation determine the reimbursement that will be provided (Table 51–3). Engaging the assistance of a professional coder to perform periodic audits and training sessions for physicians is essential to remain abreast of changes in federal auditing guidelines. Additionally, providing psychiatrists with simplified pocket billing guidelines and definitions of terms for selecting the appropriate CPT code can be helpful.

EVALUATION OF THE COSTS AND BENEFITS OF A CONSULTATION SERVICE

C-L services are rarely lucrative cost centers.[6] Moreover, providing fee-for-service psychiatric consultation by independent practitioners rarely leads to a financially viable service or career. Meaningful consultation requires that clinicians expend significant time away from the bedside. Necessary tasks include the review of the medical record and case discussion before and after the consultation with the referring physician, nursing staff, and social service. Ancillary meetings with family members are often necessary to collect critical information unobtainable from a medically compromised patient. A cost–benefit analysis that sees cost as the psychiatrists' salary and the benefit as the lowest expenditure of finances to provide the service without severely compromising the service is far too common.

In contrast to the preceding scenario, we support a "value accounting" methodology that approaches the consultation service in a broader systemic manner.[7] This methodology looks at cost, clinical outcome, and consumer satisfaction as interrelated domains. With a broader view, we can examine the impact of a C-L service on the care of the patient, the educational or academic mission of the hospital, *and* the financial function of the hospital. From a fiscal perspective, the availability of C-L services results in decreased length of stays (LOSs)[8] and recidivism rates, outcomes especially critical in a capitated, managed care environment. Decreasing the LOS lowers overall hospital costs.[9] Moreover, a proactive C-L service identifies co-morbid medical, psychiatric, and substance abuse problems that result in increased payments to the hospital under the Diagnosis-Related Groups (DRG) payment system by including previously overlooked complications and co-morbid diagnoses.[8] For example, delirium is significantly underrecognized, with a prevalence of approximately 10% of hospitalized patients. Alcoholism in the general hospital has been reported in 20% to 40% of hospitalized patients.[9] Identifying and treating co-morbid

TABLE 51–3 Definitions of Medical Decision-Making

CODE	DECISION-MAKING	NUMBER OF DIAGNOSES/OPTIONS	COMPLEXITY OF DATA REVIEWED	RISK OF COMPLICATIONS
99221	Straightforward	Minimal	Minimal or none	Minimal
99221	Low complexity	Limited	Limited	Low
99222	Moderate complexity	Multiple	Moderate	Moderate
99223	High complexity	Extensive	Extensive	High

Straightforward: One or more self-limiting minor problems.
Low complexity: Two or more self-limiting or minor problems or one stable problem.
Moderate complexity: One or more chronic illnesses with mild exacerbations or progression of, or side effects, or two or more stable chronic diseases.
High complexity: One or more chronic illnesses with severe exacerbation or progression, side effects of treatment, or acute or chronic illness that poses a threat to life or bodily functions.

delirium, substance abuse, and psychiatric problems have a salutary impact on patient outcome as well as on the financial health of the general hospital. There is some evidence that effective consultation reduces the use of other medical services as well.[9] This additional revenue is quite separate from the financial savings in staff time expended while managing aggressive, confused, uncooperative, or "undesirable" patients; the costs of security; and the use of restraints and secondary problems of injuries or infections (e.g., from catheters placed in agitated elderly patients or pneumonias or aspirations secondary to patients being restrained in bed to control aggression and agitation).

From a public health perspective, the involvement of the C-L psychiatrist may lead to improved disease-management protocols and best practices, helping patients understand and cope with chronic illness states. Enrolling patients in smoking-cessation or weight-control programs may initiate or support their general health and wellness. Consider that 25% to 40% of patients in the general hospital are being treated for ailments secondary to alcoholism and that the societal losses secondary to alcoholism may exceed $115 billion per year.[9,10] With effective interventions as part of the medical team, future medical utilization and cost may be reduced.[11,12]

The impact on consumers of consultation services, with a focus on medical providers, results in many of the less tangible or nonspecific outcomes of that consultation. These outcomes include direct and indirect education of hospital staff about psychopathology. Such education, along with demonstration by a familiar consultant of an easily identified medical approach to psychiatric problems, serves the dual role of de-stigmatizing mental illness and psychiatry itself. Ideally, future patients then benefit from more effective psychiatric treatment, including better deployment of psychiatry C-L services. These activities occur within actual consultations as well as through the C-L psychiatrist's participation in in-services, clinically oriented committees, and collaborative care teams. All have the potential to improve patient care and satisfaction, but many are not reimbursable, reinforcing the need to obtain fair reimbursement for those services that are. Diligent attention to rules and regulations associated with billing and documentation can help improve patient care and help C-L services become financially viable.

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Quality Assurance and Quality Improvement on a Psychiatric Consultation Service

52

Anthony P. Weiss, M.D., M.B.A.
Theodore A. Stern, M.D.

The quality of health care is a hot topic. In an era of increasing accountability throughout our society, it is not surprising that questions about the efficacy and efficiency of our health care system are also being raised. Scrutiny is coming from the three major constituencies (i.e., providers, purchasers/payers, and patients) within the system. Providers (including physicians and nurses) have begun to realize that flaws exist in the current health care delivery system and they have proposed large-scale efforts to improve care.[1] Purchasers and payers (including insurance companies and the government), who are being squeezed during difficult economic times, are demanding to know what they are getting for their money. And finally, patients themselves are now asking questions about their care, with an increasing emphasis on consumerism and advocacy.

In response to these pressures, the quality of health care is increasingly being carefully measured and reported. "Transparency" is the buzzword, with quality dashboards and provider performance report cards becoming commonplace as part of the public reporting efforts on health care quality. In addition, measures of quality are increasingly being tied to reimbursement, whether as part of pay-for-performance (i.e., increased reimbursement for better outcomes) or nonpayment for so-called "never events" (e.g., medical errors, such as wrong-side or wrong-site surgery). Whether or not there is wholesale health care reform, we expect that these early trends will continue to expand.

Interestingly, though the care provided by proceduralists (e.g., surgeons) and hospitalists (e.g., internists) has come under the most scrutiny, the care provided by consultants has to date been off the radar. We suspect this state is only temporary. Given the prevalence of co-morbid medical/surgical and psychiatric illness, the percentage of hospitalized patients who are seen by a psychiatric consultation service (as high as 13% in some settings), and the role consultants have in either reducing or increasing the cost of care (through their ordering of diagnostic tests as well as their impact on length of stay and on re-admissions), we are likely to see increasing efforts to define, to measure, and to report the quality of consulting across all medical disciplines, including psychiatry.

Many physicians will bemoan this prediction, highlighting the innumerable challenges of this endeavor to argue for maintenance of the *status quo*. While we share their concerns about the challenges (and the potential for unintended consequences), we believe there is value in physicians being proactive in outlining the best approach to quality assessment. In so doing we can work to craft measures that are more than just boxes to be checked, but that actually serve to identify added value of the consulting service and to illuminate which aspects of care and the service need improvement. Perhaps more importantly, this type of introspective self-assessment (when coupled with efforts to improve deficiencies in care) has been often cited as a core aspect of medical professionalism.[2]

This chapter represents an initial attempt to illustrate how the quality of a general hospital psychiatry consultation service can be assessed, assured, and improved. To do this we will present the work of the general hospital psychiatrist on the prevailing model of health care quality: the structure/process/outcome triad developed by Dr. Avedis Donabedian.[3]

DONABEDIAN'S MODEL

Donabedian was an epidemiologist and health services researcher who many consider to be the father of the modern health care quality movement. Among his contributions was a simple model that identified three types of interconnected pieces of information (i.e., structure, process, and outcome) from which one could draw inferences about the quality of care delivered.

By structure, he referred to both the material and human resources required to provide health care. By process he referred to the actual activities that comprised care delivery. By outcome he referred to a wide-ranging set of changes (positive or negative) in patients that could be attributed to the processes of care delivered. These three components are not attributes of quality *per se*, but rather they are windows through which quality of care can be viewed and assessed.

The model is elegant in its simplicity; it has stood the test of time as a framework for the assessment of health care quality in a number of settings. Defining exactly how these general concepts apply to a specific aspect of health care (e.g., general hospital psychiatry) has proven more difficult. In addition, the hypothesized linkages between structure, process, and outcome may not always be robust causal connections. Nevertheless, we believe this is a good starting point to guide our discussion (Figure 52–1).

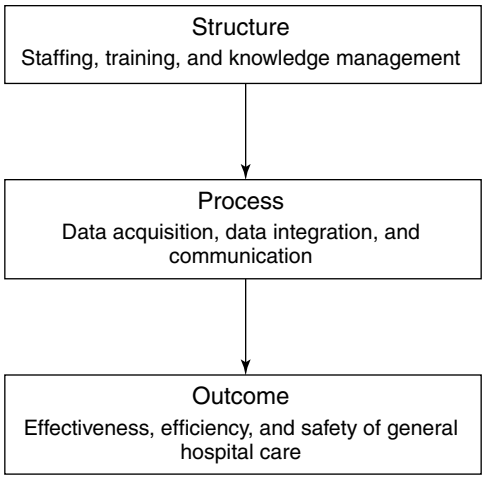

Figure 52–1. Donabedian's quality triad.

STRUCTURAL MEASURES OF CONSULTING QUALITY

A consultation service is only as good as the consultants who comprise it. Unlike other technical areas of medicine, psychiatric consultation is knowledge work, and as such, the key measure of structural quality relates to the human resources (consultation psychiatrists) that form the team. In this regard two questions need to be asked: (1) Is the team well staffed? and (2) Is the team well trained?

Staffing refers to the quantity of psychiatrists that provide coverage to the general hospital (based on recruitment, retention, and full-time equivalents). The size of the roster will depend on multiple factors (e.g., the size of the hospital, the prevailing patient mix, the presence of trainees, the full-time/part-time status of staff, and the referral frequency). Defining "adequate coverage" is certainly up for discussion; no doubt there is a minimum threshold below which the timeliness of consultations becomes an issue and the burden on individual practitioners so substantial as to promote burnout. Beyond the raw number of staff on the service, the turnover rate of psychiatric consultants is another important structural measure of quality. One cannot underestimate the value of in-depth knowledge of the structure and culture of the specific setting in which one is employed—high rates of turnover make it difficult to develop this inside knowledge that is so critical to the framing of recommendations that are actually accepted.

Training refers both to the formal educational and training background of the psychiatrist and his or her actual clinical experience within general hospital psychiatry. The former would include measures such as the percentage of board certified staff, the percentage of staff with subspecialty training in psychosomatic medicine, or the percentage of staff with formal subspecialty certification. The latter refers more to the years of experience, numbers of total cases seen, and markers of expertise in specific domains (such as publication of peer-reviewed articles and chapters). There is evidence that both physician certification[4] and volume of cases seen[5] can be associated with clinical outcome, though to our knowledge these relationships have not yet been established for psychiatry.

One final structural indicator relates to the degree of organizational learning that occurs with experience. This concept, sometimes referred to as "knowledge management," is an important aspect of major management consulting firms (e.g., McKinsey or Boston Consulting Group). How can the consultation service use the combined wisdom and experience of thousands of cases seen over time and bring this to bear on the next consult request? Can the service itself have value beyond the sum of the individuals that comprise it? We believe the answer is yes, but methods of knowledge management within hospital-based consultation services are at present rudimentary when compared to that used by our business colleagues. This may improve with the more widespread use of electronic medical records for inpatient care. Until then, services might consider other aspects of knowledge management, such as the use of daily team rounding, the creation of an anonymous consult registry with "lessons learned," and publication of important observations in peer-reviewed literature.

PROCESS MEASURES OF CONSULTING QUALITY

As outlined in Chapter 2, there are a core set of processes that make up the actual practice of "consultation psychiatry" (see Table 2–1 for example). These processes can be broadly construed under the categories of data gathering (speaking with referring clinician, reviewing the chart, interviewing and examining the patient); data integration (formulating a diagnosis and crafting a plan); and communication (writing and discussing impressions and recommendations). The skill with which we carry out these activities likely influences the outcomes of patients that we are asked to evaluate. It will also influence the service's reputation within the general hospital, in turn influencing the volume of referrals. For high-performing consultation services this can set up a positive reinforcement loop (Figure 52–2) in which a high-quality consult leads to high perceived value, which leads to increasing consultation requests, which leads to increased experience, which when captured leads to greater process skill, and so forth.

Despite the widely acknowledged importance of process excellence in these three domains, they are only rarely, if ever, assessed once a physician has completed his or her

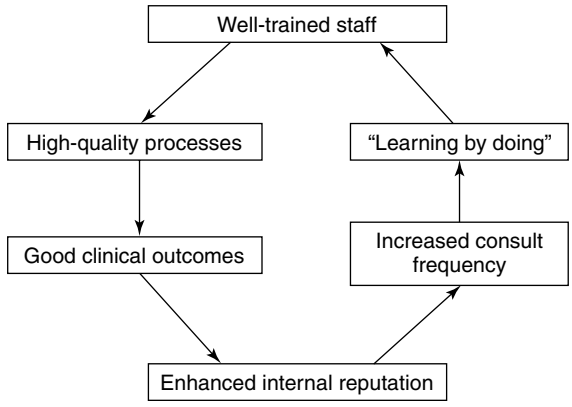

Figure 52–2. Positive feedback loop of high-performing consultation services.

postgraduate training. For example, "How often are we called to account for our review of the old record?" Or, "How often are our efforts in eliciting a history from an intubated patient assessed?" Yet these examples of going beyond the basics are likely key to distinguishing quality with respect to data gathering. Myriad examples could be developed for data integration and communication as well.

Unlike efforts to promote hand washing by staff, the timely use of antibiotics for community-acquired pneumonia, and administration of aspirin after a myocardial infarction (to cite just three examples of process measures within general medicine), there are no national standards for process quality in consultation psychiatry.

OUTCOMES MEASURES OF THE CONSULTANT'S QUALITY

When a well-staffed and trained service implements high-quality processes, good outcomes are bound to occur. Donabedian identified seven domains of outcomes (Clinical, Physiological, Physical/Functional, Psychological, Social, Mortality/Longevity, and Patient Satisfaction) that ran the gamut from enhanced patient understanding of their condition to prolongation of life. Even a cursory glance at these items makes clear that high-quality psychiatric consultation can have a substantial impact on many, if not all, of these outcomes.

In addition, there are a number of patient safety issues that could be addressed by timely and effective psychiatric consultation. Within-hospital suicides, suicide attempts, and staff assaults are a few dramatic and important examples. Other events may include removal of intravenous lines, tubes, or wires by delirious patients. Tracking the frequency of these events on a hospital-wide basis may be a useful marker of the effectiveness of care implemented as a result of a psychiatric consultation. This of course requires a robust and reliable event reporting system, so that bad outcomes (and even "near misses") can be tallied and used as the basis for discussion.

GUIDING PRINCIPLES OF QUALITY MEASUREMENT

We believe there is benefit in measuring the structure, processes, and outcomes associated with a psychiatric consultation service. Through measurement we can better identify the value we add to the mission of the general hospital, serving to justify the expense of maintaining this type of internal consultancy to hospital leadership. It may also enhance the standing of knowledge-based specialties in the eyes of health care purchasers and payers, while working toward equilibrating reimbursement disparities that have long favored our proceduralist colleagues. Most of all, this type of measurement can provide the type of feedback we need to continually improve the quality of the service we provide to patients.

That said, we know full well that these attempts at measurement in and of themselves are potentially costly and time-consuming. All too many measurement efforts in today's health care landscape seem to be nothing more than costly box-checking exercises; they often do little to create actual practice change. To avoid a similar fate we put forward the following three suggestions:

1. Measurements should be devised, conducted, and reviewed by those at the front lines of care, sometimes called clinical microsystems.[6] In this way, those with the greatest knowledge of the care delivery processes and expected outcomes can play the central role in the measurement effort. This type of bottom-up effort is critical in the change process, because it engenders "buy-in" from the beginning, rather than pushing mandates down the throats of providers in a top-down fashion.
2. Measurement cannot be considered a stand-alone process. It must be integrated with quality assurance and quality improvement activities. A quarterly report on the frequency of in-house suicide attempts is meaningless unless it is linked with careful efforts to reduce the rate of occurrence through root cause analysis of reported adverse events (Figure 52–3)[7] and the implementation of rapid cycle change. In addition to formal quality assurance review and specific project-based quality improvement efforts, a wide variety of tools are available (and often underutilized) to promote change within the hospital setting. These include presentations at grand rounds, discussions at case conferences, systematic surveillance for complex cases with early intervention, and supervision with feedback for both trainees and staff.
3. The actual cost of measurement (in time and dollars) should be accounted for, and measurement efforts reassessed periodically to determine whether they are providing an adequate return on this investment. In this way the hospital (or hospital microsystem, such as the consultation psychiatry service) can make certain that quality assessment actually enhances, rather than detracts from, the core capacity of the institution—to provide excellent clinical care.

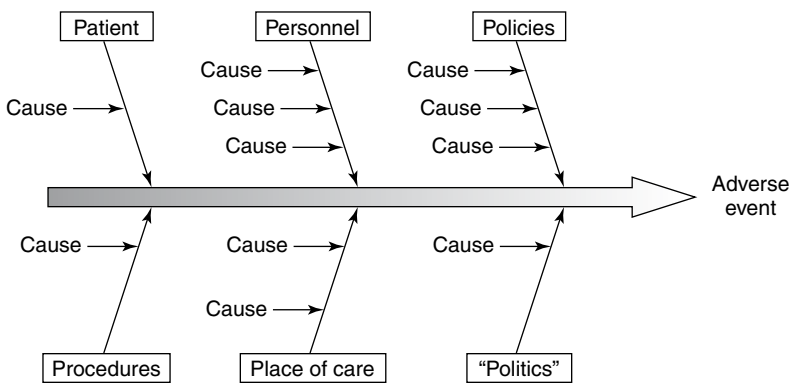

Figure 52–3. Ishikawa ("fishbone") diagram to identify root causes of adverse events.

CONCLUSION

Over the past half-century psychiatric consultation in the general hospital has advanced from a novelty to a full-fledged medical subspecialty. As part of this coming of age the time has come to not simply ask—"Do you have a psychiatric consultation service?," but rather "How good is the psychiatric consultation service at your institution?" This question is posed to initiate introspection by all who are involved in this field. Only through considering that we can and must do better for our patients will improvement be possible.

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Psychiatric Research in the General Hospital

53

Adrienne O. van Nieuwenhuizen, B.A.
Dan V. Iosifescu, M.D., M.Sc.

The goal of this chapter is to highlight the importance of pursuing research in the context of a busy clinical psychiatry department. This chapter is also intended as a primer for the clinician who is interested in research activities but has minimal experience with clinical research. So, why should a busy clinician consider pursuing research? First, research is necessary. Without research studies, psychiatric treatment would be limited to old treatments or treatments that lack empirical validation. Clinical research is the only way to accumulate the evidence necessary to practice evidence-based medicine. We need clinical research to push the boundaries of what we know, and to evaluate new definitions of disorders or the efficacy of new treatments. However, a great deal of clinical research is published each year, and we already have a hard time keeping up with new results. This brings us to our second point: Why is it important for clinicians to be involved in research? The answer is that clinicians are in direct contact with the existing unmet clinical needs of their patients. Therefore, they are in the best position to know which research is most needed and which research topics will have the most profound impact on the field. Pure scientists are more likely to pursue topics of great intellectual complexity but of less direct practical importance.

Although it is true that clinical experience is crucial for the planning and prioritizing of clinical research, the reverse is also true. Involving ourselves in the research process is great training for our clinical work. Research requires us to be critical and iconoclastic; it trains us to pay attention not only to the results but also to the details. Thus, we are better able to evaluate the strength of the evidence and to differentiate between high-quality and poor-quality research. The former should be trusted and may justify changes in our clinical practice, whereas the latter should not be trusted; at best, it may serve as a rationale for further studies.

Engaging in research also serves to demystify the process. Clinicians are frequently reluctant to refer patients to research studies out of concern that such studies may involve ineffective treatments and use subjects as "guinea pigs." When engaged in research studies, clinicians can experience first hand the elaborate planning required of a research trial that aims for the highest level of protection of participants, as well as the extensive evaluations in research that are on par with the very best of clinical encounters.

We will next describe the most significant parts of a research study, the most common types of research, and the steps that must be gone through, from the first outline of a research idea to the publication of the research results.

THE RESEARCH QUESTION AND PLANNING THE STUDY

Pursuing an intriguing clinical observation or anecdote is one of the best ways to choose a research question. The topic of interest might be as general as the prevalence of depression after myocardial infarction and the relationship between these two illnesses. Alternatively, it might be the relationship between depression and a much rarer condition, such as depression associated with a mitochondrial disorder. It is important to choose an innately compelling research question, as this is the best defense possible when coping with the trials and tribulations inherent in research. Designing, implementing, and completing a study can be tedious, so a deep, personal interest in the research question is necessary to push through the challenges that will inevitably arise.

Once a potential research question has been identified, the next task is to meticulously define each aspect of the question. Conducting a thorough review of the literature relating to the research question is essential and is best done by searching the National Library of Medicine PubMed database (www.ncbi.nlm.nih.gov/pubmed) for related articles. If the literature search reveals that similar research has already been done, learning about the methods used and the suggestions for further research will be helpful for designing a new study. Familiarity with the relevant literature is also important for describing how the proposed research would differ from what has already been done, and what important research question it would address. These arguments will be invaluable when submitting the research proposal for approval by funding agencies and ethics committees.

To study depression in patients who have had a myocardial infarction, the particular phenomena that are of interest must be operationally defined. Depression and cardiovascular disease encompass broad fields of research, so the research question must be narrowed to a specific subtopic in this field (e.g., prevalence, risk factors, or outcomes with a particular intervention). On the other hand, almost any research project can be undertaken on the association of depression with mitochondrial myopathy, encephalopathy, or lactic acidosis with stroke-like episodes syndrome, as very few reports exist on this topic. The rarity of this disorder is a mixed blessing for researchers, as it entails significant challenges for recruitment.

Defining the research topic begins with the currently accepted gold standard, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR). The DSM manual was originally drafted for

research purposes, but its influence now reaches far beyond the research world. If the research question involves a narrower subtype of disorders that is not yet defined in the DSM (such as pathologic grief), appropriate and validated scales should be selected to operationally define and assess this subtype.

The next step is to specify the clinical population of interest. Naturally, this will be constrained by one's access to such patients (see Recruitment, under Executing the Study, later). Access to potential research subjects is often gained through clinical care contacts or from research collaborators. Some of the common population parameters that must be specified include the age range, exclusionary co-morbid disorders, the minimum and maximum number of treatments a patient may have failed (e.g., a patient who has not responded to two or more treatments may be different from a treatment-naive patient in ways that are clinically important), and exclusionary concomitant medications. Defining the study's population requires determining how many subjects are needed and can be feasibly recruited; this, in turn, requires taking into account drop-out rates and noncompliance rates (these are best based on similar clinical trials that have recently been conducted nearby). Necessary considerations for planning an adequate sample size are discussed later (see Statistical Methods later).

Once all aspects of the research question have been clearly defined, measures must be chosen that can quantify these concepts. Possible types of research measures range from clinical research scales to electroencephalograms to neuroimaging assessments. One useful exercise is to imagine the study proceeding exactly according to plan, and then to review the hypothetical data that would confirm the study's hypotheses. What findings would confirm these hypotheses? Will the research scales' individual item scores be analyzed, or only the scales' total scores? Confronting these questions early will benefit the study database's design greatly. The importance of carefully designing a database tailored to the study's objectives *before* initiating enrollment cannot be overemphasized (see Choosing the Research Tools, later).

The design of the study should minimize two common methodological flaws. The first involves clinical reliability in a study. *Reliability* refers to raters' consistency in determining whether to include patients in the study, and their agreement in measuring symptom severity. Two raters scoring the answers of the same patient with the same research scale and yet producing very different scores would signal a potential problem with reliability. The second common weakness relates to *validity*—the study's ability to correctly target the symptoms or illness of interest. The symptoms or illness must be very clearly defined to avoid inadvertently assessing *other* symptoms or illnesses. For example, an assessment of depression that is limited to questions about difficulties with concentration and lack of motivation might assess cognitive deficits just as much as depression, and therefore this measure would have poor validity. These concerns highlight an important issue: One of the many challenges in research is the tension between (1) the desire to purify the subject population as much as possible, to minimize variability related to other patient characteristics (i.e., to compare apples with apples) and (2) the need for results to be generalizable to the larger population (as accomplished by including patients of different genders, of different ethnic and racial backgrounds, and with multiple associated co-morbid conditions).

Although designing a study solely on these theoretical considerations is ideal, in reality the research question is often shaped, at least in part, by more practical considerations. These may include the resources of one's hospital, department, or clinical practice; access to research funds directly or indirectly through colleagues; and the physical and financial limitations of the target population's ability to participate in research.

TYPES OF PSYCHIATRIC STUDIES

Once the research question has been determined, it is possible to choose the type of clinical research that best suits it. In prospective studies, the data are collected after the selection of subjects. In contrast are retrospective studies, in which a population of interest is identified (e.g., all depressed adults with co-morbid anxiety admitted in a 6-month period), and then data already collected for clinical purposes are reviewed for the parameters of interest (e.g., how many of the depressed adults received additional psychopharmacologic treatment for their anxiety). Although retrospective studies are easier and cheaper, they are limited to data already collected, and thus to the variability in the quality and completeness of such data over time. Some research questions are specific enough to make the choice between prospective and retrospective design a moot point (e.g., the rate of mortality in Revolutionary War soldiers would clearly require a retrospective study), but most research questions can be explored using several different approaches. The discussion of study types that follows is meant to serve as an introduction to some of the different options, but they are not necessarily mutually exclusive. For example, prospectively acquired data on the effects of one intervention can be compared to already-gathered, retrospective data on the effects of another intervention. This design is not ideal, as these two sets of data probably differ with regard to more than just the type of intervention, but this may be the only ethical option when the new therapy under investigation appears strikingly superior to all other therapies.

Retrospective Studies

Case-control studies are usually conducted retrospectively, via chart reviews. Cases are selected from subjects affected by the illness of interest, and controls are selected from individuals not affected by that illness.

Literature reviews can yield a qualitative and a quantitative product. If a review article is written summarizing all the publications on a particular topic in the literature, the literature is qualitatively reviewed.

Meta-analyses can be conceptualized as quantitative literature reviews, but they represent a major genre of research in their own right. A meta-analysis requires quantitatively reviewing all the studies that have been conducted on a certain disorder, following specific rules for statistical analysis of such data. The large sample size amassed by aggregating studies in a meta-analysis can reveal better-substantiated conclusions than those that small, individual

studies can detect. Although up to 10,000 clinical trials are published in English-language journals every year, their small sample sizes lead to many contradictory conclusions. In contrast, the results of meta-analyses are often consistent with those of clinical trials with very large sample sizes, so this study design may provide a faster and cheaper means of obtaining conclusive data on the safety and efficacy of new therapies.

Epidemiologic Studies

Epidemiologists interested in mental health study the causes and prevalences of various psychopathologies in well-defined populations. Most epidemiologic studies are cross sectional, and their purpose is often to determine the prevalence of a disorder at a specific point in time. Alternatively, some epidemiologic studies follow a population over an extended period; these are known as longitudinal epidemiologic studies.

Cohort studies are mostly done via longitudinal epidemiologic studies. Research subjects are chosen on the basis of whether they were exposed to a certain condition at a specific point in time. Longitudinal data (such as symptoms, diagnoses, and mortality rates) are then collected over time to determine the clinical consequences of the initial exposure. These studies can be conducted prospectively or retrospectively; the former naturally allow greater control over what data are collected, whereas the latter have the advantage of being faster and cheaper.

Prospective Studies

Prospective clinical trials gained popularity in the mid-1900s as a means of comparing the feasibility and efficacy of various therapeutic agents. Clinical trials can range from those on a very small scale (such as single case reports) to those on a very large scale (such as international, multisite clinical trials). In the process of developing a novel treatment, the scale of the study often correlates with the phase of the investigational product (see The Phases of Drug or Device Development, later). For example, phase I studies are always small, as safety is at issue, whereas phase III studies are often very large, because comparing the efficacy of potentially similar therapeutic agents requires well-powered studies.

Randomized controlled trials are the most common and are the gold standard of studies for the evaluation of the efficacy and safety of a new therapy. These trials always include a control group (either placebo or an accepted treatment), and the decision of whether a subject receives the investigational drug or a control is made by randomization. Randomization is the random assignment of research subjects to one of several preselected treatments, usually by a computer program. The goal of randomization is to reduce the risk of biased assignment (e.g., enrolling patients who are more likely to improve in one of the treatment groups). Although clinical trials represent the most common kind of prospective study, they are generally very costly and there may be ethical issues associated with the use of control treatment. (See What Is a Randomized, Placebo-Controlled, Double-Blind Clinical Trial later.) Another disadvantage of this type of trial is the possible ethical issue associated with the use of a control treatment (see discussion on placebos, later).

Crossover designs are used in studies that assign half the subjects to the control group and half to the treatment group, and then switch the two groups. Typically, half the subjects might be assigned to treatment A, and half to treatment B; at the midpoint of the study, all the subjects are switched to the treatment they have not received, so that the first group receives treatment B and the second group receives treatment A. This design has the advantage of reducing the number of patients required, as each group serves as its own control and as the control for the other group. One complication of the design is that the first treatment may sometimes have lasting effects that could influence the measurements in the second half of the study. Also, data from subjects who drop out during the study are difficult to compare, because they did not complete both treatments. On a much smaller scale, the crossover design can be applied with one or several subjects, in the form of an intensive, repeated single-case design. In this case, each subject is his or her own control, and there is no averaging of data. Because the intensive single-case design does not involve many subjects, there can be one crossover, or two or more crossovers (e.g., the subject experiences the side effect on treatment A, then no side effect on placebo, and then the side effect again on treatment A, which stops again while on placebo). This can be done in a nonblinded, single-blind, or double-blind fashion. The benefit of repeated single-case designs is that one is left with a very well documented case in which one treatment can be shown to be more efficacious than another.

Case-control studies can sometimes be conducted prospectively as well. Subjects recruited as cases are affected by the illness of interest, whereas controls are unaffected by that illness (but may be affected by another).

AN IN-DEPTH LOOK AT PROSPECTIVE CLINICAL TRIALS

What Is a Randomized, Placebo-Controlled, Double-Blind Clinical Trial?

Randomized, placebo-controlled, double-blind clinical trials are frequently encountered in psychiatric literature. These are the three elements of modern clinical trials.

Randomization: The purpose of clinical trials is often to investigate the efficacy of a particular treatment. This is often accomplished by giving an active treatment to half the subjects in a study and giving the other half a placebo treatment. The term *randomization* refers to the technique used to assign patients to either the active group or the placebo group. The consequence of randomization is that every patient entering a clinical trial has an equal chance of being assigned to any treatment group. As discussed previously, the role of randomization is to reduce selection bias. In a *simple randomization*, each time a subject is enrolled in a trial, a computer program randomly assigns him or her to one of the treatment groups. This leaves open the risk that an important variable could be unequally represented between the groups. For example, if a clinical trial is investigating a potential anxiolytic and the recruitment includes subjects with co-morbid depression, it would be important to ensure that the drug and placebo groups have equal numbers of subjects with co-morbid depression

(as these subjects could be more treatment refractory). Stratification allows the researcher to specify the variables that should be equally distributed, such as gender, co-morbid diagnosis, and age range. Simple randomization alone does not ensure that the groups will be homogeneous, as all the subjects with co-morbid depression could accidentally end up in one group, so stratification allows active manipulation of assignment to avoid such an outcome. However, stratification reduces the statistical power of the study, and there are limits on the numbers of strata that are feasible.

Ethically and scientifically, randomization cannot be used unless the investigators view all treatments as equally favorable. This means that current clinical evidence cannot favor one treatment in the study over another treatment in the study. It would be unethical for an investigator to know that a certain treatment was superior therapeutically, and yet still expose half (or more) of the subjects to an alternative (inferior) treatment. Also, if the treatment had already been demonstrated to be superior, there would be no point in pursuing the research. This is different from a researcher's intuition or desire to believe that a certain treatment might be superior. Some patients enrolled in clinical trials secretly hope they will be exposed to the "real" (i.e., active) treatment as opposed to a placebo (conceptualized as ineffective); the investigator should be able to explain there is not sufficient evidence to suggest that any treatment is superior. If the investigator does not believe that statement, or if the current literature does not support it, the study should not be conducted in the first place.

Placebo: The placebo is another key element in most modern clinical trials. Placebos have been included in medication, surgery, device, and even psychotherapy studies. For studies examining the effectiveness of a certain medication, placebos are often inert pills containing no pharmacologically active compound. In studies assessing the efficacy of a device, the placebo may involve sham applications of the device, in which the patient receives the application of the device but a key component is disabled. Psychotherapy studies may involve generic interactions with patients without making use of formal psychotherapy or enrolling subjects on a wait list. Thus, the objective is for the subjects to be incapable of detecting whether they are receiving active treatment or placebo. The placebo effect is very significant in most psychiatric illnesses, so many psychiatric studies make use of a placebo control. The use of placebo in psychiatric research is hotly debated. Some researchers maintain that for a disease where active treatments have already been approved and are considered efficacious, new medications should be approved only on the basis of equivalence with existing treatments. However, when ineffective treatments might have been approved or are in widespread use, demonstrating that new treatments are as effective as the old ones is not very useful. Only a placebo can measure the true magnitude of the nonpharmacologic healing effect of the clinical and research interaction.

Use of a placebo helps to clarify the real magnitude of clinical improvement associated solely with the active treatment. If a study comparing two active treatments measures a 35% response rate for both treatments, the investigators might conclude that roughly a third of patients improved due to pharmacologic effects. Including a placebo control might reveal that the placebo group had a 30% response rate, which could lead to the alternative conclusion that the patient–doctor relationship and interactions may have been responsible for most of the improvement.

Blinded-trials: Like randomization, double-blinding is a strategy to further homogenize the characteristics of active group and placebo group so as to improve the likelihood that the main difference is in the treatment that is received. A clinical trial can be an open trial, a single-blind trial, or a double-blind trial. In an open trial, clinicians, subjects, and research staff are all aware of the treatment received by the subject. This very closely resembles standard clinical practice. In a single-blind study, one of the parties involved in the research is blinded. The subject could be blinded, while the rest of the research team is aware of what the subject is receiving. Many clinicians dislike this situation, as it can erode the trust and alliance usually present in the doctor–patient relationship. Alternatively, the clinical rater might be blinded, while the subject and study clinician both know which treatment the subject is receiving. In a double-blind study, the clinician, study rater, and subject all are naive as to which treatment the subject is receiving. Double-blind trials reduce the chance that the data collected will be influenced by clinician or subject bias, but the risk is not completely eliminated. Positive or negative changes in patients may suggest which treatment they are receiving. For example, if the treatment being studied is known to cause dry mouth, the clinician may suspect that the subject reporting the side effect is receiving the active treatment. However, patients receiving placebo may also report side effects similar to those expected with the active treatment, as they are led to expect the possibility of a specific group of side effects. This highlights the importance of including a placebo arm, as it reveals the possibility that not all side effects observed are a consequence of the pharmacologic effects of the active treatment. It can be helpful to assess the clinician's and the patient's intuition or expectation regarding which treatment was administered. This may reveal a correlation between extent of improvement and the expectation regarding the treatment received.

When a trial makes use of blinding, questions about the nature and timing of the unblinding inevitably arise. If all the subjects were enrolled at the same time, it may be feasible to unblind them when they simultaneously finish the trial. However, most clinical trials enroll subjects over a long period of time, and this complicates the issue. If patients are unblinded whenever they finish the study, the risk is that the research staff and current and future subjects will be unblinded. For example, if all the patients who were on active treatment had complained of increased appetite, staff and future subjects may associate increased appetite with active treatment. The alternative to unblinding patients in long trials can be equally challenging, as it requires arranging follow-up care without making use of information regarding treatment assignment during the study. If patients have experienced significant improvement during the trial, it will be unclear which intervention they should continue receiving (placebo or medication). These issues must be clearly thought out and resolved by the clinician before initiating the trial.

The Phases of Drug or Device Development

A medication or device under development passes through four phases of investigation. Because studies in these phases involve investigating the novel use of a medication or device, these studies require an Investigational New Drug (IND) application form to be submitted to the U.S. Food and Drug Administration (FDA) (the form can be found on the FDA website). Phase I is initiated when an agent has successfully demonstrated some safety and efficacy in animals. At this point, an investigator (usually the pharmaceutical company) can apply for permission from the FDA via an IND to explore the tolerability and safety of the agent in humans. If the results are positive for these criteria, phase II studies may be initiated, with a larger number of subjects than phase I; this time, the objectives are to determine whether the agent can demonstrate any therapeutic efficacy and to suggest the range of effective doses. If the results are once again positive, phase III trials may be initiated. These include classic, large, randomized, double-blind, placebo-controlled studies, and they can result in the approval of a new medication or device. Once a treatment has successfully passed phase III, phase IV trials may be undertaken to explore the treatment's safety and efficacy for other populations, or for the treatment of other disorders.

IMPORTANT SUBTYPES OF CLINICAL TRIALS

The following subtypes of clinical trials come with their own set of challenges and benefits. These categories are not necessarily mutually exclusive; for example, biological markers (via neuroimaging) can be explored and correlated with psychological assessments (via computer tasks).

Biological Markers

A number of biological variables (metabolic, endocrine, neurologic, and genetic) have been investigated as potential diagnostic markers for psychiatric illness or as predictors of treatment outcome. The diagnosis of most psychiatric illnesses relies primarily or exclusively on subjective information. Objective biological markers would be very helpful in increasing the inter-clinician agreement (reliability) for certain psychiatric diagnoses. Moreover, partial or inadequate response to treatments is common in many psychiatric disorders. Nonresponse to treatments is associated with disability and higher medical costs, and partial response is associated with higher relapse and recurrence rates. The absence of clinical or biological predictors of treatment outcome that can guide treatment selection for major depressive disorder is frustrating to both clinicians and patients, as the patient's suffering is extended through ineffective treatment trials. Moreover, the choice of next-step strategies after a failed trial is not clear, especially because some patients do well with a medication even if they previously failed another medication in the same class.

Metabolic studies: Many studies have focused on the changes in brain and body metabolism that occur with psychiatric illnesses. Other studies have focused on the increased associations with obesity, diabetes, dyslipidemia, and other metabolic abnormalities in relation to psychiatric illness or to the treatments used.

Endocrine studies: Dysfunctions in multiple endocrine glands (e.g., thyroid, adrenal, gonads) have been associated with psychiatric illness as well as the side effects of specific treatments.

Imaging studies: Structural neuroimaging studies have investigated changes in brain morphology in patients with psychiatric illness. Functional neuroimaging studies (single-photon emission computed tomography, positron emission tomography, and functional magnetic resonance imaging) allow investigators to observe the functionality of specific brain areas by measuring blood flow and metabolic rates. These can be compared between subjects and controls or within subjects before and after treatment, to understand changes in brain function associated with treatment effects. Magnetic resonance spectroscopy studies allow investigators to perform an *in vivo* chemical analysis by measuring brain levels of key neurochemicals. Such studies may also reveal the metabolic effects of treatments.

Genetics studies: Genetic research has been very successful in the past decade in associating candidate genes with many important psychiatric disorders. Because of the large numbers of genes under investigation, such trials are very large and expensive. It is hoped that genetic research may reveal the specific biological pathways that are involved in psychiatric illnesses. A separate area of investigation is pharmacogenomics, the study of variations in the efficacy of pharmacologic treatments in relation to genetic predisposition. It is possible that certain populations may be more responsive to specific treatments and that genetic information may lead to personalized medicine, through which the most susceptible individuals are identified, and patients receive the pharmacologic treatment most effective for them. Another area of investigation is genetic epidemiology, which studies the causes, rates, and treatments of illnesses in families. This type of research uses genetic and clinical information about as many individual members of a family as possible to determine the relative influences of the environment and genes on each individual's risk for developing an illness. Geneticists also seek to determine which genes and single nucleotide polymorphisms are associated with a particular illness. Mathematical models are used to assess all of these possible factors, and to weigh their predictive importance, as well as to model possible relationships between different variables.

Psychological Assessments

Some studies focus on, or include, assessments of psychological features (e.g., cognitive deficits, mood traits and mood reactivity, associative thinking, reward response). For example, a subject's cognitive function may be first assessed before they receive treatment for their psychosis and then again after several months of treatment. Alternatively, mood reactivity might be compared between patients with unipolar depression and psychotic depression in order to study psychological differences between these two clinical populations. Such studies may focus on psychological characteristics and function with certain disorders, or on changes in psychological measures in relation to treatment. Increasing use has been made of computer tasks for assessing patients, particularly for assessing their cognitive function.

Treatment Studies

Inpatient unit: Research on an inpatient psychiatric unit comes with its own set of advantages and disadvantages. One of the advantages to this research environment is that a steady stream of symptomatic patients is guaranteed. The disadvantage is that patients are often admitted to inpatient units only when their symptoms are particularly difficult to treat, and therefore they require acute, intensive treatment. This challenge can be dealt with by tailoring research studies to the inpatient population. If mood disorders co-morbid with substance use is the most common diagnosis for patients admitted to a unit, designing research for this population will greatly aid recruitment. Another challenge is the unpredictability of admission and discharge. Patients are generally kept on a unit only as long as their need meets the level of care of inpatient hospitalization, and because current lengths of stay are short, most patients would be discharged within a week of enrolling in a study. If possible, studies should be designed to have inpatient–outpatient status flexibility, so that patients can continue to participate in the study even after they are discharged. Finally, it is very important to assess whether these subjects have the capacity to provide informed consent and thus are voluntarily consenting to a study. This can be particularly difficult when patients are admitted to the hospital against their will.

Neurotherapeutic studies: Recently, there has been an explosion of studies on neurotherapeutic interventions. These include electroconvulsive therapy, vagus nerve stimulation, repetitive transcranial magnetic stimulation, and deep brain stimulation. Although some have suffered from stimatizing media coverage (e.g., electroconvulsive therapy) or have had controversy surrounding their efficacy (e.g., vagus nerve stimulation, repetitive transcranial magnetic stimulation), a growing body of literature supports the use of such treatments. As these means of treating psychiatric illnesses become more common, further research will be needed.

Natural remedies: Over the past few decades, natural or alternative remedies have become dramatically more popular in the United States and worldwide. Increasing numbers of patients now ask whether they might benefit from natural treatments, and many patients will visit a variety of practitioners, including herbalists, naturopaths, and other healers, in addition to physicians. Because natural remedies are readily available over the counter, many individuals choose to self-medicate without professional supervision. Frequently used treatments that have benefited from positive research in psychiatric disorders include St. John's wort *(Hypericum)*, *S*-adenosylmethionine, the omega-3 fatty acids, *Ginkgo biloba*, L-methylfolate, and acupuncture. The benefits and liabilities of herbal remedies and other natural treatments are still largely unclear. Medical research has historically overlooked this area, and nutraceutical companies do not routinely fund studies on these medications. The public has the unfortunate misconception that just because something is called natural, it is safe. Natural medications, with the exception of homeopathic remedies, are not generally regulated by the FDA. Consequently, optimal dosages for these medications are poorly established, as are the active ingredients, contraindications, drug–drug interactions, and potential toxicities. Additional research in this field is needed.

Psychotherapy studies: Psychotherapy research has a reputation for being particularly challenging, but it is also filled with opportunities for novel research because many important questions remain to be addressed. One of the biggest challenges involves clearly defining and standardizing the psychotherapeutic intervention. Although ensuring that patients are all receiving the same pharmacologic agent in a psychopharmacologic study is fairly straightforward, ensuring standardized interventions in a psychotherapy trial is much more challenging, because psychotherapists' therapeautic techniques may vary greatly. One way this challenge has been overcome is by using psychotherapy treatment manuals, in which the psychotherapy protocol is extensively detailed. A second challenge is the difficulty of designing a placebo-control arm. Again, this is relatively straightforward in psychopharmacologic studies, where an inactive pill can be used. In psychotherapy, attempts at simulating the placebo condition have included use of nontreatment groups, wait lists for treatment groups, and talk sessions in which topics of therapeutic importance are avoided. A third challenge in psychotherapy research is that various psychotherapies and placebos have a high rate of response, which means that much larger studies are needed to detect meaningful differences. Again, this is more feasible in psychopharmacologic studies, where larger enrollment is less costly in time for the research clinician.

Several recent studies have combined pharmacologic interventions and psychotherapy (e.g., comparing patients receiving a medication with patients receiving a medication plus psychotherapy). This combination addresses some of the challenges mentioned, and it is likely to be an area of continued research in the future.

Alternative support studies: Another domain for research relates to studies of collaborative care or culturally sensitive support for patients. Studies of collaborative care have been developed to assess whether the assistance of a mental health clinician (such as a social worker) can be effective in boosting mental health services in the primary care setting. Studies on culturally sensitive support examine the effects of tailoring clinical care to patients' cultural backgrounds.

CHOOSING THE RESEARCH TOOLS

Which tools? Choosing the best research tools, including a study's clinical rating scales, is a very important process. It requires determining which assessments will best measure the constructs of interest, how often they should be completed, and who should be responsible for administering them. As mentioned earlier (see The Research Question and Planning the Study), it is important to ensure that reliability and validity are maintained when choosing the most appropriate study tools. Reliability can be improved by thoroughly training raters in the use of the study's scales, and by establishing a clear protocol for the ratings. For example, some scales direct raters to "rate up" whenever more than one answer could fit a subject. In addition, it is important to assess test–retest reliability as well as interrater reliability. Validity can be improved by clearly defining the symptoms or disorder of interest. For example,

studies on traumatic brain injury have resulted in many conflicting findings, some of which may result from differences in the severity of the brain trauma in each case (e.g., severe versus mild), or from different etiologies of the brain injuries.

The first step is to choose rating scales that match the research question and have been validated for the population of interest. For most major psychiatric diagnoses, there is a wide range of scales to choose from—from fully structured rating scales that leave the rater little discretion in making an assessment, to semistructured and open-ended assessments that give the clinician a fair amount of flexibility in how to proceed with the assessment. The degree of structuring will probably depend on who is responsible for doing the assessments (see later). Next, a clear plan should be designed for entering the data into the study database, and for regular quality-control sessions. This is much easier when the initial assessments are entered on a computer in real time, so that no data transcription from paper forms to computer files is necessary. Entering data directly into a computer program immediately reveals problems with data quality (such as items not completed by the clinician or patient). Ensuring data quality can improve the study's power, whereas attempting to conduct analyses for a study where significant amounts of the data are missing is much more challenging.

Used by whom? The delegation of responsibility for clinical assessments will depend on which scales are used, as staff with less clinical experience can be trained to complete fully structured rating scales, whereas scales with less structure may be better left to experienced clinicians. Raters with limited clinical experience may adhere more closely to rating protocols, whereas seasoned clinicians may be more likely to override rating guidelines in favor of their own clinical judgment. Regardless of the raters' degree of experience, it is also necessary to determine whether one clinician will be responsible for all of a patient's ratings, or whether different clinicians will rotate in assessing a patient. Having the subject always rated by the same clinician can improve the reliability of the ratings. On the other hand, rotating the clinicians ensures that an individual clinician's rating biases are averaged out. For example, clinicians on an inpatient psychiatric unit will be accustomed to more severe symptoms and may therefore underrate moderate depression symptoms; including clinicians less accustomed to severe presentations can balance this out. Rotating clinicians also reduces the risk that patient improvement will be the result of a powerful therapeutic alliance rather than the more generalized aspects of the studys intervention.

Because clinical assessments may be biased for a variety of reasons, several checks and balances have been developed for assessing patients' symptoms. The most common alternative source of assessment is the subject himself or herself. Self-rated scales reduce the risk that the patient is revealing only the symptoms he or she is comfortable sharing verbally with a clinician. Patient-completed scales also reduce the risk that a clinician might score them in such a way as to ensure enrollment of the patient into the study.

Another source of assessment is off-site monitoring. External rating consultants can be employed to verify the screening or study assessments completed by the clinician. For example, if the clinician-rated scores of a patient achieve the symptom severity needed for a study, an off-site rater then conducts the ratings a second time to verify that the required symptom severity is in fact present. Off-site self-rated assessments can also be done by interactive voice recognition. Patients call an automated program and answer a series of self-rated questions. The interactive voice recognition system can then confirm whether the required degree of symptom severity is present.

EXECUTING THE STUDY

Recruitment: Finding funding for a study may be the number one challenge in research, but meeting recruitment goals is often a close second. It is easy to underestimate the difficulty of enrolling patients, and this is why larger grants often require some pilot data to demonstrate the feasibility of the study. Finding out what the no-show and dropout rates are for local research clinics can provide a good forecast of the challenges ahead. Funding agencies often require regular updates (e.g., on the number of potential subjects screened, the number enrolled, and the number completed). Some institutions, such as the National Institutes of Health (NIH) and the local institutional review board (IRB), require a breakdown of enrollment according to gender, race, and ethnicity. Recruitment requires constant attention, so weekly meetings with study staff to review successes and challenges with enrollment can be helpful. These meetings should track the enrollment rate and attempt to identify factors responsible for increases or decreases in enrollment. It can also be helpful to meet with clinicians working with the clinical population of interest, as these clinicians can refer patients for study participation. If recruitment is much slower than expected, it will be necessary to assess whether the study will still have enough statistical power to draw meaningful results and conclusions. If this does not appear to be the case, the remaining options include requesting a no-cost extension from the funding agency to achieve adequate recruitment, modifying some of the exclusion criteria (as long as this is not too detrimental to the study's validity), providing more compensation for participation in the study, or, if all else fails, making significant changes to the protocol and objectives of the study.

The informed consent process: Clinical research has had its dark moments both internationally and in the United States, so ethics committees were developed to review all clinical research. (For more information on working with IRBs, see Regulatory Responsibilities, later.) Requiring informed consent from study subjects is probably the most significant measure IRBs have implemented to reduce the risk of unethical research. Informed consent forms are written documents that clearly explain, in simple, accessible language, what the study involves, and the risks and possible benefits of participating in the study. This form should clearly state how the study will differ from standard clinical care, what the alternatives are to participating in the study (e.g., receiving clinical care through other means), under what circumstances the subject may be withdrawn from the study, and the subject's right to withdraw from the study at any time. If the study involves randomization and use of placebos, these concepts must also be clearly explained. Once the subject has had a chance to learn about the study and to ask questions, the subject and clinician can then sign

the informed consent form and proceed with the screening visit. If the nature of the study, or the risks and benefits of participating in the study, change during a subject's participation, the subject should sign a revised consent form, to ensure that fully informed consent has been acquired for the current study.

Submitting protocols and consent forms to the IRB may seem tedious, and this process is often a source of delays in starting a study, but a clear understanding of the IRB's goals and concerns can help reduce these delays. Two sources of information should be consulted when drafting consent forms. First, there are federal regulations on requirements for consent forms, and these are detailed in the Department of Health and Human Services' general requirements for informed consent, in 45 CFR 46.116 (see www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm). Second, most institutions' review boards provide clear instructions for all required study documents, particularly for drafting consent forms.

There is ongoing debate about the informed consent procedure, how best to acquire consent, and which subjects do not have the necessary capacity to provide informed consent. However, there are some generally accepted thoughts on this issue. The NIH's Office for Protection from Research Risks identifies mentally disabled persons as needing additional safeguards to protect them when participating in research. There are no federal regulations on the specific nature of the safeguards, however, so the key is to determine whether the population is at risk for lacking capacity, and then to proceed with the consent procedure accordingly. When a study is recruiting patients with severe dementia, a guardian or proxy will need to provide the informed consent, and the subject will need to provide assent. In intermediate cases, such as studies on a bipolar disorder, subjects with severe mania may not be able to provide informed consent, so an assessment of symptom severity should accompany the consent procedure to ensure there is capacity for consent.

The screening visit: Only after the informed consent procedure has been completed can any other study-related procedures be completed at the screening visit. This visit often includes completing clinician-rated and self-rated scales to determine whether the subject meets criteria for enrollment. Completing these scales also provides useful baseline information for the subject, which can then be compared to their ratings during and after the intervention. It is important to keep detailed information on the participants who were scheduled for a screen, which ones showed up for the screen visit, which ones provided consent, and, of those, which ones met the study criteria. These data can reveal obstacles to enrollment (such as particular exclusion criteria) and which referral sources are particularly fruitful. Some institutions, including the NIH, require detailed information on how many subjects granted consent, how many were not eligible, why, and so on.

The baseline visit: Some studies also include a baseline visit. The primary aim of the baseline visit is to ensure that the subject meets the inclusion criteria for a certain period (the interval between screen and baseline), rather than solely at the screening visit. In some cases, participating in the screen itself can cause significant clinical improvement, so assessing a patient a second time at baseline can improve the likelihood that changes observed during the study result from the intervention and are not a nonspecific effect.

Further visits: After the screen and baseline visits, the rest of the visits are often similar to one another. Subjects may be scheduled for a predetermined number of visits, but in some cases the length of their participation is determined by the speed of their clinical improvement. Clear criteria should be in place specifying at what points subjects should leave a study. Ideally, most subjects will leave when they have completed all of the study procedures, but other circumstances can also necessitate leaving a study. Possible grounds for withdrawing subjects from a study include failure to see improvement in the patient's condition, worsening of the patient's condition, the development of suicidal ideation or intent, and nonadherence to study protocol.

Nonadherence, a common phenomenon in psychiatric studies, is a complex issue. It is helpful to define the required dosage adherence for participation in a trial; many protocols require that subjects take at least 80% of the medication or therapy specified in the protocol. If adherence is a major concern, studies can include a lead-in phase, with participation limited to subjects who adhere to the protocol in that phase. Taking the time to fully explain the study and the importance of compliance can greatly boost adherence. Making study participation as painless as possible is also helpful (e.g., by reducing wait times, maintaining a positive and patient attitude toward subjects, and being responsive to their concerns and frustrations).

Although several steps can be taken to address adherence, struggles to enroll perfectly adherent subjects are reminiscent of the desire to enroll a very "pure" sample. Pursuing purity may mean sacrificing generalizability, so a careful compromise should be struck between these two ideals. In any case, regardless of what is done to mediate adherence rate, careful documentation on adherence should be maintained. This can be done by having participants maintain drug diaries in which they note the medication they consumed each day, and study coordinators can request that any leftover medication be returned to them so as to track adherence rates.

Final visit: Subjects should be reminded in advance that their final visit is approaching, so that completion of the study does not come as an unpleasant surprise. The final visit should be carefully planned, particularly because subjects often have ambivalent feelings about ending their participation. If the study is unblinded at this point, the unblinding should be done in a thoughtful manner; if unblinding will not yet take place, the protocol should specify how to appropriately refer subjects to follow-up care.

Concluding the study: Once the study is completed, the focus quickly turns to analyzing the results, and to publishing a manuscript that details the study's findings in a peer-reviewed journal. There is an ethical obligation to funding agencies, subjects, and the clinical community to share the study's findings in a timely manner. The investigators are also interested in publishing as quickly as possible, as this will influence their ability to secure future research opportunities.

WRITING THE PROTOCOL

Once the details have been determined, formally drafting the protocol should be relatively straightforward. The protocol may initially be drafted for submission to the IRB or to a funding agency, or perhaps for simultaneous submission to both. Although there may be some variation in different organizations' preferences for protocol style and organization, most protocols are expected to review the same basic information. Regardless of where it is being submitted, the key to a good protocol is to make it as detailed as possible, thereby eliminating ambiguity and the risk of different interpretations of the protocol.

Many protocols start by describing the study's *hypotheses and objectives*. These include the primary set of hypotheses as well as any secondary hypotheses of interest. This section is meant to outline the purpose of conducting the study. Next, the *background and rationale* for the study explain and support the hypotheses based on the existing literature. The importance of the study's research question should be defended, including relevant theory and current empirical data. A general literature review should be provided, highlighting what information is still missing and how the proposed study will address this void. The background section is greatly strengthened if a pilot study has been done, as this reassures the reviewer that the study is feasible. The study's *population* should be described, with details on how many subjects will be enrolled and whether the study will take place at one or multiple sites. For clinical drug trials in adult populations, 18 to 65 years is a typical age range for subject inclusion, but this is adjusted depending on the focus of the study. Other inclusion and exclusion criteria should also be clearly detailed and justified. As previously discussed, the desire for a pure sample must be balanced with the generalizability of the study. This tension should be carefully and realistically considered when the study is being designed. If overly stringent criteria are set, the planned enrollment may not be feasible. In such circumstances, inclusion criteria may need to be relaxed at some point over the course of a study, but increasing the study population's heterogeneity may then require achieving an even greater sample size to draw meaningful conclusions.

The protocol should also clearly discuss what data will be collected during the study, and when. This involves detailing all of the study elements described earlier (see Executing the Study). The protocol should also review the same issues addressed in the consent form, including ways in which the study protocol differs from standard of care, the risks and benefits of participating in the study, measures that will be taken to reduce risks to subjects (including steps taken to protect subjects' privacy), the circumstances under which participants may need to be withdrawn from the study for their own protection or for the integrity of study data, and how the study is being funded. An explanation should also be given as to how the data will be monitored, who will have responsibility for monitoring the data and any adverse events, and how the study will be analyzed.

FUNDING

Once a clear protocol exists, the most challenging aspect of a grant application has been addressed. Some grants require all of the information discussed earlier, whereas smaller grants often require less information, such as a brief one- to two-page description of the study. It is helpful to find out from colleagues and mentors what some common sources of funding are in the field of interest. Additional information can be obtained from an Internet search, as most foundations or institutions aiming to fund research have searchable websites with detailed information for research applicants. It is important to read the information provided about the key areas of research focus for each institution, as proposals are more likely to get funded if they are in line with the sponsor's research interests. A university's or hospital's research administration office should also have a database of the existing funding opportunities (or those successfully used by other researchers). Smaller foundations tend to have more narrowly defined research interests and can provide only small grants, but those can be very helpful for funding the initial (pilot) projects required to secure funding for larger studies. Larger organizations such as the NIH have grant awards specifically designed to assist new clinicians in developing their research skills. There are also research training awards and research fellowships to assist new researchers in developing experience and training. Institutions vary with respect to what study costs they are able to assist with, so it is important to find this out when drafting the budget, and to contact the home institution's grants office to find out what institutional costs must be accounted for (e.g., overhead fees and IRB fees). Most funding agencies include salaries for study staff, as well as study materials, tests, or devices, among the supported costs.

Pharmaceutical companies or device manufacturers are a source of potential funding, as most have programs for Investigator-Initiated Trials that can support small- to medium-size studies (usually involving the pharmaceutical product or device manufactured by the company, but sometimes also funding more general research in the disease area of interest). The contact between the academic investigator and the pharmaceutical company is usually mediated by the company's medical science liaison for the specific geographic area. Investigator-Initiated Trials are designed and conducted by the investigator, not by the research staff at the pharmaceutical company. Thus, the research should prevent concerns that studies may be biased toward finding and reporting results that are favorable to the sponsor. Research contracts should specify that the academic investigator has the right to publish the data generated as part of the study (while usually having to give advance notice to the company regarding the results).

The very large clinical studies sponsored by the NIH tend to be led by senior investigators and typically require pilot data for the grant application. Thus, they would not be immediately available to new investigators. The large studies sponsored by pharmaceutical or device companies (usually during phases II and III of drug or device development) tend to be designed and conducted by researchers from the industrial sponsor, usually in close consultation with experts at the FDA and with academic experts in the field.

REGULATORY RESPONSIBILITIES

It is usually preferable to submit research protocols to the IRB after funding is secured, as the study may not be feasible in the absence of such funding. However, some studies

may be done without external funding. After having decided on all the details and after having written up at least some of them for a funding agency, drafting and submitting the required protocols, consent forms, and other forms for the IRB should be fairly easy. Because IRBs are particularly concerned about the safety of clinical subjects, some sections may need to be added to the protocol, or expanded upon, to fully address this. It is advisable to seek guidance from a mentor or another investigator familiar with the IRB, at least for the initial submission of the study for IRB approval. Once this has been approved, communication with the IRB will continue throughout the study. Any adverse events or requests for amending the protocol should be submitted to the IRB as they arise, and an annual review of the progress to date and problems that have arisen should be submitted in advance of the study's yearly expiration date.

Study sponsors (foundations, federal agencies, or commercial companies) have their own reporting requirements. Amendments that affect the design of the study, reports of serious adverse events, and annual updates must be submitted to the study's sponsors, have to be approved by the study sponsors, as do annual updates. Detailed records on the subjects enrolled, any adverse events, any subject discontinuation, and any changes to the protocol must be maintained to meet these reporting requirements.

STATISTICAL METHODS

It is beyond the scope of this chapter to provide a detailed presentation of statistics. We want, however, to emphasize the importance of statistical methods at every step of planning, conducting, or reporting the results of a research study. A statistician or a researcher with extensive statistical experience should be involved from the very first stages of designing a study. Waiting until the end of the study may lead to significant study design or execution errors that could have been prevented and are difficult or impossible to correct at a late stage.

The first concept to consider in the study design phase is the *statistical power* of the study. There are two major types of statistical errors in regards to a clinical trial. The type I error (alpha, α) is the probability of a false-positive result (i.e., finding a difference when in reality none exists). The type II error (beta, β) is the probability of a false-negative result (i.e., finding no difference when one exists in reality). Studies are designed to minimize these two errors to acceptable levels. Frequently, α is arbitrarily chosen as 0.05. Beta (β) and the commonly used "statistical power" ($1-\beta$) are dependent on alpha, on the number of subjects in the study, and on the magnitude of the expected difference to be detected. It is not only possible but also very important at the beginning of the study to estimate the number of subjects required to detect a difference between the groups of subjects studied. Such a computation can be performed with several statistical software packages. Not doing this computation exposes researchers to the risk of performing an underpowered study (i.e., one in which there is a very low chance of detecting a difference, even if such a difference does exist). Performing an underpowered study is scientifically wrong, and it might even be unethical because it exposes research subjects to risks related to the study intervention when there is an insufficient chance that the study can provide useful results.

Although a final statistical analysis is conducted once the study is over, the importance of designing a database and choosing statistical analyses before starting the study cannot be overemphasized. With a database already established, study data can be entered as they are collected, revealing quickly whether the rating scales are being scored completely and correctly. In real-life situations, some of the data will be missing, either because subjects do not complete the study or because forms are lost or incomplete. If data are not checked, there is a serious risk that only after the study is completed will it be discovered that too many data points are missing for any conclusions to be drawn from the study. A plan for dealing with missing data can help prevent some avoidable data losses, and it should include statistical rules for when the losses are not avoidable. Also, creating the database in advance often reveals ambiguities in the study protocol that can then be resolved before enrolling patients.

Investigators should know before they start analyzing data which analyses will be performed and why they were chosen. Many good statistical software packages are available (e.g., SPSS, Stata, SAS); the choice rests with the investigators and should be based on their intimate knowledge of the study and the data to be analyzed. Investigators should be fluent in the basics of statistical methods, even when they collaborate with statisticians. The data analysis methods have to be matched to the research questions and to the data collected. For example, the investigator will have to choose between methods used to compare data (e.g., gender or diagnosis) such as the chi-square test, and tests aimed for continuous data (e.g., symptom severity or age). Some tests allow comparison of only the main variables (*t* tests), whereas others allow correction of the analysis for differences between groups in other secondary variables (e.g., analysis of variance [ANOVA] or linear regression). For example, in a study comparing clinical improvement after antidepressants A and B, ANOVA can be used to test the difference between the two treatment groups while correcting for baseline depression scores, age, and gender (used as co-variables). Variables that are not normally distributed, or comparisons between groups with low numbers of subjects, require nonparametric methods (e.g., the Mann–Whitney *U* test).

The first analysis reported for any study is the one that answers the main question of the research, and it includes all randomized patients. When further analyses are reported, it must be clear why those were performed, which patients were excluded, and what corrections for multiple comparisons were performed. Although by convention a type I error ($\alpha = 0.05$) is considered acceptable for most clinical studies, performing many comparisons in the same subject increases the chance of type I errors. The value of α will need to be adjusted to avoid false-positive results.

PUBLISHING RESEARCH RESULTS

The first rules of good scientific writing are those of any good writing: be clear, be concise, and focus on the essentials. The aim is to present the data in detail and to make the complexities understandable to clinician readers who may not be familiar with the specific methods used in the study.

The typical research paper presenting original data has four parts. The *introduction* summarizes the research done before the current study and justifies the study being conducted. A common mistake made by junior researchers is to write the introduction as an extensive review of the entire field of research; this can be confusing and should be avoided. The introduction should highlight primarily the research hypothesis that started the study, as based on the literature. If an extensive review is desirable, it could be written as a separate review paper. The *methods* section describes in detail all the components of the study, as previously discussed in this chapter. By the end of the study, the methods section should be mostly written, as all the steps have already been planned, documented, and implemented. The *results* section is the most important; it includes all important results, tables, and figures. Presenting too many results can confuse readers and overshadow the important ones; secondary results and figures can be left as an Internet-only supplement (an option now offered by many journals). The *discussion* targets the research presented and the way it agrees, completes, or contradicts previously published results. The focus is on the current results, their importance, and their relationship with the pre-existing published data. A paragraph summarizing the limitations of the study is also advisable and helps the reader evaluate the quality of the data and the conclusions presented. When writing the conclusions, authors should avoid bold statements or extrapolations, especially when study limitations (e.g., low numbers of subjects and imperfect methods) may not justify such categorical statements.

Several aspects are important when deciding where to submit the paper. First, the author needs to find the publications that are most likely to be interested in publishing the research topic. The impact factor of the journal (a measure of how many of the published papers are cited in the literature) should also be considered, but this should not be the sole determining factor. Once a journal is targeted, its instructions for authors should be reviewed for specific requirements (e.g., length, format, specific sections). Ignoring such requirements can lead to a negative first impression from reviewers. After the peer review is complete, authors are frequently faced with critical reviews, formulated as requests for revision or as outright rejections. When asked to revise, the author should carefully read the critiques and edit the paper on the basis of their substance, providing a point-by-point, detailed list of all modifications. When faced with rejection, the author should avoid taking it as a personal failure, choose a more appropriate journal, and reshape the report for this other publication, incorporating suggested changes from the previous reviews.

CONCLUSION

We have stressed the importance of clinical research and summarized common research methods and pitfalls. Research involves a compromise between ideal conditions and feasible conditions. Quality research requires intelligence and innovation while designing the study, and then enduring enthusiasm and meticulous attention to detail while executing it. All this effort, however, is justified by the final result: our ability to better understand psychiatric disorders and validate new, more efficacious methods of treating them. Thus, clinical research is a fundamental part of our efforts to help our patients, now and in the future.

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Medical Psychiatry and Its Future

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Benjamin C. Silverman, M.D.
Paul Summergrad, M.D.
Scott L. Rauch, M.D.
Gregory L. Fricchione, M.D.

The formal introduction of psychiatric services into general hospitals in the 1930s and their subsequent growth have been among the most important institutional developments that have affected modern American psychiatric practice. Psychiatric units in general hospitals have proliferated since 1934, when 96% of psychiatric beds were under government control and generally found in state or veterans' hospitals.[1–5] Consultation, outpatient, and emergency psychiatric services in general hospitals have grown dramatically during this period as well.[6–8] Including data on the admission of patients to general medical services for primary psychiatric illness, it has been estimated that general hospitals provide nearly 60% of all inpatient psychiatric care in the United States.[9–12]

Reviews of the growth in general hospital psychiatry have often attempted to define its proper role. Commentators about these issues have generally split into two groups. The social-reformist group has seen the development of general hospital psychiatry as a function of its social position. General hospital psychiatry emerged in this view because it was seen as the setting in which mental illness could be treated in a more open manner, replacing custodial state hospital care. The general hospital's proximity to family and community resources was perceived as a central therapeutic element in this clinical efficacy.[11–15] Psychiatric wards should be therapeutic communities, and psychiatric consultants should be standard-bearers for a biopsychosocial model of illness, who would educate physicians to this new style of medical practice.[16,17]

The medical group, especially Hackett,[6] emphasized the links to medicine as central to the identity and growth of general hospital psychiatry. These authors stressed the development of psychopharmacology and the need for consultation services for patients with serious medical illness.[18–20] Institutional expressions of this perspective include the development of medical–psychiatric units, psychiatric consultation services stressing the medical care of patients rather than the education of caregivers, and the growing use of neurobiological discoveries in many areas of psychiatric practice.[21,22] The development of a sophisticated psychiatric pharmacopoeia, new insights into the molecular biology of psychiatric illness, and this handbook are a testimony to the correctness of this latter point of view.

This chapter reviews the forces that are currently affecting general hospital psychiatry and its major responses: medical/psychiatry units, consultation–liaison (C-L) services, psychiatric neuroscience, and psychiatry within integrated medical delivery systems.

FORCES AFFECTING GENERAL HOSPITAL PSYCHIATRY

Forces that contribute to change within contemporary general hospital psychiatry include intense economic pressures to reduce costs, restrictions on access to health care by insurers, new theoretical models within psychiatry, larger populations in need of psychiatric care, geographic areas underserved by psychiatric care, and privatization of public mental health care.

Controlling Health Care Costs

Attempts to control health care expenditures in the United States abound. Faced with the largest economic crisis of the past hundred years and fierce international competition, the pressures applied by government and industry to reduce these expenditures have been unrelenting.[23–26] These economic pressures have led to significant changes in the way expenditures for health care services have been controlled and have prompted reforms and proposed overhauls in health care insurance and delivery systems. For psychiatric services, negative operating margins threaten their viability, particularly in general hospital settings, making them vulnerable to downsizing or closure.[27]

In the 1980s and 1990s, the growth of health maintenance organizations (HMOs) and prepaid health plans, including capitation and other forms of health care financing that shift risk to providers, were among mechanisms that attempted to reduce the duration of hospitalization and the cost of health care. The net effect of these changes has been to shorten hospital stays for all classes of medical and psychiatric patients and to increase the acuity of illness necessary to allow admission to the general hospital.[28,29]

The growth of carve-outs (the removal of contracts for psychiatric services from the rest of medical services so that they are independently bid on and separately managed) has been one of the most difficult developments affecting general hospital psychiatry. These carve-out arrangements are particularly pernicious for medical psychiatry, placing newer and more competitive pressures on services and limiting the quality of care. In this model, psychiatry is divorced from primary care. Patients are not allowed to be cared for

by psychiatrists who in the past were well-known colleagues of primary care physicians (PCPs), and thus patients often face interruptions in basic psychiatric care.[30,31] In addition, carve-out models falsely assume that the medical and psychiatric needs of patients are distinct (both clinically and fiscally)—often to the detriment of patient care and leading to even higher costs in the end.[32,33]

In response to the ongoing economic pressures and public dissatisfaction with the availability and cost of medical care,[34] legislation in the United States has aimed to reform the health care system. In 2008, the federal government enacted mental health parity legislation designed to require equal insurance benefits for medical and psychiatric services by 2010.[35] The impact of this change has yet to be determined, but it has shown the potential to improve outpatient psychiatric follow-up in acute depressive episodes or after inpatient hospitalizations, without substantial increases in costs.[36–38] Mental health parity carries the potential to counteract the effects of carve-out models noted earlier, but only if the full costs associated with psychiatric disorders are understood and payment and care models allow care to be provided in an integrated way.

Movements toward health care reform and universal health care continue to gain momentum.[39–42] In 2006, Massachusetts became the first state in the United States to enact near-universal health care legislation.[43–47] Through expansions in the state Medicaid program, creation of income-related subsidies for health insurance, reform of the insurance market, and required mandates for both individuals and employers to participate in the program, Massachusetts aimed to insure between 90% and 95% of its previously uninsured population within 3 years of implementation. Although the long-term effects and viability of these changes remain uncertain, the short-term positive results have included increased enrollment in health insurance plans (e.g., the uninsured rate for working adults fell by nearly one half, with 93% insured 1 year after implementation), improved access to routine and preventive medical care, and decreased out-of-pocket costs for consumers, who reported less difficulty paying medical bills. The reform has produced negative outcomes as well, including higher-than-anticipated costs and increased unmet needs for health care, likely due in part to the large pool of newly insured patients entering the already overcrowded market of individuals looking for (and struggling to find) an available health care provider.[48]

In 2008, the United States presidential election focused heavily on health care reform, including the promise of accessible health insurance for all Americans.[49,50] It is not yet clear how such programs might be implemented or how they would affect the delivery of psychiatric care.

In the context of proposed health care reforms, the idea of patient-centered medical homes has the potential to reunite psychiatry and medical care under the same roof. Adapted from models of pediatric care, a patient-centered medical home is a comprehensive and personalized primary care setting, focused on accessibility, continuity, compassion, cultural sensitivity, evidence-based treatments, commitment to quality and safety, and coordinated or integrated care; it is an approach and attitude toward care, rather than a specific location. The medical home can provide patients with preventive care and a first contact in the medical system, decreasing acute care utilization rates and associated costs at the same time as improving the quality of care.[51]

Coordinated care in a medical home would ease referrals for mental health care, a process currently limited by insurance as discussed earlier. Smith and Sederer[51] have proposed the related idea of a mental health home: Mental health clinicians working with patients with severe mental illness would function as generalists, providing accountable, continuous, compassionate, and evidence-based care, coordinated with behavioral, medical, and rehabilitation service providers, including primary care providers, inpatient teams, day treatment programs, intensive case managers, assertive community treatment teams, housing services, and addictions specialists, among others.[52] A mental health home would not be a new form of psychiatric care delivery (e.g., similar characteristics to community mental health centers), but it would mark a return to the comprehensive, coordinated, and better-quality services of the past that existed before carve-outs and cost-cutting led to currently fragmented systems of mental health care and would meet the need to include the provision of some medical services to psychiatric patients where they receive their mental health care.

New Treatments and New Technologies

The development of new treatments and technologies has some roots in the development of effective psychopharmacologic agents in the mid 1950s.[7] Medications previously used in other areas of medicine have been used to treat psychiatric illness. Psychopharmacologic evaluation and treatment are often a focus of psychiatric hospitalization, especially for patients not safely treated outside of the hospital.

The efficacy of these new agents has also increased the emphasis on accurate diagnosis in psychiatry. Semistructured diagnostic interviews and rating scales have targeted observable elements in psychiatric illness.[53] Newer neuroimaging techniques, such as magnetic resonance imaging (MRI) or positron emission tomography (PET) scanning, have revealed evidence of previously unsuspected abnormalities, such as enlarged lateral ventricles in patients with schizophrenia or abnormal white matter in elderly patients with affective illness.[54] Studies using these technologies have begun to define fundamental neurobiological abnormalities underlying major psychiatric disorders. The combined effect of these changes is to make psychiatric care even more focused on neuromedical diagnostic evaluation, on medical care, and on psychopharmacologic management. Reflecting this shift at Massachusetts General Hospital (MGH), our psychiatric residents receive cross-specialty training by psychiatrists, neurologists, and neuropsychologists working on the same team so as to best provide them with a psychiatric education including neuroscience, neuroanatomy, neuroimaging, neuropsychopharmacology, and genetics, among other collaborative disciplines ideally suited to lead future developments in the understanding of the brain.[55,56]

New Populations in Psychiatric Treatment

Changing populations have also affected the focus and organization of general hospital psychiatric care. This happened, in part, due to the willingness of general hospital

psychiatrists to care for a broader range of patients: elderly patients, demented patients, patients with concomitant medical and psychiatric illness, patients with substance-related disorders, and patients with other neurobehavioral disorders. Psychiatrists are now established caregivers in intensive care and critical care settings.

New patient populations, including patients with drug-induced illness and those with human immunodeficiency virus (HIV)-related illness, have emerged that have required psychiatric care. Acquired immunodeficiency syndrome (AIDS) has now been recognized to have significant psychological, psychiatric, and neuropsychiatric sequelae. The capacities of the medical–psychiatric unit are an important resource for the response to the HIV epidemic.[57–59]

At the same time, new medical technologies, although sometimes life-saving, have in some instances put patients at risk for psychiatric morbidity. For example, undergoing cardiac electrophysiologic studies, having an automatic implantable cardioverter defibrillator (AICD) implanted, and then having it discharge appears to lower the threshold for panic or phobic anxiety and for posttraumatic stress disorder (PTSD).[60]

Changing Relationship with State Hospital Systems

Another factor that has affected the use and demographics of general hospital inpatient services has been the attempt to increase the admission of patients previously cared for in state hospital systems.[61–64]

Medical–Psychiatric Units

The development of medical–psychiatric units has represented an important conceptual shift in general hospital inpatient psychiatric care.[65–76]

The development of the medical–psychiatric concept has been, in some measure, a response to the limitations of the therapeutic milieu model.[67–76] The medical–psychiatric unit established the appropriate medical role of the attending physician. Where traditional units required attendance at group meetings as a condition for admission, patients on medical–psychiatric units might be so ill (e.g., with catatonia, feeding tubes, central lines, or severely psychotic behavior) that they might not be able to leave their bed, let alone their room. Patients with severe medical–psychiatric illness, excluded from traditional general hospital units, became the *raison d'être* of medical–psychiatric units. Such populations require traditional medical rounds, physical examinations, and the use of active treatments (such as psychopharmacologic agents). The role of the general hospital psychiatric unit, as it transitioned into a medical–psychiatric unit, became more medically traditional. Patients needed to receive an active medical intervention to get well. Community activities were relatively de-emphasized, and a normative medical hierarchy was approximated.[65,66,73,74]

Models

Kathol and others[77–80] have described a typology of medical–psychiatric units that has been useful in defining levels of medical–psychiatric acuity and the physical and staff organization to manage such services appropriately. Kathol defined four types of medical psychiatry units; type I and II units are traditional psychiatric units without medical capacity and standard medical units respectively, and types III and IV units are medical–psychiatry units proper. They differ predominantly in the severity of medical illness for which they can care. Both types III and IV units can care for patients needing intravenous fluids or medications, blood products, hemodialysis, peritoneal dialysis, or the care of other acute medical conditions. Type IV units are usually staffed by both internists and psychiatrists. These units can care for patients with high medical acuity (up to, but not including, patients who might require admission to the intensive care unit). Patients on such units may include those with significant congestive heart failure and co-morbid depression, delirium while undergoing chemotherapy, or peri-transplantation issues.

All medical–psychiatry units require cross-training of nursing and medical staff to allow the provision of high-quality care for patients with co-morbid acute medical and psychiatric illness. Psychiatrists on such units need to be able to provide general medical care and to collaborate with medical consultants. This conjoint care should include in-house internists for medical emergencies and possibly hired internal medicine consultants. Some units have handled this by hiring directors who are board certified in both psychiatry and either internal medicine or neurology or by maintaining medical and psychiatric physicians in a co-attending model.

In an environment that tends to carve out psychiatric care from medical care, close attention needs to be paid to define how medical–psychiatry units are reimbursed. To the extent that such units can shorten the overall length of stay (LOS) for patients with combined medical and psychiatric illness, they may be fiscally advantageous, especially in a capitated environment. For example, patients with complicated co-morbid psychiatric and medical conditions treated on type IV units have been shown to have enhanced psychiatric improvement compared to similar patients on general internal medicine wards and shorter length of inpatient stays than would have occurred with the traditional sequential approach to care (i.e., inpatient medical admission followed by transfer for inpatient psychiatric admission).[80]

As medical–psychiatry services become more oriented to acute symptomatic care, a variety of outpatient, partial hospital, and holding facilities are being created to decrease the need for hospitalization and to provide for the longer-term psychological, social, and medical rehabilitation of psychiatric patients. It is clear that medical–psychiatric units need to be closely integrated with such outpatient and partial hospital facilities to allow medical–psychiatry units to be used for patients in need of acute care; moreover, this will facilitate shorter admissions and successful operation within integrated delivery systems.

Psychosomatic Medicine and Consultation-Liaison Psychiatry

Kornfeld[81] has written an elegant review on the impact of C-L psychiatry on medical care in general hospitals. He surveyed, among others, the major contributions of Hackett and Cassem, Frasure-Smith, and Reich in psychocardiology; his own team in helping to understand

why some patients want to sign out against medical advice; Sutherland, Holland, Oken, and Spiegel in psychooncology; Abrams, Denour, Levy, and Viederman in psychonephrology; Robinson in poststroke syndromes; Perry in HIV care; and Musselman on the relationship between interferon and depression. He then recounted the effects of C-L psychiatry on cost-benefit analyses, medical teaching, clinical ethics, end-of-life care, and clinical genetics. He concluded that psychosomatic medicine through C-L psychiatry has substantially influenced medical practice for the better, and he predicted that the field will flourish especially as medicine becomes increasingly technological. Indeed, formal added qualifications in the subspecialty field of psychosomatic medicine are now available from the American Board of Medical Specialties and fellowship programs in psychosomatic medicine are now accredited by the Accreditation Council for Graduate Medical Education, signifying the maturation of this subspecialty.

Here at MGH, advances in the psychopharmacology of medical psychiatry patients are worth noting. The use of intravenous (IV) haloperidol for agitated delirium, the use of methylphenidate for depression in medically ill patients, and the first-line use of IV lorazepam for catatonic states were pioneered and then advocated by MGH consulting psychiatrists; these have become part of standard medical practice.[82–84]

Alert and well-trained consulting psychiatrists will continue to make key contributions to our understanding of pathophysiology and therapeutics. More and more will be learned from clinical experience and from research about how the visceral paralimbic and limbic brain influences human disease processes, and vice versa. Take the functional gastrointestinal disorders, for example. Up to 50% of all patients who present with gastrointestinal complaints have no known pathophysiologic basis for their complaints or have complaints that are out of proportion to their physiologic abnormalities.[85] In the future, the intricate interrelationship between the intrinsic enteric nervous system of the gut and the extrinsic peripheral and central nervous systems will be better understood, thereby improving our ability to manage these painful and costly disorders. Consulting psychiatrists have the skill set and knowledge of both the brain and the body to make major contributions in this effort.

In an environment of cost-cutting in the general hospital, consulting psychiatrists also play important roles on multidisciplinary teams, identifying and taking care of the medical inpatients with the highest utilization, specifically, those who commonly have psychiatric co-morbidity.[86] The drive toward shorter hospital stays has propelled research into ways of identifying high-utilizers of medical and psychiatric care at the time of admission and of minimizing their impact on the health care system.[87–92] Using screening instruments and red flags at the time of admission (e.g., based on physician and nurse predictions, disease or treatment type, frequency of doctor visits, number of medications, noncompliance, mobility, frailty, negative health behaviors, and biopsychosocial stressors, among others), multidisciplinary teams can identify high-utilizers early in their hospital stay and provide them with complex care coordination and case management in an effort to improve their quality of care and to prevent obstacles to discharge (such as lack of a safe home, lack of family or social support, lack of insurance, and dementia and need for guardianship, among others).

Characteristically, the high-utilizers tend to have multiple chronic medical and psychiatric co-morbidities and are best served by integrated interdisciplinary care. Here at MGH, a multidisciplinary medical team called *Team 5* has been established with full-time medical, C-L psychiatry, and case management staff specialized in treating medical inpatients at risk for long LOS (defined as longer than 20 days, compared to the hospital's average LOS of less than 6 days). Team 5 admits medical inpatients (directly and as transfers from other inpatient teams) at risk for long LOS, identified by a number of characteristics, including psychosocial stressors, substance abuse, and previous failed discharge plans, among others similar to those described earlier.[93] In 2007, Team 5 discharged more than one third of the high-utilizers before day 20 and allowed 200 additional inpatient medical admissions during the fiscal year.

Outpatient Psychosomatic Medicine and Consultation–Liaison Psychiatry

As general hospitals shorten medical admissions and shift more care to observation, nonacute settings, and ambulatory settings, traditional inpatient C-L activities will need to shift as well. In many cases, this will require locating these services within PCP groups.

Approximately 6% of all patients receive psychiatric services within the general medical sector. In addition, other patients who present for medical care have undiagnosed or undertreated psychiatric or substance-abuse disorders. In situations in which PCPs are financially at risk for all medical services, the ability of outpatient C-L psychiatrists to offset unneeded medical utilization will be important in reducing the cost of care and improving outcome.

The co-location of psychiatrists who are able to provide immediate consultation to PCPs in a variety of non-inpatient settings, while caring for patients in the specialty care sector, will be important for the further development of medical psychiatry. Medical psychiatrists are also performing teleconsultations (i.e., telepsychiatry) and using computer-based systems to provide immediate consultations to a larger network of PCPs and their patients at risk.

Telepsychiatry permits psychiatrists with specialized knowledge to reach previously underserved populations, especially in geographic areas lacking available psychiatric care, and has been shown to be as effective as in-person sessions for psychiatric and psychosomatic consultation, as well as to assess and treat conditions ranging from depression and obsessive–compulsive disorder to schizophrenia.[94–100] Patients enrolled in studies of telepsychiatry have reported equal satisfaction with in-person treatments. Teleconsultation services allow PCPs to consult with psychiatrists in real time, while their patients are still in their office.

In Massachusetts, for example, pediatricians can access child psychiatry consultation services through the state-funded Massachusetts Child Psychiatry Access Project (MCPAP).[100] MCPAP provides all pediatricians in the state with timely, cost-free access to child psychiatry consultation and can assist with transitioning to ongoing behavioral health care. Composed of teams of child psychiatrists, social

workers, and care coordinators and coordinated through regional hospitals (psychiatric departments) including ours, MCPAP can provide live telephone consultation to pediatricians (available via a paging system), referrals to follow-up mental health care, and educational activities for pediatricians. With 96% of pediatricians in Massachusetts enrolled in MCPAP as of June 2008, this service has helped meet the psychiatric needs of children and adolescents across the state.

PSYCHIATRIC NEUROSCIENCE

Looking forward to the future of psychiatry, in the best tradition of the medical model, pathophysiology-based diagnostic entities will be ascertained through history and examination, as well as more direct tests of brain structure and function (e.g., neuroimaging tests) and by probes of genotype. Thus, the diagnostic process and classification system in psychiatry will inevitably evolve in tandem, incorporating contemporary advances in psychiatric neuroscience.[101]

The emergence of contemporary neuroimaging techniques has provided a new class of information, allowing characterization of regional brain activity or chemistry in time and in three dimensions of space.[102] Investigators have come to realize that psychiatric diseases are not simply reducible to a three-dimensional map of generic regional brain dysfunction. Rather, neuroimaging will help to characterize pathophysiology in terms of dysfunctional distributed networks and provide for multidimensional assessments of computational deficits at any given locus.

Psychiatric neuroscience in the 21st century will continue to rely heavily on neurotransmitter pharmacology, as well as on the newly found power of neuroimaging methods, to establish phenotypes at the level of the brain. This will accompany a progressive focus on molecular biology, which is necessary to understand the genetic and epigenetic bases of resiliencies and selected vulnerabilities, as well as the presynaptic and postsynaptic and second-messenger processes that mediate neural health and dysfunction.

Implications for Psychiatric Treatment in the General Hospital

Developing valid and reliable predictors of treatment response will enhance treatment efficacy. If such predictors can be gleaned from easily accessible clinical information (e.g., age, gender, and constellation of symptoms), this would be most cost-effective. However, it may be that the most powerful predictors of treatment response will be ascertained via more fine-grained probes of brain function, such as those obtained via neuroimaging or pharmacogenomic laboratory testing. Already, brain-imaging studies have produced preliminary findings that suggest that particular brain activity profiles predict antidepressant and anti-obsessional responses to medication.[103–104] Such predictors of treatment response will be most important in the context of candidate treatments that are of long duration, high cost, or great risk (e.g., anti-obsessional medication trials, electroconvulsive therapy [ECT], or neurosurgical treatment).[105] Reliable predictors of bad outcomes can be just as valuable as reliable predictors of treatment success. Pharmacogenomic blood tests, for example, may soon offer the possibility of predicting adverse reactions (such as agranulocytosis from clozapine or metabolic syndrome from antipsychotics) before treatment is initiated.[106]

New Concepts in Somatic Therapies

As we discover the core pathophysiology of particular diseases, optimal therapies might include a capacity to direct medications to specific cell types or brain regions. It is difficult to know whether or not transplantation methods will evolve into useful interventions for psychiatric conditions. To date, this strategy has been adopted as a means to compensate for gross degeneration, such as in Parkinson's disease.[107]

Advances in psychiatric neurosurgical treatments have accelerated over the past decade. Vastly different from the crude free-hand lobotomies of the mid-20th century, much-refined stereotactic procedures have emerged in the last 25 years, culminating in noninvasive ablative radiosurgical applications using the gamma knife.[108] Developed initially for the treatment of epilepsy, vagus nerve stimulation (VNS) received approval from the U.S. Food and Drug Administration (FDA) in 2005 as an adjunctive treatment for treatment-resistant depression in patients who have failed multiple trials of antidepressant medication.[109] Deep brain stimulation methods have been adapted for use in psychiatric conditions, receiving FDA approval for treating severe, intractable cases of obsessive-compulsive disorder (OCD) in 2009. Paralleling advances in surgical treatment for Parkinson's disease, deep brain stimulation promises the potential for adjustable and reversible means of modulating brain function and hence ameliorating psychiatric symptoms, including depression and cognitive impairment, among others.[110]

Over the next decade, the promise of transcranial magnetic stimulation as an alternative to ECT for treatment-resistant depression will continue to be rigorously tested.[111–113] In 2008, the FDA passed the first approval of a transcranial magnetic stimulation device for treatment-resistant depression in patients who had failed one trial of antidepressant medication. Although it is appealing to propose that localized, noninvasive brain stimulation could provide advantages in terms of efficacy and adverse effects (compared to ECT), this remains a source of uncertainty, debate, and research. Certainly, advances in our understanding of pathophysiology will help guide the study of this potential treatment modality.

BUILDING INTEGRATED DELIVERY SYSTEMS

It will become progressively more important that occupation of general hospital psychiatric beds be increasingly focused on cases that require highly integrated medical and psychiatric care, because these units carry inherently higher direct and indirect costs, which are often poorly compensated by current public and private payers. Given that the general hospital sector admits the largest number of acute psychiatric patients, it will be important to evolve a care system that can link such units across regions to free-standing psychiatric hospitals for patients who require

inpatient care but are without such complex clinical needs. This will be essential as a matter of cost efficiency given the lower costs of freestanding hospitals. Due to the unique demands for consultation and emergency services in general hospitals, as well as the close linkage to other physicians, cost and reimbursement systems supporting the entire system of care will be critical. Free-standing psychiatric hospitals should become progressively better positioned to offer efficient, high-quality specialty psychiatric services by virtue of greater numbers of beds that can be specialized. Further, care within modern free-standing psychiatric hospitals must evolve to incorporate the best practices and influences of medical psychiatry, including the direct provision of some general and specialty medical services, and to become progressively evidence-based in their treatment models.[27] This would help address one of the major reasons for the shift to general hospital psychiatry units, namely that psychiatry, as practiced in free-standing facilities, had distanced itself from the rest of medicine in the 19th and for most of the 20th centuries.

Managed care organizations (MCOs) are able to lower costs in part by controlling where the large number of patients they insure will receive care. In an environment in which the supply of hospital services (e.g., inpatient beds) is high and the demand for services is dropping (as in managed care), prices for care (e.g., hospital *per diems*) decline. In response to this concentration of buying power by payers, providers have formed integrated delivery systems.

The growth of integrated delivery systems allows the creation of a balance between the payers and providers. Also, integrated delivery systems allow the management of care to be returned to providers. Many integrated delivery systems organize around PCP groups or physician–hospital organizations. Such integrated delivery systems often place PCPs at financial risk (in a gatekeeper role) and discourage excessive care by specialists and hospitals.

How does medical psychiatry fare within these integrated delivery systems? In large measure, it depends on the available conditions in given localities. In some areas, separate psychiatric or behavioral health integrated delivery systems may be strong. If these are also areas where carve-out models of care are prominent among payers, the task facing medical psychiatrists may be more complex and difficult. Psychiatrists in these circumstances might need to fight a two-front war—building relationships with primary care while competing for carve-out contracts and internally reintegrating care. Given that a significant percentage of all primary care visits are psychiatric, psychiatrists need to be actively involved in creating integrated delivery systems and in educating payers, PCPs, and others about the suboptimal nature of disaggregated care. The development of medical or mental health homes, as discussed earlier, may be one future solution to fragmentation of care, but only if payment systems become more flexible and the full impact of psychiatric illness on medical costs is well understood.

MEDICAL PSYCHIATRY IN A MANAGED ENVIRONMENT

Medical psychiatrists have to struggle with a variety of tensions regarding how to provide effective care in the context of managed care.

As discussed earlier, medical–psychiatry units are under intense pressure to reduce hospital LOS. Often, clinicians must explain to cost-conscious reviewers why their patients who have recently been suicidal require continued hospitalization or why their elderly patients cannot safely receive the rest of their ECT on an ambulatory basis. MCOs, operating within a carve-out model (and thus eager to shift costs) might ask why they should pay for the care of a patient with post-stroke depression. When conflicts arise with reviewers, physicians should request a formal review by a physician who is board certified in psychiatry. Such physicians often have greater latitude in allowing extended stays for patients with complex medical–psychiatric illness. In other situations, patients might fall under a catastrophic case definition, which might allow greater flexibility of care.

National managed care benchmarks for average LOS or for days of inpatient care per 1000 covered members can reflect distinctly different psychiatric populations. It is important for clinical and administrative leadership in general hospitals to be aware of this population variability before agreeing to contract benchmarks or payments that can compromise patient care.

The efficacy of a medical–psychiatry service that operates in a carve-out environment requires careful education of payers, administrators, clinical leadership, and the general physician community. Because psychiatric illness is common in the primary care setting and because effective care requires the availability of psychiatric services, the lower cost of a mental health carve-out may be both short-lived and illusory, especially in a capitated environment. Unless these groups are aware of the impact of carve-out models, they will not be able to prevent the exclusion of psychiatrists from contracts or the erosion of clinical standards.

INTERNATIONAL MOVEMENT TOWARD PSYCHOSOMATIC MEDICINE

Most of the discussion has centered on the development of and challenges facing medical psychiatry (and general hospital psychiatry) in American psychiatric practice. In the 21st century, the economic pressures faced by psychiatry have worldwide significance in a global marketplace where historical and geographical divisions between countries grow increasingly irrelevant; however, each country's response to the pressures varies based on the systems of health care delivery in place, such as a traditionally employer-based insurance system in the United States versus a government-funded national health plan in the United Kingdom.

In spite of such differences, the international community has supported movements toward improving mental health care, particularly with efforts toward removing the stigma of mental illness, strengthening the human rights of persons with mental illness, acknowledging the worldwide burden of mental illness, and highlighting the inseparable relationship between psychiatric and medical illness. In a series of articles in *The Lancet*, representatives of the Lancet Global Mental Health Group called for a scaling up of evidence-based care for mental illness across the globe, especially in low-income and middle-income countries.[114–118] This advocacy followed from World Health Organization

research that identified mental disorders as a substantial contributor to the burden of disease worldwide, accounting for 13.5% of all disability-adjusted life-years (DALYs: the sum of years lived with disability plus years of life lost).

From the perspective of medical psychiatry, the *Lancet* articles highlight the bidirectional intersection between mental and physical illness: Mental and physical disorders are risk factors for and consequences of one another, and their co-morbid occurrence leads to significantly greater decrements in health than from one or more of the conditions alone and to resultant increases in health care costs. For example, Prince and colleagues[115] analyzed the relationships between mental disorders and health conditions (e.g., heart disease, stroke, diabetes, HIV/AIDs, malaria, tuberculosis, and infant mortality), and produced models to predict the public health effects of extending evidence-based treatments of mental illness: Treating 50% of maternal depression in Pakistan might prevent 13,800 cases of infant stunting and save nearly $2 million per year.[115]

No matter the type of health care system in place, the costs of fragmented health care are felt across the globe, including as a substantial barrier to expanding the availability of psychiatric care. As highlighted by the *Lancet* series, medical psychiatrists need to play an essential role in guiding the integration of psychiatric care into primary health care as a means of improving global psychiatric services. Such efforts will require close attention to the deep levels of stigma that surround psychiatric illness, especially in more traditional cultures, and the need to place the care of mental illness on a strong evidence and biomedical basis. Medical psychiatrists are ideally suited to act as trainers, supervisors, researchers, advocates, and leaders for this process.

SUMMARY AND CONCLUSIONS

As we face the future, we can anticipate continuing pressures on general hospital services that will require local, national, and international responses. It is unlikely that pressures to decrease LOS, to admit only sicker patients, or to respond to the competition inherent in managed care will diminish. In some locations, general hospitals may be asked to assume more responsibilities for state hospital care. It is likely that overall economic pressures will require a coherent system of care that might, with local variations, include private psychiatric hospitals, state hospitals, and outpatient and partial hospital functions as well as integration with the general medical care system. General hospital inpatient services might have to offer involuntary locked care or other specialized psychiatric units and emphasize attending physician involvement and daily walk-rounds. Developments in the neurosciences are likely to enhance the role of medical–psychiatry physician leadership.

The decision about how much general hospital psychiatric services should specialize will be affected by the range of psychiatric and medical services available in a particular area. Affiliation agreements between private and general hospital units, as well as the types of general hospital units in a community, will also affect these decisions. As pressures intensify from large managed care contracts to provide extensive integrated systems of care, general hospital psychiatric services may be forced to provide specialty medical–psychiatric or psychiatric services for more severely ill populations. Such networking arrangements could create fiscal risks for the care of patients with combined medical and psychiatric illness because these patients might not be easily discharged into available aftercare resources. When constructing integrated systems, we need to attend to the continuity of care and minimize the number of transitions between providers.

The concept of the general hospital developed in the 19th and early 20th centuries in response to advances in medical science, urbanization, and economic forces that surrounded the practice of medicine.[119] It was not until the early 1930s that a similar movement in psychiatry began, bringing psychiatry into the general hospital. Beginning in the 1930s,[120] general hospital psychiatry was poised for the rapid growth of the post-war years that was to make it the dominant institution in American psychiatry.

The entry of psychiatry into the general hospital meant more than a change of locale. It meant a shift from a "moral" to a medical model of psychiatric illness. It was a shift from methods of investigation and treatment that ran counter to the ethos of the general hospital and academic medicine to methods that were consonant with it. Psychiatry's entry into the general hospital brought it closer to the thinking of medicine, which was transforming illness into a treatable and comprehensible phenomenon.

The period that lies ahead will provide great opportunities for general hospital psychiatry in training, models of clinical care, and medical–psychiatric treatment and research. Advances in neurobiology and psychopharmacology, as well as the broadening clinical population of general hospital psychiatry, will make it the setting in which the most sophisticated and comprehensive psychiatric care can and should take place. In this era of growing efficacy and research, attention to these opportunities and to the pressures outlined herein is crucial for the further development and viability of medical psychiatry, of general hospital psychiatry, and of psychiatry as a whole.

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