CURRENT TREATMENTS OF OBSESSIVE-COMPULSIVE DISORDER

Second Edition

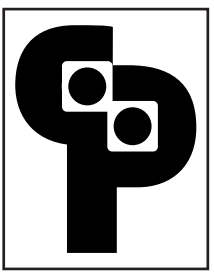
Edited by

Michele Tortora Pato, M.D.
Joseph Zohar, M.D.

CURRENT TREATMENTS OF OBSESSIVE-COMPULSIVE DISORDER

Second Edition

CLINICAL



PRACTICE

Judith H. Gold, M.D., F.R.C.P.C.
Elissa P. Benedek, M.D.
Series Editors

CURRENT TREATMENTS OF OBSESSIVE-COMPULSIVE DISORDER

Second Edition

Edited by

Michele Tortora Pato, M.D.

Joseph Zohar, M.D.

American Psychiatric Publishing, Inc.

Washington, DC
London, England

Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or the care of a member of their family.

Books published by American Psychiatric Publishing, Inc., represent the views and opinions of the individual authors and do not necessarily represent the policies and opinions of APPI or the American Psychiatric Association.

Manufactured in the United States of America on acid-free paper

04 03 02 01 4 3 2 1
Second Edition

American Psychiatric Publishing, Inc.
1400 K Street, N.W.
Washington, DC 20005
www.appi.org

Library of Congress Cataloging-in-Publication Data
Current treatments of obsessive-compulsive disorder / edited by Michele Tortora Pato, Joseph Zohar.-- 2nd ed.
p. ; cm. -- (Clinical practice ; no. 51)
Includes bibliographical references and index.
ISBN 0-88048-779-8 (alk. paper)
1. Obsessive-compulsive disorder--Treatment. I. Pato, Michele Tortora, 1956– II. Zohar, Joseph. III. Series.
[DNLM: 1. Obsessive-Compulsive Disorder--therapy. WM 176 C976 2001]
RC533 .C87 2001
616.85'22706--dc21

00-053119

British Library Cataloguing in Publication Data
A CIP record is available from the British Library.

Contents

Contributors

Andrea Allen, Ph.D.
Assistant Professor of Psychology, Department of Psychiatry, Mount Sinai School of Medicine, New York, New York

Wayne K. Goodman, M.D.
Professor and Chairman, Department of Psychiatry, University of Florida, Gainesville, Florida

David Greenberg, M.D.
Director, Jerusalem Mental Health Center, Hadassah Medical School, Jerusalem, Israel

Eric Hollander, M.D.
Professor; Director of Clinical Psychopharmacology; Director, Compulsive, Impulsive, and Anxiety Disorders Program; and Clinical Director, Seaver Autism Research Center, Department of Psychiatry, Mount Sinai School of Medicine, New York, New York

Henrietta L. Leonard, M.D.
Professor, Department of Psychiatry and Human Behavior, Brown University School of Medicine; and Director of Training, Child and Adolescent Psychiatry and Combined Pediatrics/Psychiatry/Child Psychiatry Residency Training Programs, Rhode Island Hospital, Providence, Rhode Island

Michele Tortora Pato, M.D.
Associate Professor, Department of Psychiatry; Director, OCD Research and Treatment Program, State University of New York at Buffalo, Buffalo, New York

Joseph V. Penn, M.D.
Clinical Assistant Professor, Department of Psychiatry and Human Behavior, Division of Child and Adolescent Psychiatry, Brown University School of Medicine; and Director, Department of Child and Adolescent Forensic Psychiatry, Rhode Island Hospital, Providence, Rhode Island

Teresa A. Pigott, M.D.
Vice President, Medical Affairs, and Executive Director, Clinical Trials Division, Comprehensive Neuroscience, Inc., Chevy Chase, Maryland

Lawrence H. Price, M.D.
Professor, Department of Psychiatry and Human Behavior, Brown University School of Medicine; and Director of Research and Clinical Director, Butler Hospital, Providence, Rhode Island

Margaret A. Richter, M.D.
Staff Psychiatrist, Anxiety Disorders Clinic, Centre for Addiction and Mental Health; and Assistant Professor, Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Kim M. Schindler, Ph.D.
Research Assistant, Laboratory of Psychiatric and Molecular Genetics, State University of New York at Buffalo, Buffalo, New York

Sheila Seay, M.A.
Research Assistant, University Psychiatric Center, Houston, Texas

Soraya Seedat, M.B.
Medical Research Council Unit on Anxiety Disorders, University of Stellenbosch, Cape Town, South Africa

Nathan Andrew Shapira, M.D., Ph.D.
Assistant Professor, Department of Psychiatry, University of Florida, Gainesville, Florida

Dan J. Stein, M.B.
Research Associate Professor, Department of Psychiatry, University of Florida, Gainesville, Florida; and Medical Research Council Unit on Anxiety Disorders, Department of Psychiatry, University of Stellenbosch, Cape Town, South Africa

Gail Steketee, Ph.D.
Professor and Chair of Clinical Practice, Boston University School of Social Work, Boston, Massachusetts

Barbara L. Van Noppen, M.S.W.
Doctoral Candidate, Simmons College School of Social Work, Boston, Massachusetts; Research Associate, Department of Psychiatry and Human Behavior, Brown University; and Angell Street Wellness Collaborative, Providence, Rhode Island

Eliezer Witztum, M.D.
Associate Professor, Division of Psychiatry, Beer-Sheva Mental Health Center, Ben Gurion University of the Negev, Beer-Sheva, Israel

José A. Yaryura-Tobias, M.D.
Professor, Department of Psychiatry, New York University, New York, New York; Professor of Psychiatry (invited), Department of Psychiatry, Universidad del Salvador School of Medicine, Buenos Aires, Argentina; and Medical Director, Department of Research, Bio-Behavioral Institute, Great Neck, New York

Joseph Zohar, M.D.
Director, Department of Psychiatry, Sheba Medical Center, Tel Hashomer, Israel; and Associate Professor, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

This page intentionally left blank

Preface to the Second Edition

It has been more than 10 years since the first medication for obsessive-compulsive disorder (OCD), clomipramine, received U.S. Food and Drug Administration approval and since the first edition of this book was published. It seems an appropriate time to stop and summarize the data that have accumulated regarding current treatment approaches to OCD. Progress in neuroscience has had direct and immediate clinical implications not only in the pharmacologic arena but also in the psychologic arena. This second edition reflects this progress in many ways. Instead of three chapters devoted to phamacotherapy (clomipramine, fluoxetine, and fluvoxamine), there are now six (sertraline, paroxetine, and citalopram have been added). Chapter 8, on the diagnosis and treatment of OCD in children and adolescents, has been expanded to include the newest findings in immunology, namely pediatric autoimmune neurologic disorders associated with streptococcal infection (PANDAS). The behavioral therapy chapter (Chapter 9) now includes not only detailed treatment schedules for both individual and group treatments but also up-to-date empirical data to support their use. Finally, all of the chapters have been updated to include the most current data on the use of these treatments in special populations such as the elderly, children and adolescents, and pregnant women.

We still feel that the best way to understand and treat OCD is through the clinical examples provided by our patients, and our intention is for this book to be a practical but comprehensive "how-to" manual for treating OCD. Thus, this second edition—as was true in the first—maintains a strong emphasis on describing OCD by sharing the stories of patients whom we have treated. The case histories presented in each chapter have been carefully selected to highlight specific treatments and diagnostic issues involved in treatment. Several of these case histories are new, and others have been reproduced or updated from the first edition. The authors of these chapters have extensive clinical and research experience in treating OCD.

Not only has the number of compounds now available for treatment

of OCD doubled, but knowledge of the pharmacokinetics, receptor profiles, interactions, and comparative efficacy has also greatly increased. Thus, in this edition we hope to provide the clinician with the most current available data to better match treatment approaches with the patient's unique needs.

In the area of psychology, a vast amount of clinical experience and some research in behavioral and cognitive therapy have accumulated. As a reflection of the changes in our health economy, the use of more economic and probably even more effective strategies such as group therapy or multifamily therapy have been implemented; these strategies are described in Chapter 9.

Increased public awareness of OCD has in turn raised expectations for its treatment. Patients expect to be cured; however, about 30% of patients do not respond or respond only partially to treatment. We often must combine all of our current knowledge and focus it on the treatment of one individual, and the chapter on treatment resistance (Chapter 12) addresses this challenge in a multidisciplinary way.

Reaffirmation of the OCD diagnosis is the first step when managing treatment-resistant cases. In addition to raising treatment expectations, increased awareness of OCD has raised its profile, and we have started to expand the boundaries of the disorder to include a spectrum of other disorders, such as body dysmorphic disorder, trichotillomania, pathologic gambling, and Tourette's syndrome. The clinical implications of this new, broader definition are discussed in Chapter 11. Recognition that obsessive-compulsive symptoms can present in different disorders has led to an intriguing finding in schizophrenia. The prevalence of OCD among schizophrenic patients is approximately 15%; these patients require innovative treatment approaches such as those discussed briefly in Chapter 1. The intimate relationship between OCD and schizophrenia also raises intriguing questions about the relationship between obsession, delusions, religiosity, and OCD. These complicated diagnostic and management issues are discussed in Chapter 10.

Because early detection of OCD may help minimize its devastating effects, a considerable effort has been made to identify and treat childhood OCD. Moreover, meticulous research has opened the door to a new entity, PANDAS, that bridges immunologic, neurologic, and psychiatric boundaries. All of these issues are discussed in Chapter 8.

Editing and updating of this kind of book requires significant attention and effort. We would like to thank our contributors for their scholarly chapters as well as our patients for all that we have learned from them and for pushing us to better understand this fascinating but frustrating disor-

der. Our pursuits in this field have only been possible with the continuous support and understanding of our families. Our love and thanks go to our spouses, Carlos Pato and Rachel Zohar-Kadouch, and our children, Michael and Eric Pato and Karmit, Zeev, and Mishael Zohar.

Michele Tortora Pato, M.D.
Joseph Zohar, M.D.

This page intentionally left blank

CHAPTER 1

General Considerations in Diagnosis and Treatment

Michele Tortora Pato, M.D.
Joseph Zohar, M.D.

The past 15 years have seen a threefold increase in publications about obsessive-compulsive disorder (OCD), which reflects the growing interest in this disorder. Currently, research ranges across a spectrum of approaches such as brain imaging, genetics, epidemiology, immunology, neuropsychology, and treatment interventions including biologic and behavioral modalities. Each area represents an important piece in the complex jigsaw puzzle of OCD (see Sasson and Zohar 1996 for a review).

Epidemiologic studies during the 1980s found a prevalence of 2%–3% for OCD in five communities in the United States. This finding indicated that OCD was not a rare disorder—the prevailing perception at the time—but was, in fact, more prevalent than schizophrenia (Karno et al. 1988; Robins et al. 1984). Since this seminal work, other studies within general population samples have established a rather consistent worldwide prevalence of OCD. For example, the cross-national collaborative study that surveyed community samples in Canada, the United Kingdom, Puerto Rico, Germany, Taiwan, Korea, and the Netherlands suggested a prevalence of 1.9%–2.5% (Weissman et al. 1994), although later reports by Nelson and Rice (1997) and Stein et al. (1997) reexamined the epidemiologic data and proposed lower prevalence rates of 1%–2%. Epidemiologic research focused on children and adolescents reported prevalence ranges of 2%–3.6% (Flament et al. 1988; Zohar et al. 1992), and the same range was

found among a cohort of older adults (age greater than 65 years) in the United Kingdom and Spain (Saz et al. 1995). Based on this figure, the number of patients with OCD worldwide is estimated to be 50 million, making OCD a global problem (see Sasson et al. 1997a for a review).

In this chapter, we provide the therapist with an overview of OCD symptom clusters, differential diagnoses, clinical courses, and general treatment guidelines that we believe to be essential before specific treatments can be considered.

The diagnostic criteria for OCD on Axis I of DSM-IV-TR (American Psychiatric Association 2000), the new text revision of DSM-IV (American Psychiatric Association 1994), include the presence of recurrent, persistent, and unwanted thoughts, impulses, or images (obsessions) and/or the performance of repetitive, often seemingly purposeful, ritualistic behaviors (compulsions) (Table 1–1). These obsessions and compulsions are often ego-dystonic, are often resisted by the patient at some point in the illness, and interfere with patients' daily function—characteristics that are clinically important in differentiating OCD from other diagnoses such as obsessive-compulsive personality disorder, schizophrenia, and phobic disorders.

Despite these straightforward criteria, in actual clinical practice the diagnosis of OCD is not always easy or obvious. For example, Rasmussen (1985) noted that patients often were referred to dermatologists for treatment of dermatitis caused by excessive hand washing, but these patients were not referred for psychiatric evaluation for this symptom. In addition, many patients do not seek psychiatric care for specific complaints of obsessive-compulsive symptoms but rather for complaints of depression, phobic disorders, and panic disorder, all of which can occur concurrently with OCD (Goodwin et al. 1969; Jenike et al. 1986; Mellman and Uhde 1987).

Increased awareness and better treatment of OCD has not reduced the lag time for patients seeking treatment, which is reported to be 7 years both in recent studies (Hollander et al. 1997; Rasmussen and Tsuang 1986) and in studies dating back to 1957 (Pollitt 1957). It may be postulated that this lag reflects the severe embarrassment and consequent secretiveness that many patients with OCD experience in relation to their symptoms.

In a study of discharge diagnoses, an increased incidence of OCD but not other psychiatric disorders (e.g., paranoid disorder) was observed (Stoll et al. 1992). This increase was associated with an increasing number of publications on the treatment of OCD, which suggests a positive sequence of increased interest, more clinical research, better treatment, and increased diagnosis.

Table 1–1. Diagnostic criteria for 300.3 Obsessive-Compulsive Disorder

A. Either obsessions or compulsions:
   Obsessions as defined by (1), (2), (3), and (4):
   (1) recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
   (2) the thoughts, impulses, or images are not simply excessive worries about real-life problems
   (3) the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
   (4) the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)
   Compulsions as defined by (1) and (2):
   (1) repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
   (2) the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable.

Note: This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Specify if:

With Poor Insight: if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable

Source. American Psychiatric Association 2000, pp. 462–463.

Symptom Clusters

Although initially the diversity of the clinical presentations of OCD is striking, it become evident over time that the number and types of obsessions and compulsions are limited and stereotypical (Rasmussen and Tsuang 1986). Patients with OCD are often relieved when they learn that other patients engage in the same behaviors. Furthermore, cross-cultural analysis of OCD symptoms reveals that the content of obsessions and compulsions is relatively similar across geographic locations (see Sasson et al. 1997a for review).

Many subclassifications of OCD symptoms have been proposed. One possible approach is to cluster OCD into four groups based on the factor analysis by Leckman et al. (1997) and Summerfeldt et al. (1999). These proposed clusters are presented in Table 1–2.

Table 1–2. Four clusters of obsessive-compulsive symptoms

Obsessions	Compulsions
1) Contamination	Cleaning
2) Aggressive, sexual, religious, somatic	Checking
3) Symmetry	Ordering and arranging, counting, repeating rituals
4) Hoarding	Hoarding and collecting

Source. Adapted from Leckman et al. 1997.

Cleaning

Patients who are obsessed with dirt, contamination, germs, or bugs may spend several hours each day washing their hands, showering, or cleaning. Typically, they try to avoid sources of "contamination" such as door knobs, electric switches, and newspapers. Paradoxically, some of these patients are quite slovenly (see, for instance, the description of Howard Hughes [Bartlett and Steele 1979]). Although these patients are cognizant that nothing will happen if they resist washing, they may refuse to touch even their own bodies, knowing that if they do, they will not be at ease until they execute extensive washing rituals.

Checking

Patients in the "checking" symptom cluster are obsessed with doubt, usually tinged with guilt. Frequently, they are concerned that if they do not check something carefully enough they will hurt others. However, rather

than resolving uncertainty, their checking often contributes to even greater doubt, which leads to further checking. "Checkers" often enlist the help of family and friends, seeking reassurance that they have checked enough or correctly. Ultimately, by some inscrutable means, the patient resolves a particular doubt only to have it replaced by another. Resistance, which in this case is the attempt to refrain from checking, leads to difficulty in concentrating and to exhaustion from the never-ending assault of nagging uncertainties.

Common examples of these concerns and doubts are related to fundamental life themes such as aggression, sex, religion, and health. When the obsession is an aggressive impulse, it is most often directed at the person most valuable to the patient. In addition, the obsession might be a fear that the patient will act on other impulses (e.g., to kill somebody, rob a bank, steal) or that he or she will be held responsible for something terrible (e.g., fire, plague). For example, a fear of hurting somebody while driving may lead a patient to drive back and forth over the same spot for hours after hitting a bump in the road. These checking rituals may be combined with avoidance and may expand over time. In one such case, a mother who was afraid that she would stab her daughter struggled with this impulse by avoiding sharp objects and then by avoiding touching her daughter until she ultimately left the house altogether. Occasionally, checkers are not even certain why they are checking, expressing a vague feeling that they "just have the urge to do it until it feels right."

Sexual obsessions include forbidden or perverse sexual thoughts, images, or impulses that might involve children, animals, incest, and homosexuality. Patients with aggressive and sexual obsessions might not reveal them, even if asked directly, because they fear being "locked up." Clinicians should make a special effort to create an atmosphere that enables patients to disclose these types of obsessions. One approach is for clinicians to explicitly mention these types of obsessions as ones already heard many times and to reassure patients that these obsessions are part of OCD.

Obsessional thoughts can often carry a religious rather than a sexual or violent theme. These thoughts might lead to repetitive silent prayer or confession or may result in more obvious rituals such as repeated bowing or never-ending trips to church to make confessions. Such behavior presents a particular problem to both clinicians and clergy as they try to draw the line between disorder and devotion (see Chapter 10). At times, obsessive thoughts may take on a more nondescript quality. Examples include a need to know or remember what was eaten for breakfast, a need to say or not say a particular word or phrase, or a need to keep a certain musical phrase in one's head.

Symmetry

Obsessions about symmetry are dominated by a need to have things "just right"—rearranging and repeating rituals—as well as a need to have objects or events in a certain order or position, to do and undo certain motor actions in an exact form, or to have things "evened out." These patients may take an inordinate amount of time to complete even the simplest of tasks because they are obsessed with completing their routine precisely. This need for precision and accuracy becomes a major source of interference with daily functioning. In the past we called this behavior *obsessional slowness*, but now we tend to include it within the symmetry cluster.

Another maladaptive feature of symmetry is the elaborate compulsion to count; for example, these patients may repeat actions, thoughts, or words a certain number of times or may be compelled to add up license plate numbers or digital clock displays.

Hoarding

Hoarding behavior is characterized by the patient's refusal to throw out junk mail, old newspapers, or even used tissues because he or she is in doubt about throwing away something important in the process. It seems that these patients are more treatment resistant, both psychopharmacologically and behaviorally (Black et al. 1997).

Differential Diagnosis

Obsessive-Compulsive Personality Disorder

There may be some similarities between the diagnosis of OCD (an Axis I disorder in DSM-IV-TR) and that of obsessive-compulsive personality disorder (OCPD) (an Axis II disorder in DSM-IV-TR). Both disorders reveal a preoccupation with aggression and control and both use the defenses of reaction formation, undoing, intellectualization, denial, and isolation of affect. Because psychoanalytic formulation suggests that OCD develops when these defenses fail to contain the obsessional anxiety, OCD is often considered to be on a continuum with OCPD pathology (Salzman and Thaler 1981). Epidemiologic evidence, however, reveals that a concurrent diagnosis of OCPD is not necessary for an OCD diagnosis on Axis I (Black et al. 1988; Lo 1967; Rasmussen and Tsuang 1986). In one study, only 6% of 96 patients with OCD met the criteria for OCPD on the Structured Clinical Interview for DSM-III-R for Personality Disorders (SCID-P; Baer et al. 1990). Keeping in mind that the symptoms of OCD are ego-dystonic,

whereas compulsive character traits are ego-syntonic and rarely provoke resistance, can help lessen diagnostic confusion. When it is difficult to differentiate between Axis I and Axis II disorders, a trial of pharmacologic or behavioral treatment may be warranted (if the patient is willing) to test whether any of the obsessions or compulsions improve. At least one study bears out this recommendation and questions the very nature of the personality disorder diagnosis in patients with OCD on Axis I. Riccardi et al. (1992) treated 17 patients who met criteria for OCD and a personality disorder. Among the 10 patients who responded to treatment, 9 no longer met criteria for a personality disorder.

Other Anxiety Disorders

Although OCD is classified as an anxiety disorder in DSM-IV-TR, it appears to be somewhat different from other anxiety disorders in several key characteristics: 1) The age of onset for OCD is young compared with that for patients with panic disorder. 2) In OCD, there is an equal distribution of men and women, whereas in other anxiety disorders women are more common. 3) Patients with OCD do not develop increased symptoms after administration of anxiogenic compounds such as lactate, yohimbine, and caffeine, whereas patients with agoraphobia do (Zohar et al. 1990). Patients with OCD are also refractory to anxiolytic medications such as benzodiazepines. Moreover, OCD is refractory to tricyclic antidepressants (TCAs) (with the exception of clomipramine), medications that are typically found to be effective in anxiety and panic disorder, as well as in major depression. 4) Making a diagnosis of OCD can help clinicians avoid the use of nonserotonergic medications that will likely be ineffective.

It is not surprising, then, that in the International Classification of Diseases (ICD)-10, OCD is classified as a stand-alone disorder and not part of the anxiety disorders.

Certain patients with OCD may resemble individuals with simple or social phobias. Patients with obsessions about contamination may even describe their problem as a "germ phobia." Although the distinction may be difficult to make in individual cases, many times the patient's fear involves harm to others rather than harm to him- or herself. When phobic, patients with OCD are usually afraid of a stimulus that is usually unavoidable, such as a virus, germs, or dirt, as opposed to classic phobic objects such as tunnels, bridges, or crowds.

Depression

Depression is the most common complication of OCD (Goodwin et al. 1969; Rapoport 1989). By recognizing this relationship between OCD and

depression, DSM-IV-TR does not exclude a diagnosis of OCD if depression is present but stipulates that the obsession not be related in content to the guilt-ridden rumination of major depression. However, a precise definition of the relationship between OCD and depression remains elusive. At the clinical level, the illnesses often seem inseparable—one worsening or improving in synchrony with the other as illustrated by numerous clinical trials in which both OCD and depressive symptoms improved during the course of treatment. However, in other clinical cases, OCD symptoms may remain in remission while depression recurs (Pato et al. 1988). Researchers have reported some similarities in the biologic markers for depression and OCD, but differences have also been noted (for review see Weizman et al. 1991).

What seems most clinically relevant is that only those antidepressant medications with serotonergic properties—i.e., clomipramine (Chapter 2), fluoxetine (Chapter 3), fluvoxamine (Chapter 4), sertraline (Chapter 5), paroxetine (Chapter 6), and citalopram (Chapter 7)—have consistent efficacy in decreasing OCD symptoms. However, many serotonergic and nonserotonergic antidepressants are effective in treating depression.

Psychotic Disorders

Unlike patients with major psychosis, patients with OCD retain some insight about their symptoms. Although in some cases the behavior of these patients may appear extremely bizarre, they recognize their obsessions or compulsions as internal, as opposed to the psychotic "ideas of influence."

Another way to distinguish between obsession and delusion is that patients with OCD try to resist the obsessions. However, in very severe cases of OCD, patients may briefly relinquish this struggle, and at such times the obsession appears to shift from an ego-dystonic obsession to a psychotic delusion. (Insel and Akiskal 1986). DSM-IV-TR has a subtype classification for these patients termed *poor insight*. Although it may be tempting to label such a patient schizophrenic, extremely poor insight may occur in many truly obsessive patients who never develop schizophrenia (analogous to the psychotic features that may accompany major affective illness). In those patients who are classified as having only poor insight and no other psychotic symptoms, the treatment of choice is still an antiobsessional, and there is probably no need to add an antipsychotic (Eisen and Rasmussen 1993; Eisen et al. 1998). In one study (Eisen et al. 1998), patients with poor insight alone were not noted to have a worsened prognosis, but those who actually met criteria for a comorbid psychotic disorder were more resistant to treatment (see Chapter 12).

Schizophrenia

Some patients with schizophrenia also have obsessive-compulsive symptoms or meet criteria for OCD. Approximately 25% of patients with chronic schizophrenia may also present with obsessive-compulsive symptoms (range 5%–45%) (Dominguez et al. 1999; Zohar et al. 1998). Initial reports from the Epidemiologic Catchment Area study revealed a 12.5% comorbidity between OCD and schizophrenia (Karno 1988; Nelson and Rice 1997). As in OCD, the obsessive-compulsive symptoms in schizophrenic patients will not necessarily surface unless specific questions are asked. Many patients with schizophrenia can distinguish the ego-dystonic obsessive-compulsive symptoms—perceived as coming from within—from ego-syntonic delusions perceived as coming from without. Follow-up studies demonstrate stability over the years, and it seems the comorbidity of OCD and schizophrenia predicts a poor prognosis. Several studies among schizophrenic patients with OCD reported an improvement in OCD symptoms after an antiobsessional medication was added to the ongoing neuroleptic treatment (Sasson et al. 1997b) The role of the new atypical neuroleptics in this subset of schizophrenic patients is not yet clear; however, risperidone and olanzapine have been used with some success as augmenting agents in treatment-resistant OCD (Koran et al. 2000; McDougle et al. 1990, 2000).

Pathologic Gambling and Substance Abuse

Pathologic gambling and substance abuse may superficially resemble OCD because people engage in these activities excessively and with a sense of compulsion. However, in DSM-IV-TR these behaviors are distinguished from true compulsions because, to some degree, they are experienced as pleasurable, whereas compulsions are inherently not pleasurable.

Obsessive-Compulsive Spectrum Disorders

There appears to be a group of disorders that, based on clinical presentation, family history, and treatment response, might be called obsessive-compulsive spectrum disorders (see Chapter 11). These include body dysmorphic disorder, monosymptomatic hypochondriacal delusional disorder, hypochondriasis, trichotillomania, eating disorders, and perhaps bowel obsessions (for case histories see Chapters 8 and 11). If these patients have multiple other obsessions or compulsions, then the diagnosis of OCD is appropriate. However, even if they do not have multiple obsessions or compulsions, some data still indicate that patients with obsessive-

compulsive spectrum disorders respond to the antiobsessional agents used for patients with OCD. Exactly what this implies about the relationship between OCD, serotonin, and obsessive-compulsive spectrum disorders awaits further study. Detailed diagnostic considerations for these patients are discussed in Chapter 11.

General Guidelines for Pharmacotherapy

Before beginning any treatment, whether pharmacologic or behavioral, it is important to get a careful and full assessment of the extent of symptoms. For pharmacotherapy, this assessment helps to establish a good baseline for treatment; for behavior therapy it helps to establish the symptom targets as well as the development of a behavioral hierarchy. Details about the use of the Yale-Brown Symptom Checklist and Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS; Goodman et al. 1989a, 1989b) are provided in Chapter 9. The reliability and validity of the Y-BOCS is well established, and it also exists in a self-administered form; however, we usually recommend that initial assessments be done by a trained rater because patients often have poor insight and significant denial about the extent and severity of their symptoms (Goodman et al. 1989a, 1989b).

OCD is unique in its specificity of pharmacologic response to serotonin reuptake inhibitors. Based on the unique clinical response to serotonergic medication, it has been hypothesized that serotonin dysregulation plays a pivotal role in the pathophysiology of the disorder (Barr et al. 1992; Goodman et al. 1990; Hollander et al. 1992; Zohar and Insel 1987a, 1987b). TCAs such as desipramine, nortriptyline, imipramine, and amitriptyline have proven ineffective for the treatment of OCD (Goodman et al. 1990; Jenike 1992). The specific serotonergic properties of clomipramine over other TCAs have been implicated in its proven efficacy in OCD (Clomipramine Collaborative Study Group 1991).

Currently, six agents have proven efficacy for treating OCD, and these six—clomipramine (Chapter 2), fluoxetine (Chapter 3), fluvoxamine (Chapter 4), sertraline (Chapter 5), paroxetine (Chapter 6), and citalopram (Chapter 7)—are each covered in individual chapters in this volume. Thus, in this chapter we simply highlight some common principles related to the use of these agents as a group (see also March et al. 1997).

According to current knowledge, these agents work primarily by blocking the reuptake of serotonin into the presynaptic nerve terminal, which is believed to be mediated by their effects on the serotonin transport system. Alteration in receptor number and sensitivity occurs as an adaptation to the increase in neurotransmitter availability. Although the mech-

anism of action is not fully understood, it is believed that the therapeutic effect of these agents relates to the eventual downregulation of the postsynaptic receptors (Zohar et al. 1988).

Dosing

The rest of this book discusses the use of individual medications in great detail; however, some general principles and recommendations for administering antiobsessional agents warrant comment here. First, with regard to dosing, most studies have supported the notion that although some response may be noted within 4 weeks, an adequate trial of any medication at an adequate dose usually requires 8–12 weeks. The actual dose of medication may vary. One fixed-dose study with sertraline (Griest et al. 1995) showed efficacy at the lowest recommended dose, whereas two fixed-dose studies with fluoxetine (Tollefson et al. 1994a, 1994b) and paroxetine (Wheadon et al. 1993; Zohar and Judge 1996) suggested that medium to high doses are required. It seems, therefore, that a medium to high dose is more likely to work in patients with OCD and that, in nonresponders or partial responders, the highest recommended dose of medication over a full 8–10-week trial is warranted.

Use During Pregnancy

Use of antiobsessionals in pregnancy has not been adequately or systematically studied. The largest body of anecdotal data exists for fluoxetine, which appears safe for use in pregnancy (Diaz et al. 1997; Goldstein 1995). At present, the only negative data about antiobsessional use in pregnancy come from the use of clomipramine, which causes neonatal seizures, hypothermia, and respiratory acidosis (Ben Musa and Smith 1979; Cowe et al. 1982; Diaz et al. 1997; Schimmell et al. 1991; Zahle Ostergaard and Pedersen 1982) shortly after delivery. This reaction, however, can be circumvented by gradually tapering the dose by approximately 50 mg every 3–4 days beginning 3–4 weeks before the estimated date of confinement. No specific reports have been made of antiobsessional agents appearing in large quantities in breast milk or in the serum of breastfed babies. However, use of antiobsessional medications in the puerperium is still recommended only if the symptoms are affecting the general health of the mother and child (fetus), and doses should be kept at minimal therapeutic levels. Fluoxetine may be a good first choice because more anecdotal data on its safety has been accumulated. Breastfeeding should not necessarily be prohibited for mothers receiving medication; instead, assays of breast milk and neonatal blood may be done periodically to assess whether sig-

nificant levels of medication are being transferred to the baby. In addition, breast feedings could be given when serum levels would be expected to be at their lowest.

Drug Interactions

We caution clinicians against using antiobsessional agents in combination with monoamine oxidase inhibitors (MAOIs), given the serotonergic properties of the antiobsessionals. When discontinuing an antiobsessional, a 2-week washout period is recommended before beginning an MAOI except in the case of fluoxetine, for which a 5-week washout period is necessary because of the agent's long half-life (see Chapter 3).

General prescribing recommendations for these antiobsessional agents must also include an awareness of their effects on the metabolism of other agents via the hepatic cytochrome P450 microsomal enzymes. Table 1–3 indicates the relative potency of these agents in inhibiting various hepatic microsomal enzymes.

Table 1–3. Inhibition of hepatic microsomal enzymes

SSRI	1A2	2C9	2C19	2D6	3A3/4
Citalopram	0/+	0	0/+	0/+	0
Fluvoxamine	+++	++	+++	+	++
Fluoxetine	+	++	+/++	+++	+/++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+/++	+	+

Note. 0=minimal or no inhibition; +=mild; ++=moderate; +++=strong. SSRI=selective serotonin reuptake inhibitor.

Source. Adapted from Preskorn 1997

For example, because paroxetine, sertraline, and fluoxetine all exert some inhibition on the 2D6 isoenzyme system, serum levels of coadministered medications such as TCAs may rise precipitously and unpredictably, which is particularly worrisome if the elevated serum level is in some way toxic. Thus, clinicians should refrain from mixing these agents, particularly fluoxetine and clomipramine, because clomipramine levels can rise greatly and nonlinearly into the cardiotoxic range and lead to serious arrythmias and even death. Because an interaction between the isoenzyme 1A2 and fluvoxamine has potential cardiac toxicity, mixing fluvoxamine with Seldane (terfenadine) or Hismanal (astemizole) is also prohibited.

Serotonin Syndrome

Serotonin syndrome is a rare but serious side effect that may result from excessive availability of serotonin in the synaptic cleft. Coadministration or subsequent administration of MAOIs can lead to this syndrome, the symptoms of which are confusion, slurred speech, diaphoresis, nausea, diarrhea, abdominal cramps, hyperreflexia, myoclonus, insomnia, psychosis, problems with coagulation, and flushing. Treatment involves discontinuing the medication and providing supportive and symptomatic medical care. Failure to treat can lead to serious consequences, including seizure and even death.

Discontinuation/Withdrawal Syndrome

The typical symptoms for withdrawal syndrome are dizziness, tinnitus, and stomach pain that can last up to 2–4 weeks (Lejoyeux and Ades 1997). Treatment usually includes reinstitution of the same medication with a more gradual taper. Sometimes, switching to another antiobsessional will help if side effects or clinical urgency prohibit reinstitution of the original agent. Although some variablity exists among the antiobsessionals in the frequency and severity of their discontinuation side effects, clomipramine and paroxetine are among the most frequent culprits at 30.8% and 20.0%, respectively, and sertraline and fluoxetine are the least frequent at 2.2% and no reported cases, respectively. This low occurrence of withdrawal syndrome with fluoxetine is usually attributed to its extremely long half-life (LeJoyeaux and Ades 1997).

Length of Treatment

Although large discontinuation studies of fluoxetine and sertraline are presently under analysis, to date only a few small systematic trials and anecdotal reports of discontinuation have been made. These studies have shown that relapse is frequent with clomipramine discontinuation and occurs within 4–7 weeks after treatment ends (Flament et al. 1987; Leonard et al. 1991; Pato et al. 1988; Pigott et al. 1990; Thoren et al. 1980). Reports for fluoxetine discontinuation show that relapse also occurs but could take several months (Pato et al. 1991). Thus, the recent recommendations of the 1997 consensus report are that patients who have had an adequate response to an antiobsessional medication should remain on that medication at least 1 year before discontinuation and that chronic treatment may be warranted (March et al. 1997). It is our recommendation, however, that patients should be very gradually tapered off of the medication (approxi-

mately a 25% drop in dose every 2 months), monitored for relapse, and restabilized on an effective dose if relapse occurs during taper. The role of behavioral therapy in modulating relapse is still under study.

Summary

OCD is a common, chronic, and disabling disorder marked by obsessions and/or compulsions that are ego-dystonic and cause marked distress to patients and their families. Despite well-defined criteria, a diagnosis of OCD can be complicated by patient secrecy, confusion with other psychiatric symptoms, and a waxing and waning clinical course. Recent advances in pharmacologic and behavioral treatment for OCD emphasize the clinical importance of making an accurate diagnosis.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision. Washington, DC, American Psychiatric Association, 2000

Baer L, Jenike MA, Riccardi JN, et al: Standarized assessment of personality disorders in obsessive-compulsive disorder. Arch Gen Psychiatry 47:826–830, 1990

Barr L, Goodman W, Price L, et al: The serotonin hypothesis of OCD: implications of pharmacologic challenge studies. J Clin Psychiatry 53:17–28, 1992

Bartlett DL, Steele JB: Empire: The Life, Legend, and Madness of Howard Hughes. New York, Norton, 1979

Ben Musa A, Smith CS: Neonatal effects of maternal clomipramine therapy (case report). Arch Dis Child 54:405, 1979

Black DW, Yates WR, Noyes R, et al: Axis I/Axis II: comorbidity findings. Paper presented at the annual meeting of the American Psychiatric Association, Montreal, Quebec, May 1988

Black DW, Monohan PO, Clancy GP, et al: Hoarding predicts poor response in OCD. Paper presented at the annual meeting of the American Psychiatric Association, San Diego, CA, May 1997

Clomipramine Collaborative Study Group: Clomipramine in the treatment of patients with OCD. Arch Gen Psychiatry 48:730–738, 1991

Cowe L, Lloyd DJ, Dawlings S: Neonatal convulsions caused by withdrawal from maternal clomipramine. BMJ 284:1837–1838, 1982

Diaz SF, Grush LR, Sichel DA, et al: Obsessive-compulsive disorder in pregnancy and the puerperium, in Obsessive-Compulsive Disorder Across the Life Cycle: Section III of American Psychiatric Press Review of Psychiatry, Vol 16. Edited by Pato MT, Steketee G. Washington DC, American Psychiatric Press, 1997, pp 97–112

Dominguez RA, Backman KE, Lugo SC: Demographics, prevalence, and clinical features of the schizo-obsessive subtype of schizophrenia. CNS Spectrums 4:50–56, 1999

Eisen JL, Rasmussen SA: Obsessive-compulsive disorder with psychotic features. J Clin Psychiatry 54:373–379, 1993

Eisen JL, Phillips KA, Baer L, et al: The Brown Assessment of Beliefs Scale: reliability and validity. Am J Psychiatry 155:102–108, 1998

Flament M, Rapaport J, Murphy D, et al: Biochemical changes during clomipramine treatment of childhood OCD. Arch Gen Psychiatry 44:219–225, 1987

Flament MF, Whitaker A, Rapaport JL, et al: Obsessive-compulsive disorder in adolescence: an epidemiological study. J Am Acad Child Adolesc Psychiatry 27:764–771, 1988

Goldstein DJ: Effects of third trimester fluoxetine exposure on the newborn. J Clin Psychopharmacol 15:417–420, 1995

Goodman W, McDougle C, Price L, et al: Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive-compulsive disorder? J Clin Psychiatry 51:36–43, 1990

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive-Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive-Compulsive Scale, II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Goodwin DW, Guze SB, Robins E: Follow-up studies in obsessional neurosis. Arch Gen Psychiatry 20:182–187, 1969

Griest JH, Jefferson JW, Kobak KA, et al: Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 46:289–295, 1995

Hollander E, DeCaria C, Nitescu A, et al: Serotonergic function in obsessive-compulsive disorder: behavioral and neuroendocrine responses to oral m-CPP and fenfluramine in patients and healthy volunteers. Arch Gen Psychiatry 49:21–28, 1992

Hollander E, Stein DJ, Kwon JH, et al: Psychosocial function and economic costs of obsessive-compulsive disorder. CNS Spectrums 2:16–25, 1997

Insel TR, Akiskal HS: Obsessive-compulsive disorder with psychotic features: a phenomenologic analysis. Am J Psychiatry 143:1527–1533, 1986

Jenike M: Pharmacologic treatment of OCD. Psychiatr Clin North Am 15:895–919, 1992

Jenike MA, Baer L, Minichiello WE: Obsessive-Compulsive Disorders: Theory and Management. Littleton, MA, PSG Publishing, 1986

Karno M, Golding JM, Sorenson SB, et al: The epidemiology of obsessive-compulsive disorder in five U.S. communities. Arch Gen Psychiatry 45:1094–1099, 1988

Koran LM, Ringold AL, Elliott MA: Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry 61:514–517, 2000

Leckman JF, Grice DE, Broadman J, et al: Symptoms of obsessive-compulsive disorder. Am J Psychiatry 154:911–917, 1997

Lejoyeux M, Ades J: Antidepressant discontinuation: a review of the literature. J Clin Psychiatry 58(suppl):11–16, 1997

Leonard H, Swedo S, Lenane M, et al: A double-blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive-compulsive disorder. Arch Gen Psychiatry 48:922–927, 1991

Lo WH: A follow-up study of obsessional neurotics in Hong Kong Chinese. Br J Psychiatry 113:823–832, 1967

March J, Frances A, Carpenter D, et al (eds): The expert consensus guideline series: treatment of obsessive-compulsive disorder. J Clin Psychiatry 58(suppl):10–72, 1997

McDougle CJ, Price LH, Goodman WK, et al: Neuroleptic addition in fluvoxamine refractory obsessive-compulsive disorder. Am J Psychiatry 147:652–654, 1990

McDougle CJ, Epperson CN, Pelton GH, et al: A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 57:794–801, 2000

Mellman TA, Uhde TW: Obsessive-compulsive symptoms in panic disorder. Am J Psychiatry 144:1573–1576, 1987

Nelson E, Rice J: Stability of diagnosis of obsessive comulsive disorder in the Epidemiologic Catchment Area study. Am J Psychiatry 154:826–131, 1997

Pato MT, Zohar-Kadouch R, Zohar J, et al: Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. Am J Psychiatry 145:1521–1525, 1988

Pato MT, Murphy DL, Devane CL: Sustained plasma concentration of fluoxetine and norfluoxetine four to eight weeks after fluoxetine discontinuation. J Clin Psychopharmacol 11:224–225, 1991

Pigott TA, Pato MT, Bernstein SE, et al: Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 47:1543–1550, 1990

Pollitt J: Natural history of obsessional states. BMJ 1:194–198, 1957

Preskorn SH: Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet 32(suppl):1–21, 1997

Rapoport JL: The Boy Who Couldn't Stop Washing. New York, Dutton, 1989

Rasmussen SA: Obsessive-compulsive disorder in dermatologic practice. J Am Acad Dermatol 13:965–967, 1985

Rasmussen SA, Tsuang MT: Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry 143:317–322, 1986

Riccardi JN, Baer L, Jenike MA, et al: Changes in DSM-III-R Axis II diagnoses following treatment of obsessive-compulsive disorder. Am J Psychiatry 149:829–831, 1992

Robins LN, Helzer JE, Weissman MM, et al: Lifetime prevalence of specific psychiatric disorders in three sites. Arch Gen Psychiatry 41:949–958, 1984

Salzman L, Thaler FH: Obsessive-compulsive disorder: a review of the literature. Am J Psychiatry 138:286–296, 1981

Sasson Y, Zohar J: New developments in obsessive-compulsive disorder research: implications for clinical management. Int Clin Psychopharmacol 11(suppl):3–12, 1996

Sasson Y, Zohar J, Charpa M, et al: Epidemiology of obsessive-compulsive disorder: a world view. J Clin Psychiatry 58(suppl):7–10, 1997a

Sasson Y, Bermanzohn PC, Zohar J: Treatment of obsessive-compulsive syndromes in schizophrenia. CNS Spectrums 2:35–45, 1997b

Saz P, Copeland JRM, de la Camara C, et al: Cross national comparison of prevalence of symptoms of neurotic disorders in older people in two community samples. Acta Psychiatr Scand 91:18–22, 1995

Schimmell MS, Katz EZ, Shaag Y, et al: Toxic neonatal effects following maternal clomipramine therapy. Clin Toxicol 29:479–484, 1991

Stein MB, Forde BR, Anderson G, et al: Obsessive-compulsive disorder in the community: an epidemiologic survey with clinical reprisal. Am J Psychiatry 154:1120–1126, 1997

Stoll AL, Tohen M, Balldessarini R: Increased frequency of the diagnosis of obsessive-compulsive disorder. Am J Psychiatry 149:638–640, 1992

Summerfeldt LJ, Richter MA, Antony MM, et al: Symptom structure in obsessive-compulsive disorder: a confirmatory factor-analysis study. Behav Res Ther 37:297–311, 1999

Thoren P, Asberg M, Crohnholm B, et al: Clomipramine treatment of OCD, 1: a controlled clinical trial. Arch Gen Psychiatry 37:1281–1285, 1980

Tollefson GD, Birkett M, Koran L, et al: Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. J Clin Psychiatry 55(suppl):69–76, 1994a

Tollefson GD, Rampey AH, Potvin JH, et al: A multicenter investigation of fixed dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 51:559–567, 1994b

Weissman MM, Bland RC, Canino GL: The cross national epidemiology of obsessive-compulsive disorder. J Clin Psychiatry 55:5–10, 1994

Weizman A, Zohar J, Insel T: Biological markers in obsessive-compulsive disorder, in The Psychobiology of Obsessive-Compulsive Disorder. Edited by Zohar J, Insel T, Rasmussen SE. New York, Springer, 1991, pp 146–161

Wheadon D, Bushnell W, Steiner M: A fixed dose comparison of 20, 40, 60 mg of paroxetine to placebo in the treatment of obsessive-compulsive disorder. Paper presented at the annual meeting of the American College of Neuropsychopharmacology, Honolulu, HI, 1993

Zahle Ostergaard G, Pedersen SE: Neonatal effects of maternal clomipramine treatment. Pediatrics 69:233–234, 1982

Zohar AH, Ratzosin G, Pauls DL, et al: An epidemiological study of obsessive-compulsive disorder and related disorders in Israeli adolescents. J Am Acad Child Adolesc Psychiatry 31:1057–1061, 1992

Zohar J, Insel TR: Drug treatment of obsessive-compulsive disorder. J Affect Disord 13:193–202, 1987a

Zohar J, Insel TR: Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. Biol Psychiatry 22:667–687, 1987b

Zohar J, Judge R: Paroxetine versus placebo in the treatment of OCD. Br J Psychiatry 169:468–474, 1996

Zohar J, Mueller EA, Insel TR, et al: Seronterigic responsivity in OCD: effect of chronic clomipramine treatment. Arch Gen Psychiatry 45:167–172, 1988

Zohar J, Murphy DL, Zohar-Kadouch RC, et al: Serotonin in obsessive-compulsive disorder, in Serotonin in Major Psychiatric Disorders. Edited by Coccaro EF, Murphy DL. Washington, DC, American Psychiatric Press, 1990, pp 99–125

Zohar J, Sasson Y, Chopra M, et al: Schizo-obsessive subtype: obsessions and delusions. CNS Spectrums 3:38–39, 1998

CHAPTER 2

Clomipramine

Kim M. Schindler, Ph.D.
Michele Tortora Pato, M.D.

Any discussion of the pharmacotherapy of obsessive-compulsive disorder (OCD) will most likely begin with clomipramine (Anafranil), which was made available in the United States in February 1990. Although it had been marketed for more than 30 years outside the United States as an antidepressant, clomipramine's antiobsessional properties have made it a viable pharmacologic option for treating OCD. Despite the arrival of many other, more specific antiobsessional drugs, clomipramine remains an important alternative in the management of OCD. In this chapter we review the properties of clomipramine that may be responsible for its usefulness in treating OCD; its effectiveness in the treatment of depression, which often raises the question of whether it should be classified as an antidepressant or antiobsessive; and its history of clinical use in the treatment of OCD. We then discuss clinical considerations such as dosing, side effects, compliance, treatment response (both to oral and intravenous administration), duration, and discontinuation to guide psychiatrists who are considering prescribing this medication.

Pharmacology

Clomipramine is a tricyclic antidepressant (TCA) that is virtually identical in structure to imipramine, with the exception of a chloride substituted for a hydrogen at position 3. Consequently, its side effects are similar to those of imipramine, but it behaves differently at the neurochemical level in significant ways. In particular, clomipramine is a much more potent seroto-

nin uptake inhibitor than is imipramine (Murphy et al. 1989); it is this characteristic that is believed to make clomipramine particularly useful in the treatment of OCD. In addition, one of the primary metabolites of clomipramine, desmethylclomipramine (DCMI), is a potent norepinephrine uptake blocker as well as an effective inhibitor of the 5-HT (5-hydroxytryptamine) transporter responsible for serotonin reuptake. However, the parent compound, clomipramine, is at least 10 times as potent a serotonin uptake inhibitor as its metabolite DCMI, and this fact may have some predictive value in terms of efficacy of treatment (Murphy et al. 1989; Träskman et al. 1979).

History of Use in Obsessive-Compulsive Disorder

Clomipramine has been commercially available outside the United States since the early 1950s. The first studies of its use in the treatment of OCD appeared as early as 1967 (Fernandez and Lopez-Ibor 1967; Renynghe de Voxrie 1968). At that time the drug was used with some success in open trials for obsessional patients and depressed patients with obsessional symptoms. In the 1970s, several studies were undertaken on the use of clomipramine in the treatment of OCD and obsessional symptoms; some of these studies used intravenous administration, and others used oral dosing (Jenike et al. 1986; Thorén et al. 1980a; Yaryura-Tobias et al. 1976). By 1980, there were 15 anecdotal studies of the use of clomipramine in the treatment of OCD. To summarize the results of these studies, 184 of 226 obsessive patients receiving clomipramine at doses of 75–300 mg had some relief of their symptoms (Ananth 1986).

In the 1980s, controlled double-blind studies of clomipramine were performed in an attempt to establish the efficacy of this agent in the treatment of OCD. Among the first comparative studies done with clomipramine in addition to placebo-controlled trials were comparisons with more traditional antidepressants, including desipramine, imipramine, clorgyline, nortriptyline, and amitriptyline (extensive review of these studies can be found elsewhere—see Ananth 1986; Insel 1984; Leonard et al. 1988; Murphy et al. 1989; Thorén et al. 1980a; Zohar and Insel 1987a, 1987b). Clomipramine was found to be more effective than placebo alone in every case and more effective than desipramine, clorgyline, and amitriptyline. It also was suggested to have probable efficacy over imipramine and nortriptyline. Clomipramine also was compared with behavioral treatment in early studies. In a landmark study by Marks et al. (1980), clomipramine administered in conjunction with behavioral treatment was found to be more effective for treating OCD than was behavioral treatment

alone. Unfortunately, this study did not include a treatment group of patients who received only clomipramine for the entire study period, so conclusions about the efficacy of this agent compared with that of behavioral treatment are limited (see Chapter 9).

In the early part of the 1990s, a multicenter clinical trial was completed by the CIBA-Geigy Corporation, now part of Novartis Pharmeceuticals. The study included 384 patients, of which 194 received clomipramine and 190 received placebo over a 10-week period. Analysis of the results showed that patients receiving clomipramine experienced a significant reduction in obsessive-compulsive symptoms (Clomipramine Collaborative Study Group 1991; DeVeaugh-Geiss et al. 1989). As measured by the Yale-Brown Obsessive Compulsive Rating Scale (Y-BOCS; Goodman et al. 1989a, 1989b), symptoms decreased by 40%–45% ($P<0.05$). Furthermore, symptom improvement was noted as soon as 2 weeks after initiation of the drug, and this improvement continued throughout the 10-week study. Doses of up to 250 mg (and in rare cases 300 mg) were used. Unlike clinical trials in other disorders (e.g., depression), the placebo group experienced virtually no change in symptoms (less than 5%). In part of the multicenter trial, some patients with scores in the range of 17–21 on the Hamilton Rating Scale for Depression (Hamilton 1960) were included, and it was found that the severity of the patients' depression did not affect their outcome (DeVeaugh-Geiss et al. 1989). This continuing improvement of obsessive-compulsive symptoms through the 10 weeks is typical of clomipramine treatment for OCD. Many authors have noted that although symptom improvement may be noted in the 4- to 6-week range (Ananth 1986; Ananth et al. 1981; Insel 1984; Insel et al. 1983; Mavissakalian and Michelson 1983), it may take 12 weeks or longer to see the full benefit of the medication (Pato and Chakravorty 1998; Thorén et al. 1980a). The case examples at the end of this chapter illustrate continued improvement over 4–6 months.

An interesting finding was reported by Koran et al. (1997), who used intravenous pulse loading of clomipramine (intravenous pulse loading of clomipramine on day 1 and 2 at 150 and 200 mg, respectively, followed by oral clomipramine treatment). In a double-blind placebo-controlled trial, the authors noted a much larger and more rapid decrease in obsessive-compulsive symptoms with a more tolerable side effect profile with intravenous pulse loading than with oral pulse loading. In the group receiving intravenous pulse loading, six of seven patients showed significant improvement in Y-BOCS scores in just 4.5 days compared with the orally dosed group, in which only one of eight patients had marked response in 4.5 days. However, by 8 weeks both the oral and intravenous groups had similar improvement. These findings may be due to rapid attainment of

high plasma levels of clomipramine that are not obtainable with oral dosing because it is subject to the "first pass" liver metabolism. Some of the patients in this study had previously been intolerant of oral clomipramine.

Further studies by Fallon et al. (1998) have shown response to gradually escalating doses of intravenous clomipramine over a 14-day period in patients whose OCD was previously refractory to oral clomipramine. Of particular note is that more of these patients had responded (18 of 31 [58.1%]) at 1-month follow-up than had initially responded immediately after the 14-day infusion. Although liquid clomipramine for intravenous infusion is available in some European countries and Canada, it has not been approved by the Food and Drug Administration (FDA) for use in the United States. Additional studies supporting its efficacy are probably necessary before a pharmaceutical company can petition the FDA for approval.

Since the landmark multicenter study by the Clomipramine Collaborative Study Group (1991), many more studies of the effectiveness of clomipramine in comparison with placebo as well as with the selective serotonin uptake inhibitors (SSRIs) have followed. Meta-analyses of these studies, which pool the results of numerous other studies throughout the lifetime of clomipramine use, showed that patients with OCD who received short-term clomipramine administration demonstrated greater improvement compared with patients who received placebo (Abramowitz 1997; Greist et al. 1995; Piccinelli et al. 1995). Meta-analyses by Griest et al. (1995) and Piccinelli et al. (1995) displayed improvement over placebo for all agents (clomipramine, fluoxetine, fluvoxamine, sertraline). Although both of these studies showed a larger percentage improvement over placebo for clomipramine, head-to-head studies have not borne out this difference, which lends some strength to criticisms about the variability in the treatment naïveté of subjects, inconsistent procedures, and variability of diagnostic criteria in meta-analyses.

Several direct comparison studies have compared clomipramine with different SSRIs, including fluoxetine (Pigott et al. 1990), sertraline (Bisserbe et al. 1997), fluvoxamine (Freeman et al. 1994; Koran et al. 1996), and paroxetine (Zohar et al. 1996). These studies had similar double-blind designs to more directly compare the therapeutic effects of available OCD drug treatments. The results of the comparisons were all in general agreement that the efficacy and therapeutic benefit of clomipramine are similar to those of the SSRIs and that the effects of these agents varied primarily in their side effect profiles, with the main disadvantage of clomipramine being its anticholinergic side effects.

A discussion of OCD and clomipramine must address the role of de-

pression in OCD. Clomipramine was actually marketed for more than 30 years as an antidepressant and remains a popular antidepressant in many parts of the world. Currently, several convincing studies have concluded that the antiobsessional effect of clomipramine is separate from its antidepressant effect (Ananth et al. 1981; Insel et al. 1983; Mavissakalian et al. 1985; Montgomery 1980; Thorén et al. 1980a, 1980b; Zohar and Insel 1987a, 1987b). In particular, Mavissakalian et al. (1985) compared 10 patients with OCD—5 with high depression scores and 5 with low depression scores—and found no difference in the improvement of their OCD symptoms when treated with clomipramine. Clinically, we (Pato et al. 1988) reported on one patient who had relief of her depression with amitriptyline but had remission of both OCD symptoms and depression only when she switched to clomipramine.

Dosing

Prescribing clomipramine for patients with OCD requires consideration of not only the nature of the drug but also the nature of the disorder. On the one hand, it has been our clinical experience that patients with OCD are incredibly tolerant of side effects (see case examples at the end of this chapter). Perhaps this is because, as the patients themselves express it, they have suffered with their illness, often in secret, for so long that the improvement in their symptoms and in their overall level of functioning is well worth any side effects. On the other hand, the nature of the illness means that these patients experience a great deal of doubt and apprehension; they might obsess over actually taking the medicine at all and may require considerable encouragement and repeated explanation of its side effects. These patients can often worry excessively about the possible side effects, often imagining the worst possible scenario; therefore, they need considerable reassurance. In the initial phases of treatment, doctor availability and a slow, gradual increase in dose are particularly important in terms of the patient's long-term compliance. Although several effective treatment modalities are available for treating OCD, early rejection of the medication by the patient should be avoided because it will delay overall improvement.

Unfortunately, no specific data are available on which patients respond best to clomipramine versus other antiobsessional agents. However, in a preliminary report, it seems that a great deal of overlap exists between fluoxetine and clomipramine response (Pigott et al. 1990). A few studies have addressed which symptoms seem most resistant to pharmacotherapy. In 1988, Eisen and Rasmussen reported that among patients

with psychotic features and OCD, those with a paranoid or obsessional quality to their delusions had a better prognosis than did those with magical thinking or schizophrenia as part of their psychotic features. Ackerman et al. (1994) showed a better clomipramine treatment response in patients with lower Hamilton Rating Scale for Depression (Ham-D; Hamilton 1960) scores or late age of onset, whereas Alarcon et al. (1993) found a correlation between poorer response to clomipramine with higher initial Y-BOCS scores or presence of cleaning rituals. Chapter 11 further addresses the subject of treatment-resistant OCD and presents additional data on response prediction.

The starting dose of clomipramine should be low—25–50 mg the initial day—because there have been some reports of acute onset of nausea and vomiting requiring discontinuation (Ananth 1986). Doses can then be increased every 1–3 days by another 25–50 mg until a maximum dose of 250 mg is reached or until side effects become intolerable. Most studies have employed doses in the range of 75–300 mg (Ananth 1986).[1] Because no reports have been made of dose findings with clomipramine in OCD, we need to count on "accumulated clinical experience." Although some patients have shown responses at doses as low as 75 mg, traditionally a dose in the range of 150–250 mg seems to be most effective. We usually choose once-daily dosing at bedtime to allow for better compliance. In addition, we have found that this approach minimizes the side effects in many cases and that there are fewer complaints of sedation, one of the major side effects of clomipramine. Occasionally, patients cannot tolerate 200 or 250 mg of clomipramine at once, in which case the dose is split and given twice a day, once in the morning and once at bedtime, with the smaller dose (e.g., 100 mg) given in the morning to minimize daytime sedation.

When considering clomipramine, as when prescribing any TCA, therapists should use their clinical judgment and take into account differences in age response and dosing (see Chapter 9 for a discussion of treating children with OCD). We have some clinical experience with patients in their early 60s, most of whom were women weighing approximately 100 lb for whom 75–150 mg was sufficient rather than the 250 mg we give most pa-

---

[1] A cautionary note must be made about using clomipramine at doses greater than 250 mg. The CIBA-Geigy Corporation has released a warning indicating an increased instance of seizures in patients with a dose of 300 mg or more (2.1% [10 of 472 patients] versus 0.48% [12 of 2,514 patients] at doses of 250 mg or less). Thus, CIBA-Geigy has restricted the maximum dose to 250 mg/day (DeVeaugh-Geiss et al. 1989).

tients initially. In general, elderly patients may be able to get by with a smaller dose; they may, in fact, not tolerate the larger dose. Because elderly patients are more prone to side effects, clinicians must be cognizant of several points when considering clomipramine: 1) Elderly patients are more prone to orthostatic hypotension and dizziness, which can result in falling when getting out of bed and can increase the risk of hip fracture. Therefore, clinicians should ask about these symptoms, check for orthostatic hypotension, and explain to the patient that he or she needs to be very careful when getting out of bed. It is suggested that patients rise from a reclined position first to a seated position on the edge of the bed and then stand slowly, watching for dizziness. If this alone does not help the orthostatic hypotension and dizziness, then a lower dose should be considered. 2) Constipation as a side effect can result in fecal impaction or hemorrhoids; again, if the symptom is severe, lower the dose and/or add a stool softener or prune juice. 3) Another side effect is a nondescript type of mental cloudiness that some patients describe as "not thinking as clearly or quickly" or as "being forgetful." Decreasing the dose or a trial off medication may be helpful in making the differential diagnosis between this side effect and dementia. 4) Dehydration is likely to increase drug serum levels and make the patient toxic; if an elderly patient becomes ill and dehydrated, the dose may need to be decreased until the patient rehydrates. 5) Elderly patients are often taking other medications. Any potentially harmful interactions, such as risk of cardiac arrhythmias, should be assessed before starting clomipramine and should be monitored throughout treatment.

Side Effects

The side effects of clomipramine are typical of those seen with other TCAs. The literature disagrees on the relationship between side effects and plasma levels. Stern et al. (1980) found no relationship between side effects and serum levels. However, Capstick (1977) felt that the side effects were dose dependent although they, as well as the therapeutic effects, varied from patient to patient. In a recent study, Ackerman et al. (1996) correlated this differential side effect profile as a predictor of clinical response in which the presence of side effects during the first 4 weeks of treatment represented a marker of drug responsiveness. Our own clinical experience seems to indicate that a dose-dependent relationship exists for side effects but that there is considerable individual variability. In a systematic study of diminished dosing of clomipramine, we found that patients could tolerate a 40% drop in dose with no deterioration in symptom improvement but with some decrease in side effects (Pato et al. 1990).

Despite the serotonergic and noradrenergic properties of clomipramine, most of the side effects are anticholinergic in nature (Stern et al. 1980). The most commonly reported side effects are dry mouth, dizziness, tremor, somnolence, constipation, ejaculation failure in men, fatigue, nausea, headache, and increased sweating (Clomipramine Collaborative Study Group 1991). Stern et al. (1980) noted that during the first 4 weeks of a study of clomipramine, patients reported significant side effects, including eye-focusing problems, constipation, dizziness, drowsiness, unsteady hands, dry mouth, and increased sweating. However, by the end of the 7-week study, only unsteady hands, dry mouth, and sweating maintained statistically significant severity.

In general, patients habituate to most of these side effects over time. Dry mouth is considered by some to be the most significant long-term side effect because of the effects of decreased saliva on dental health. Clinicians should recommend good oral hygiene and avoidance of sugared candies to keep the mouth moist; sugarless gum and candies are preferable and saliva substitutes may even be considered.

Constipation can often be handled by having patients stay well hydrated. We often recommend to our patients a minimum of eight glasses of fluid per day, increased fiber in their diet, and a regular schedule of exercise. If this does not work, a stool softener such as docusate sodium (Colace), 100–300 mg/day, or psyllium hydrophilic mucilloid (Metamucil) is added.

If patients complain of nausea, therapists can recommend taking the clomipramine with or without food, whichever minimizes the nausea best.

Fatigue is also a problem, and for this reason we often give the full dose of medication at bedtime. If fatigue on awakening is noted, we move the evening dose from bedtime to 8:00 PM and then to 5:00 PM, and this often helps. If this adjustment does not work, decreasing the dose or dividing it to two or three times a day may help, although the major portion of the medicine is still taken at bedtime.

As with other TCAs, patients occasionally develop urinary hesitance or even urinary retention. Hesitancy, if persistent, can usually be managed with a bethanechol derivative of 25 mg up to three times a day; however, severe hesitancy or urinary retention warrants urologic consultation and probably medication discontinuation.

Mental cloudiness or mild memory deficit is a symptom that, although present in many of our patients, is usually well tolerated. Often, reassurance that the symptom is not permanent is enough to put the patient at ease. Occasionally, a patient finds this side effect intolerable, in which

case the dose must be decreased or the medication stopped.

Monteiro et al. (1987) reported a high incidence of anorgasmia in patients with OCD who were being treated with clomipramine. They noted that 22 of 24 male and female patients with OCD who had normal sexual function developed anorgasmia while receiving clomipramine. This symptom occurred in most cases within 3 days of starting treatment at very low doses of 25–50 mg. Only 2 of the 22 patients found remission of this symptom within 2–3 months on clomipramine, although all patients had return of normal sexual functioning within 3 days of stopping clomipramine. The authors pointed out that eliciting a history of this side effect was difficult. Patients were reticent to report it; in fact, in 36% of the cases it was not reported on a standardized questionnaire but revealed with direct questioning. A retrospective chart review of male patients receiving several different antidepressants found sexual dysfunction, including decreased libido, erectile difficulties, and impairment in orgasm and ejaculation, in 12 of 39 men receiving TCAs (clomipramine was not evaluated individually) (Hsu and Shen 1995). Although quite common, the dysfunction was reported less often for TCAs (30.8%) than for the SSRIs fluoxetine, paroxetine, and sertraline (50%; 24 of 48 cases) (Hsu and Shen 1995). In our clinical experience, many patients experience some decrease in orgasm or sex drive, but we have found that decreasing the dose lessens the severity of this side effect in many patients (see case examples at the end of this chapter). However, clomipramine might be helpful in those patients who experience premature ejaculation because it causes delayed ejaculation.

Sexual dysfunction associated with clomipramine as well as other serotonin reuptake inhibitors in some cases can be counteracted with additional pharmacologic agents. Clomipramine-induced anorgasmia has been reported to be successfully treated with either the alpha-2 antagonist yohimbine (Price and Grunhaus 1990) or cyproheptadine, a 5-HT_2 antagonist with antihistaminergic and adrenolytic properties (Aizenberg et al. 1995).

Use in Pregnancy

The standard precautions for use during pregnancy hold for clomipramine as with any drug (Cohen et al. 1989; Diaz et al. 1997; Elia et al. 1987). The limited data available appear to indicate that, given reports of withdrawal symptoms in neonates exposed to clomipramine in utero, this agent is not the safest choice for pregnant women. Withdrawal symptoms included infant hypothermia, respiratory acidosis, and seizure (Diaz et al. 1997). In the case of OCD, especially with the proven efficacy of behavioral

treatment, it is probably best to avoid using medication during pregnancy if possible. Of the SSRIs, fluoxetine has been better studied in the prenatal period for its reproductive safety data. Fluoxetine administration during pregnancy has not shown an increased risk of major congenital malformations; however, only limited data have been gathered on minor malformations or long-term neurobehavioral consequences (Cohen and Rosenbaum 1998). Thus, in patients who need medication in addition to behavior therapy during pregnancy, fluoxetine is the best choice. In patients who develop OCD in the postpartum period and require treatment, limited evidence has shown that breastfeeding does not substantially increase drug exposure to the infant; like most TCAs, clomipramine use during breastfeeding rarely results in detectable drug levels in the sera of the infant (Wisner et al. 1995).

Treatment Duration and Discontinuation

Because of the considerable time lag that can exist (6–10 weeks) between initial dosing and onset of significant improvement, patients will need a lot of encouragement to remain compliant with their treatment regimen. Because side effects often appear before any clinical improvement, patients are prone to early discouragement with clomipramine. Often, simply talking with them before the onset of side effects or improvement will considerably help compliance. Side effects can be at their worst when initially starting the clomipramine but usually improve over time. Occasionally, a mild exacerbation in OCD symptoms may be seen within the first few days of starting clomipramine, but this should not discourage its use because this reaction is believed to be part of the therapeutic mechanism of clomipramine (Zohar et al. 1988). It may be helpful to discuss with some patients that this might happen, but with other patients this awareness may lead to increased obsessing and avoidance of the medication. Because symptoms worsen in a minority of patients, clinicians must judge on an individual basis what to tell their patients.

Most studies have noted that although onset of improvement may be noticeable after a couple of weeks of oral dosing, it is often not significant until 6–10 weeks. Thorén et al. (1980a) found that patients continued to improve even up to 12 weeks. Thus, most researchers recommend continuing treatment for up to 12 weeks before considering a patient a nonresponder (Volavka et al. 1985; Zohar and Insel 1987a, 1987b). Initial studies with intravenous clomipramine, mentioned previously in this chapter, have shown response in less than 1 week with pulse dosing and within 14 days (up to 1 month) after gradual intravenous dosing over 14 days (Fallon et

al. 1998; Koran et al. 1997). Unfortunately, intravenous preparations do not yet have approval in the United States.

Patients should be warned that they may not see much improvement initially. The first sign of improvement is usually not a disappearance of certain obsessions or compulsions but rather a subtle decrease in the intensity of the urge to perform them or an increase in the ability to resist symptoms. Given that responses may be quite delayed, it is thought that maximizing the dose of medication allows for the least delay in improvement. It has been our clinical experience that patients may continue to have further gradual and consistent improvement for several months. As outlined below, some data show that patients can continue to do well on less medicine once they have achieved maximum improvement.

In clinical practice, we do not often obtain blood levels unless 1) the patient remains unresponsive at high doses, 2) there is a question about compliance, or 3) the patient seems to be having side effects that are inconsistent with his or her dose of medication. There is considerable variability among laboratories in the report of serum levels, and clinicians should be wary of compared results from different laboratories. It has been established that clomipramine levels reach steady state within 7–14 days after a constant dose is maintained (Luscombe et al. 1980). Traditionally, levels are drawn about 12 hours after the last dose. Some studies have recommended aiming for plasma levels of 100–250 ng/mL for clomipramine and 230–550 ng/mL for DCMI (Stern et al. 1980), although the exact relation of these doses to obsessive-compulsive symptom remission remains unclear.

Anecdotal reports of symptom recurrence with discontinuation of clomipramine have been made as well as the occasional case of patients staying symptom-free after clomipramine discontinuation (Ananth 1986; Åsberg et al. 1982; Capstick 1973; Flament et al. 1985; Leonard et al. 1989; Thorén et al. 1980a; Yaryura-Tobias et al. 1976). We performed a double-blind discontinuation study with clomipramine (Pato et al. 1988) and found that 17 of the 18 patients who completed the study had recurrence of OCD symptoms significantly severe as to require reinstitution of clomipramine. In 16 of these 18 patients, symptoms worsened significantly by the end of the 7-week study, and clomipramine was reinstituted in most patients. The duration of treatment before discontinuation (mean = 10.7 months ± 5.5 months) and the serum levels of clomipramine and DCMI (mean = 194 ± 187 ng/mL and 351 ± 189 ng/mL, respectively) did not have an effect on recurrence. These results seem to imply that clomipramine must be given for more than 1 year in most patients to maintain improvement. However, with some reports in the literature of patients remaining symptom-free after discontinuation of clomipramine, a trial to titrate med-

ication down very gradually, in 2- or 3-month steps, may be warranted (Pato 1990).

With the less-than-optimistic chance of patients remaining symptom-free off clomipramine, another possible alternative is to minimize the dose of clomipramine used. Pato et al. (1990) reported an open trial in which patients with OCD who were receiving clomipramine for a minimum of 10 (± 5) months were able to tolerate decreases in dose of 40% (from 270 [± 20] mg to 165 [± 19] mg) without deterioration in OCD symptom improvement. Dose reduction trials to half of the acute therapy dose (Ravizza et al. 1996) or even to 60% of the dose (Mundo et al. 1997; Pato and Chakravorty 1998) have maintained clinical profile without a worsening of OCD symptoms. Therefore, although discontinuation of the drug has not been effective, establishing a maintenance dose could increase compliance by maintaining therapeutic benefits while simultaneously reducing side effects.

Summary

In our experience, clomipramine is an effective and well-tolerated treatment for OCD. In most cases, doses close to 250 mg for a minimum of 10 weeks are required to obtain reasonable efficacy. The most bothersome side effects are dry mouth, constipation, decreased sex drive, and anorgasmia. Present data indicate that the antiobsessional effects of clomipramine are usually lost when the medication is discontinued. After bringing the obsessions and compulsions under control with acute therapy dosing, a reduced maintenance dosing schedule appears to be the best compromise between maintaining therapeutic effects to prevent relapses and minimizing side effects.

Case Examples

Case 1

P.J. was a 36-year-old obese man, employed full time, with a history of OCD dating from childhood. Most of his many obsessions and compulsions centered around contamination. When he first entered our clinic, his life seemed totally consumed with thoughts and rituals. In his pocket he carried a plastic bag filled with pieces of soapy, wet paper; when someone accidentally bumped into him in the subway or touched an item belonging to him, he had a set pattern of dabbing himself or the object to cleanse it. This ritual was often not enough, however; when returning from the

grocery store, he sometimes felt compelled to take a shower, wipe down the groceries, and then throw away some groceries to ensure that those left were not contaminated. He would shower up to 10 times a day, or anytime he felt contaminated. There were certain articles and areas in his apartment he could not get adequately clean, so he would, for example, not sit on the sofa or touch his stereo. His eating was accompanied by the same urge to perform and ritualize as were his obsessions and compulsions. For instance, he would have to eat a certain number of yogurt containers in one sitting.

By the end of his first month receiving clomipramine at a dose of 250 mg/day, P.J. noticed improvement. Initial improvement took the form of an increased ability to resist and a less depressed mood, but by the end of 6 weeks he began to report actual reductions in obsessive-compulsive symptoms. His showers decreased to 1–2 times a day, and his need to wipe things off at home and at work was considerably decreased. He also had less need to throw away groceries for fear they were contaminated. Unfortunately, P.J. also experienced some side effects. Most notable was carbohydrate craving, resulting in a 50-lb weight gain. He also had to tolerate dry mouth and increased sweating, for which he compensated by increasing his fluid intake. His ability to achieve orgasm decreased, and his liver serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were mildly elevated. He was more than willing to tolerate these side effects in exchange for his symptom improvement. However, because of the elevated liver transaminases, we decided on a trial off medication at 5 months.

Within 7 weeks of withdrawal, P.J. began to notice episodes of severe symptoms. For example, he would find that he had an increased urge to wipe and touch himself when he saw an indigent person on the subway, and he began to feel the urge to eat three containers of yogurt at one sitting. However, his side effects disappeared, his weight began to drop, and his levels of SGOT and SGPT returned to normal.

P.J. was restarted on clomipramine at 50 mg, which was quickly increased by 50 mg every 2–3 days up to 250 mg. Again, he noticed improvement within 3 weeks. Within 7 weeks he was able to use items in his apartment that he previously had been unable to approach because of contamination fears. Unfortunately, his side effects also returned, including craving for sweets, sweating, and mild tremor. This time, however, sexual functioning remained normal. Within 6 months of restarting clomipramine, P.J. reported he was no longer throwing away groceries and no longer had to carry a plastic bag with wet paper towels in his pocket, although when the urge to wipe became very strong, he might spit on a piece of tissue and touch himself in the proper manner. The psychiatrist and patient global assessment at 250 mg of clomipramine was 50% improvement (Pato et al. 1988, 1990). Unfortunately, side effects at this time included decreased sex drive, increased appetite, weight gain, dry mouth, increased sweating, and elevated SGOT and SGPT levels. Evaluation by a hepatologist was inconclusive as to whether this elevation was due to fatty infiltration secondary to morbid obesity or to a drug reaction.

Because of the increase in liver transaminases, clomipramine was again discontinued.

Case 2

E.M. was a 42-year-old married man and amateur athlete with a 20-year history of OCD. His compulsions included a need to pick up glass and matches on the street because of a sense of overresponsibility that if he did not, a child would get hurt. He also had an obsession that his copy of the newspaper contained national secrets and had to be destroyed and that the plastic bag in which it came might suffocate a child. He would tear the paper and bag into little pieces and then throw them away. He would often avoid reading the newspaper to avoid this obsession and its consequent compulsion. E.M. estimated that symptoms resulted in his functioning at 60% of his potential.

Within 2 months of starting clomipramine at 250 mg/day, his symptoms had reduced significantly. As he described it, "The medicine chokes off the anxiety so that the obsessions or compulsions don't have a chance to get started." His obsessions about the newspaper disappeared completely, and he had only an occasional need, not even daily, to pick up a match or piece of glass he saw on the street. His global assessment of his improvement was 80%. Side effects, however, included difficulty with orgasm and ejaculation, excessive sweating, a 10- to 15-lb weight gain, mild dry mouth, and mild constipation. The side effect most bothersome to him was a sense of heaviness in his legs that resulted in decreased exercise tolerance. Thus, instead of being able to run 10 miles a day, he was down to 3–5 miles a day.

Clomipramine was discontinued in a double-blind fashion. Within 4 weeks, marked deterioration was noted. Obsessive thoughts about national secrets had returned almost to the point of causing panic attacks, and E.M. felt that it was taking a significant effort to resist the compulsions to pick up glass or matches. He also complained of some psychomotor agitation, increased appetite, and difficulty with sleep. Side effects improved, however. In particular, E.M. noticed improved exercise tolerance. Within 7 weeks of discontinuation, he had developed a new obsession: a fear that he had been contaminated by the AIDS virus even though his risk was quite low. He could also no longer resist the urge to pick up glass off the street. His sleep problems had subsided, and he reported no specific neurovegetative symptoms.

Clomipramine was reinstituted at 150 mg/day in an attempt to minimize the exercise intolerance. Within 3 weeks, E.M. noted a remission of his symptoms—obsessions about national security in the newspaper and about AIDS and compulsions to pick up matches and glass. He was still avoiding reading some parts of the newspaper, but his anxiety had diminished significantly. However, side effects, particularly increased sweating, dry mouth, mild constipation, and problems with orgasm remained, as did some exercise intolerance, although it was less severe. At 4 months, clomipramine dose was decreased further to 125 mg. This brought no de-

terioration in his symptom relief, which he now rated at 90%–95% improved, but did reduce his side effects. His constipation cleared completely, he had only minor dry mouth and much less sweating, and he felt that his ability to exercise was within 80%–90% of his pretreatment level. After 10 months on clomipramine, a further decrease to 100 mg/day was attempted, but this was followed by mild but notable deterioration in improvement. Total time on obsessions and compulsions increased from 30 to 90 minutes per day, with a more irritable and anxious mood. A return to 125 mg brought a quick remission of symptoms to the 90%–95% improvement level within 4 weeks.

References

Abramowitz JS: Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: a quantitative review. J Consult Clin Psychol 65:44–52, 1997

Ackerman D, Greenland S, Bystritsky A, et al: Predictors of treatment response in obsessive-compulsive disorder: multivariate analysis from a multicenter trial of clomipramine. J Clin Psychopharmacol 14:247–254, 1994

Ackerman DL, Greenland S, Bystritsky A, et al: Relationship between early side effects and therapeutic effects of clomipramine therapy in obsessive-compulsive disorder. J Clin Psychopharmacol 16:324–328, 1996

Aizenberg D, Zemishlany Z, Weizman A: Cyproheptadine treatment of sexual dysfunction induced by serotonin reuptake inhibitors. Clin Neuropharmacol 18:320–324, 1995

Alarcon RD, Libb JW, Spitler D: A predictive study of obsessive-compulsive disorder response to clomipramine. J Clin Psychopharmacol 13:210–213, 1993

Ananth J: Clomipramine: an antiobsessive drug. Can J Psychiatry 31:253–258, 1986

Ananth J, Pecknold JC, van den Steen N, et al: Double-blind comparative study of clomipramine and amitriptyline in obsessive neurosis. Prog Neuropsychopharmacol 5:257–262, 1981

Åsberg M, Thorén P, Bertilsson L: Clomipramine treatment of obsessive disorder: biochemical and clinical aspects. Psychopharmacol Bull 18:13–21, 1982

Bisserbe JC, Lane RM, Flament MS, et al: A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. Eur Psychiatry 153:1450–1454, 1997

Capstick N: Psychiatric side-effects of clomipramine (Anafranil). J Int Med Res 1:444–448, 1973

Capstick N: Clinical experience in the treatment of obsessional states. J Int Med Res 5(suppl):71–80, 1977

Clomipramine Collaborative Study Group: Efficacy of clomipramine in OCD: results of a multicenter double-blind trial. Arch Gen Psychiatry 48:730–738, 1991

Cohen LS, Rosenbaum JF: Psychotropic drug use during pregnancy: weighing the risks. J Clin Psychiatry 59(suppl):18–28, 1998

Cohen LS, Heller VL, Rosenbaum JF: Treatment guidelines for psychotropic drug use in pregnancy. Psychosomatics 30:25–33, 1989

DeVeaugh-Geiss J, Landau P, Katz R: Treatment of obsessive-compulsive disorder with clomipramine. Psychiatr Ann 19:97–101, 1989

Diaz SF, Grush LR, Sichel DA, et al: Obsessive-compulsive disorder in pregnancy and the puerperium, in OCD Across the Life Cycle. Edited by Dickstein LJ, Riba MB, Oldham JM. Washington, DC, American Psychiatric Press, 1997

Eisen JL, Rasmussen SA: Obsessive-compulsive disorder with psychotic features (NR256), in 1988 New Research Program and Abstracts. Washington, DC, American Psychiatric Association, 1988, p 126

Elia J, Katz IR, Simpson GM: Teratogenicity of psychotherapeutic medications. Psychopharmacol Bull 23:531–586, 1987

Fallon BA, Liebowitz MR, Campeas R, et al: Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine. Arch Gen Psychiatry 55:918–924, 1998

Fernandez CE, Lopez-Ibor JJ: Monochlorimipramine in the treatment of psychiatric patients resistant to other therapies. Actas Luso Esp Neurol Psiquiatr Cienc Afines 26:119–147, 1967

Flament MF, Rapoport JL, Berg CJ, et al: Clomipramine treatment of childhood obsessive-compulsive disorder: a double-blind controlled study. Arch Gen Psychiatry 42:977–983, 1985

Freeman CP, Trimble MR, Deakin JF, et al: Fluvoxamine versus clomipramine in the treatment of obsessive-compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. J Clin Psychiatry 55:301–305, 1994

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Greist JH, Jefferson JW, Kobak KA, et al: Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: a meta-analysis. Arch Gen Psychiatry 52:53–60, 1995

Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–66, 1960

Hsu JH, Shen WW: Male sexual side effects associated with antidepressants: a descriptive clinical study of 32 patients. Int J Psychiatry Med 25:191–201, 1995

Insel TR: New Findings in Obsessive-Compulsive Disorder. Washington, DC, American Psychiatric Press, 1984

Insel TR, Murphy DL, Cohen RM, et al: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 40:605–612, 1983

Jenike MA, Baer L, Minichiello WE: Obsessive Compulsive Disorders: Theory and Management. Littleton, MA, PSG Publishing, 1986

Koran LM, McElroy SL, Davidson JR, et al: Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol 16:121–129, 1996

Koran LM, Sallee FR, Pallanti S: Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. Am J Psychiatry 154:396–401, 1997

Leonard H, Swedo S, Rapoport JL, et al: Treatment of childhood obsessive-compulsive disorder with clomipramine and desmethylimipramine: a double-blind crossover comparison. Psychopharmacol Bull 24:93–95, 1988

Leonard H, Swedo SE, Rapoport JL, et al: Treatment of childhood obsessive-compulsive disorder with clomipramine and desmethylimipramine in children and adolescents: a double-blind crossover comparison. Arch Gen Psychiatry 46:1088–1092, 1989

Luscombe DK, Wright J, Stern RS, et al: Plasma concentrations of clomipramine and desmethylclomipramine in obsessive-compulsive neurosis. Postgrad Med J 56(suppl):140–143, 1980

Marks IM, Stern R, Mawson D, et al: Clomipramine and exposure for obsessive-compulsive rituals. Br J Psychiatry 136:1–25, 1980

Mavissakalian M, Michelson L: Tricyclic antidepressants in obsessive-compulsive disorder: antiobsessional or antidepressant agents? J Nerv Ment Dis 171:301–306, 1983

Mavissakalian M, Turner SM, Michelson L, et al: Tricyclic antidepressants in obsessive-compulsive disorder: antiobsessional or antidepressant agents? Am J Psychiatry 142:572–576, 1985

Monteiro WO, Noshirvani HF, Marks IM, et al: Anorgasmia from clomipramine in obsessive-compulsive disorder: a controlled trial. Br J Psychiatry 151:107–112, 1987

Montgomery SA: Clomipramine in obsessional neurosis: a placebo controlled trial. Pharmaceutical Medicine 1:189–192, 1980

Mundo E, Bareggi SR, Pirola R, et al: Long-term pharmacotherapy of obsessive-compulsive disorder: a double-blind controlled study. J Clin Psychopharmacol 17:4–10, 1997

Murphy DL, Zohar J, Benkelfat C, et al: Obsessive-compulsive disorder as a serotonin subsystem-related behavioral disorder. Br J Psychiatry 155(suppl):15–24, 1989

Pato MT: When to discontinue treatment, in Obsessive-Compulsive Disorders: Theory and Management, 2nd Edition. Edited by Jenike MA, Baer L, Minichiello WE. Littleton, MA, PSG Publishing, 1990

Pato MT, Chakravorty S: Discontinuation and long-term treatment of obsessive-compulsive disorder, in Obsessive-Compulsive Disorders: Practical Management. Edited by Jenike MA, Baer L, Minichiello WE. St. Louis, MO, Mosby, 1998

Pato MT, Zohar-Kadouch R, Zohar J, et al: Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. Am J Psychiatry 145:1521–1525, 1988

Pato MT, Hill JL, Murphy DL: A clomipramine dosage reduction study in the case of long-term treatment of obsessive-compulsive disorder patients. Psychopharmacol Bull 26:211–214, 1990

Piccinelli M, Pini S, Bellantuono C, et al: Efficacy of drug treatment in obsessive-compulsive disorder. Br J Psychiatry 166:424–443, 1995

Pigott T, Pato M, Berstein S, et al: Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 47: 926–932, 1990

Price J, Grunhaus LJ: Treatment of clomipramine-induced anorgasmia with yohimbine: a case report. J Clin Psychiatry 51:32–33, 1990

Ravizza L, Barzega G, Bellino S, et al: Drug treatment of obsessive-compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors. Psychopharmacol Bull 32:167–173, 1996

Renynghe de Voxrie GV: Anafranil (G-34586) in obsessive neurosis. Acta Neurol Belg 68:787–792, 1968

Stern RS, Marks IM, Mawson D, et al: Clomipramine and exposure for compulsive rituals, II: plasma levels, side effects and outcome. Br J Psychiatry 136:161–166, 1980

Thorén P, Åsberg M, Cronholm B, et al: Clomipramine treatment of obsessive-compulsive disorder, I: controlled clinical trial. Arch Gen Psychiatry 37:1281–1285, 1980a

Thorén P, Åsberg M, Bertilsson L, et al: Clomipramine treatment of obsessive-compulsive disorder, II: biochemical aspects. Arch Gen Psychiatry 37:1289–1294, 1980b

Träskman L, Åsberg M, Bertilsson L, et al: Plasma levels of chlorimipramine and its desmethyl metabolite during treatment of depression: differential biochemical and clinical effects of two compounds. Clin Pharmacol Ther 26:600–610, 1979

Volavka J, Neziroglu F, Yaryura-Tobias JA: Clomipramine and imipramine in obsessive-compulsive disorder. Psychiatry Res 14:83–91, 1985

Wisner KL, Perel JM, Foglia JP: Serum clomipramine and metabolite levels in four nursing mother–infant pairs. J Clin Psychiatry 56:17–20, 1995

Yaryura-Tobias JA, Neziroglu F, Bergman L: Chlorimipramine for obsessive compulsive neurosis: an organic approach. Curr Ther Res 20:541–547, 1976

Zohar J, Insel TR: Drug treatment of obsessive-compulsive disorder. J Affect Disord 13:193–202, 1987a

Zohar J, Insel TR: Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. Biol Psychiatry 22:667–687, 1987b

Zohar J, Insel TR, Zohar-Kadouch RC, et al: Serotonergic responsivity in obsessive-compulsive disorder: effects of chronic clomipramine treatment. Arch Gen Psychiatry 45:167–172, 1988

Zohar J, Judge R, and the OCD Paroxetine Study Investigators: Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. Br J Psychiatry 169:468–474, 1996

This page intentionally left blank

CHAPTER 3

Fluoxetine

Teresa A. Pigott, M.D.
Sheila Seay, M.A.

Fluoxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI) that is currently approved by the U.S. Food and Drug Administration for the treatment of depression, obsessive-compulsive disorder (OCD), and bulimia nervosa in the United States. More than 19 million patients have been treated with fluoxetine worldwide. As a result, a tremendous amount of information is available about this agent. In this chapter, we present an overview of fluoxetine, highlighting data on acute and long-term treatment as well as efficacy, safety, and tolerability.

Pharmacology

Fluoxetine is a potent and selective inhibitor of the serotonin reuptake pump, and its major metabolite, norfluoxetine, produces similar effects (Lemberger et al. 1985). However, the therapeutic efficacy of fluoxetine is probably dependent on other processes besides its effects on the reuptake pump, because serotonin (5-hydroxytryptamine [5-HT]) neurotransmission remains enhanced even when fluoxetine is administered chronically. Several recent studies have provided some clues that may help to explain why fluoxetine remains effective despite chronic administration. Chronic fluoxetine administration is associated with desensitization of both presynaptic and somatic (inhibitory) autoreceptors (Blier et al. 1988; Welner et al. 1989). Fluoxetine's ability to disrupt the autoreceptors' usual feedback mechanism may be critical in maintaining enhanced 5-HT function during chronic administration. Regardless of the exact mechanism of ac-

tion, fluoxetine's effects on the metabolic pathway of 5-HT are implicated in both its antidepressant and antiobsessive properties (Blier et al. 1988; Welner et al. 1989).

Fluoxetine, in contrast with tricyclic antidepressants (TCAs), is virtually devoid of affinity for neurotransmitter and pharmacologic receptors, including alpha-1, alpha-2, and beta-adrenergic receptors; 5-HT receptors; dopamine receptors; histamine H_1 receptors; muscarinic acetylcholine receptors; opiate receptors; and GABA-benzodiazepine receptors (Wong et al. 1983). Because fluoxetine lacks significant anticholinergic and antihistaminergic effects, side effects such as dry mouth, orthostasis, cardiac conduction delay, or weight gain are absent (Richelson 1994).

Fluoxetine is well absorbed after oral administration, and its absorption appears to be unaffected by food ingestion (Lemberger et al. 1985). Although maximum plasma concentrations of fluoxetine occur approximately 6–8 hours after the initial dose (Bergstrom et al. 1988), both fluoxetine and its active metabolite have relatively extensive half-lives. During chronic administration the average half-life is 2–3 days for fluoxetine and 7–9 days for desmethylfluoxetine (Lemberger et al. 1985). Plasma concentrations are measurable for about 1 week for fluoxetine and about 4 weeks for desmethylfluoxetine after a single 60-mg oral dose. A period of 2–4 weeks is required to obtain steady-state plasma concentrations when fluoxetine is chronically administered (Lemberger et al. 1985).

There are several clinical consequences of fluoxetine's extended half-life. Because plasma concentrations of fluoxetine will not be at steady state for 2–3 weeks, rapid increases in dose are not warranted. In addition, fluoxetine's long half-life suggests minimal clinical effects will be associated with missed doses and that more liberal dose strategies, including less-than-daily dosing, may still be associated with clinical efficacy.

Fluoxetine is extensively metabolized by the liver to an active metabolite, norfluoxetine, as well as other inactive metabolites. During chronic administration, the elimination half-life of fluoxetine (4–6 days) and norfluoxetine (16 days) is relatively slow. In addition, impaired hepatic function can significantly alter fluoxetine's elimination (Lemberger et al. 1985). For example, the elimination half-life of fluoxetine and norfluoxetine was increased 300% and 150%, respectively, in a study of patients with cirrhosis (Lemberger et al. 1985; Stark et al. 1985). Because the inactive metabolites of fluoxetine are eliminated primarily by renal excretion, additional accumulation of fluoxetine may occur in patients with severe renal impairment (Aranoff et al. 1984). Therefore, in patients with impaired hepatic or renal function, a lower dose or less frequent administration of fluoxetine is recommended (Bergstrom et al. 1988; Lemberger et al. 1985; Stark et al. 1985).

Fluoxetine is tightly bound to plasma protein (greater than 90%); thus, coadministration of another highly protein bound medication such as coumadin or digoxin may induce significant shifts in plasma concentrations and subsequent adverse events (Aranoff et al. 1984). Other important drug interactions that may be associated with fluoxetine administration are discussed later in this chapter.

History of Use in Obsessive-Compulsive Disorder

Fluoxetine was first reported to be an effective treatment for OCD in the mid-1980s. Fontaine and Chouinard (1985) reported that five of seven patients with OCD responded to fluoxetine at doses of 60–90 mg/day in an open trial. In a more expanded version of this study, significant improvement in OCD was noted after 9 weeks of fluoxetine treatment (40–80 mg/day) (Fontaine and Chouinard 1986). Subsequent open trials by Jenike et al. (1989), Levine et al. (1989), and Fontaine and Chouinard (1989) conducted in 61, 75, and 50 patients with OCD, respectively, demonstrated that fluoxetine (20–100 mg/day) was effective in reducing OCD symptoms. Maximum reductions in OCD symptoms were noted between 4 and 12 weeks of treatment with fluoxetine in these studies. In a single-blind placebo-controlled study, 10 patients with OCD were judged to be significantly improved after 10 weeks of fluoxetine treatment (Turner et al. 1985a). Significant improvement in OCD symptoms were noted after fluoxetine (mean dose, 75 mg/day) treatment in a subsequent double-blind study conducted in 32 patients with OCD (Pigott et al. 1990).

A randomized, double-blind, placebo-controlled, multicenter study of fluoxetine was subsequently conducted in the United States in patients with OCD ($n=355$). All patients met DSM-III-R (American Psychiatric Press 1987) criteria for OCD and were randomly assigned to one of four 13-week treatment groups (20, 40, or 60 mg/day of fluoxetine or a placebo) after a 1-week single-blind placebo period. The primary efficacy variable was the Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS; Goodman et al. 1989), and efficacy criteria included group changes in the Y-BOCS from baseline to the last value after randomization. Response was defined as a 25% or greater improvement in Y-BOCS score from baseline to the last recorded value (minimum of 7 weeks of study drug administration). All three fluoxetine-treated groups (20, 40, and 60 mg/day) demonstrated significantly greater improvement on the Y-BOCS than the placebo-treated group (Tollefson et al. 1994a). There was a trend for greater efficacy at 60 mg/day of fluoxetine (mean Y-BOCS score reduction, 27%) versus 20 mg/day (mean Y-BOCS score reduction, 20%) or 40 mg/

day (mean Y-BOCS score reduction, 22%). Response rates were 12% for the placebo-treated group, whereas the response rates for the 20 mg, 40 mg, and 60 mg fluoxetine-treated groups were 45%, 41%, and 48%, respectively. Baseline levels of depressive symptoms did not correlate with subsequent changes in the Y-BOCS measurements (Tollefson et al. 1994a).

A second multicenter study was conducted outside of the United States in 222 patients with OCD (Montgomery et al. 1992). The same randomized, parallel cell design was used, but the patients received 8 weeks rather than 13 weeks of study drug (20, 40, or 60 mg/day of fluoxetine or placebo) administration. A significant decrease was found in Y-BOCS measurements from baseline to endpoint in each treatment group, but the decrease was greatest in the group receiving 60 mg of fluoxetine. Significantly more responders were found in the groups receiving 40 mg (20%) and 60 mg (22%) of fluoxetine than in the group receiving placebo (12%), but the group receiving 20 mg fluoxetine did not differ from placebo.

Although the safety and efficacy of fluoxetine in children and adolescents has not been established, several studies have supported its efficacy (Geller et al. 1995; Piacentini et al. 1992; Riddle et al. 1988, 1990).

Few head-to-head comparisons have been made in the literature between the antiobsessional agents, and those that do exist usually involve comparison with clomipramine. In one such study, 32 patients meeting DSM-III-R criteria for OCD were enrolled in a controlled crossover trial in which clomipramine was compared with fluoxetine in the treatment of OCD. The patients consisted of two cohorts: a randomized group and a nonrandomized group (Pigott et al. 1990). Patients in the randomized group entered a 2-week placebo-controlled washout period followed by a 24-week random-assignment crossover portion that consisted of two 10-week periods of active drug treatment separated by a 4-week interval of medication taper and placebo substitution. Of 11 randomized patients with OCD, 10 completed 10 weeks of clomipramine treatment and 10 weeks of treatment with fluoxetine. Both the clomipramine (mean dose, 75 mg/day) and fluoxetine (mean dose, 210 mg/day) treatments were associated with similar and significant improvement in OCD symptoms. Patients reported a consistently higher incidence of side effects with clomipramine than with fluoxetine treatment. Interestingly, significant increases were found in OCD and depressive ratings during the placebo substitution period between the active drug treatments. Both medications were also associated with substantial lags in therapeutic efficacy (6–10 weeks), despite previous substantial improvement during the first medication treatment period.

Another part of this study (Pigott et al. 1990) included a cohort of patients with OCD (n=21) who had originally been stabilized on clomi-

pramine and who had voluntarily elected to be "crossed over" to fluoxetine. In a double-blind fashion, they received the same dose of clomipramine for 2 weeks followed by a 1-week placebo substitution period and then 10 weeks of fluoxetine treatment. Of the 21 patients, 20 completed 10 weeks of treatment with fluoxetine (80 mg/day). After 10 weeks of fluoxetine treatment, 85% of the patients received a Y-BOCS score that was similar to the score they had received during clomipramine treatment. Fewer side effects were reported with fluoxetine than with clomipramine. Lopez-Ibor et al. (1996), in an 8-week double-blind controlled study, also found that overall safety and tolerability were slightly better for fluoxetine than clomipramine (Lopez-Ibor et al. 1996).

To date, direct comparisons have suggested that the SSRIs have equivalent efficacy to clomipramine in the treatment of patients with OCD (Freeman et al. 1994; Jenike 1990; Piccinelli 1995; Pigott et al. 1990). These studies have also supported the superior tolerability of SSRIs, especially their absence of anticholinergic side effects, in comparison with clomipramine. Although further studies are needed, the available data from direct comparison studies suggest that fluoxetine and clomipramine are similarly effective in patients with OCD and that fluoxetine may be associated with fewer side effects than clomipramine.

Despite data supporting similar efficacy for clomipramine and fluoxetine in direct comparative trials, OCD sequential trials are still necessary to determine the best agent for the individual patient. A retrospective assessment of cross-response between clomipramine and fluoxetine treatment in 81 patients with OCD (Pigott et al. 1993, 1996) suggested that between 20% and 25% of patients did not have a substantial reduction (≤25% change from baseline) in OCD symptoms during treatment with either clomipramine or fluoxetine. In addition, a positive response to clomipramine treatment (>25% reduction) predicted a positive response to fluoxetine in 65% of patients with OCD and a positive response to fluoxetine (≥25% reduction) treatment predicted a positive response to clomipramine in 80% of the patients with OCD. Failure to respond to clomipramine (≤25% reduction) treatment was associated with a relatively scant probability of a positive response to fluoxetine treatment (20% of patients). These results suggest a considerable overlap in response between fluoxetine and clomipramine treatment.

Dosing

The optimal antiobsessive dose range of fluoxetine remains controversial. Doses between 20–80 mg/day of fluoxetine have been used in both open

and controlled studies in patients with OCD. As noted earlier, two multicenter fixed-dose studies in OCD have been performed, one in the United States and one in Europe. In the U.S. study performed by Tollefson et al. (1994a), 20, 40, and 60 mg/day of fluoxetine were all effective, and there was a trend suggesting greater efficacy at 60 mg/day in comparison to the lower fluoxetine doses. In the European study performed by Montgomery et al. (1992), only 40 and 60 mg were found to be different from placebo.

Tollefson et al. (1994a) found that higher plasma concentrations were associated with greater improvement in OCD symptoms. Unfortunately, plasma fluoxetine concentrations failed to discriminate between Y-BOCS responders and nonresponders. Therefore, routine monitoring of plasma fluoxetine concentrations is not recommended at this time.

Because partial response is generally the rule in OCD pharmacotherapy, potential adjuvant or augmentation agents are commonly prescribed in OCD patients. Various medications have been reported to "successfully" augment clomipramine, fluoxetine, and other SSRIs in the treatment of patients with OCD (Jenike 1992; Jenike and Rauch 1994). Unfortunately, most of the controlled trials of adjuvant agents have failed to demonstrate additional antiobsessive benefit.

Further improvement in OCD symptoms was reported in two open-label studies when buspirone was added to fluoxetine therapy (Jenike et al. 1991; Markovitz et al. 1990). However, a controlled trial of adjuvant buspirone in fluoxetine-treated patients showed no benefit (Grady et al. 1993). A double-blind crossover comparison of adjuvant clonazepam versus placebo administration revealed significant additional reductions in anxiety symptoms, and one of three OCD scales exhibited evidence of significant additional reductions in OCD symptoms (Pigott et al. 1992). Although promising, further studies are warranted before clonazepam augmentation can be established as an efficacious treatment (see Chapter 12 for further discussion).

Side Effects

Fluoxetine is well tolerated in most patients. Side effects that occurred significantly more with fluoxetine treatment than with placebo treatment were vasodilatation, dry mouth, nausea, decreased libido, somnolence, tremor, yawning, and sweating. There were relatively few discontinuations because of adverse events (approximately 10%) during the study by Tollefson et al. (1994b).

Patients should be instructed that anxiety and nervousness may occur with fluoxetine treatment. In fact, anxiety, nervousness, and insomnia

were the most common events associated with discontinuation in depressed patients treated with fluoxetine, although it is important to note that these events only accounted for 5% of the discontinuations. In the OCD trials, anxiety and rash were the most common events associated with discontinuation, but only 2% of the patients discontinued because of these adverse events. Data from the Tollefson et al. (1994b) study in patients with OCD demonstrated that anxiety, nervousness, or insomnia was unlikely to emerge or worsen during long-term treatment with fluoxetine. Therefore, anxiety and insomnia appear to be initial side effects associated with fluoxetine treatment that may abate or resolve during long-term treatment.

Anorexia is common during fluoxetine therapy and can contribute to weight loss. Usually, the weight loss is relatively mild, but 10% of patients in the depression (Stokes 1993) and OCD trials (Tollefson 1994a) experienced a weight loss of greater than 5% of their body weight during fluoxetine treatment. Consequently, fluoxetine should be used with caution in patients who are seriously underweight.

There was a very low incidence (<1.0%) of weight gain reported during fluoxetine therapy. In fact, weight loss was reported in 5% of the patients with OCD treated with fluoxetine. This finding is in marked contrast to the findings with TCAs, which are often implicated in weight gain (Berken et al. 1984). More recent reports of weight gain, however, have been reported when patients are treated chronically with fluoxetine. In a large-sample postmarketing study (Fisher et al. 1995), patients treated with fluoxetine reported an increased frequency of weight gain; Orzack et al. (1990) found that depressed patients whose baseline weight was considered normal gained an average of 4.4 lb over a 4-month period of fluoxetine treatment.

Antidepressants have been implicated in the activation of hypomania or mania in patients with mood disorders. There have been several reports of fluoxetine inducing mania in susceptible patients (Lebegue 1987; Settle and Settle 1984; Turner et al. 1985b); however, the incidence of mania or hypomania (estimated at 1%) in patients treated with fluoxetine is similar to that previously reported with other antidepressants. The rate of seizure induction with fluoxetine (Wernicke 1985) is comparable with that of other marketed antidepressants (approximately 0.2%).

Fluoxetine has negligible cardiac effects (Fisch 1985). However, it has not been systematically evaluated nor is it recommended in patients with a recent history of myocardial infarction or unstable heart disease (Spier and Frontera 1991). Fluoxetine has been associated with hypoglycemia, and rebound hyperglycemia has been reported after fluoxetine discontin-

uation. Therefore, blood sugar should be closely monitored, and insulin and/or oral hypoglycemic therapy may require dose adjustment when patients with diabetes are receiving fluoxetine therapy.

Fluoxetine, as with other SSRIs, is contraindicated in patients currently receiving a monoamine oxidase inhibitor (MAOI) or within 14 days of stopping an MAOI because of serious and at times fatal reactions (Sternbach 1988). It is recommended that most SSRIs be discontinued for 14 days before starting an MAOI. However, because of the long half-life of fluoxetine, a 5-week washout period is recommended before commencing MAOI treatment (Feighner et al. 1990; Sternbach 1988).

There have been a few cases of serious systemic events in patients who were continued on fluoxetine after developing a rash. Rare cases of anaphylactic reactions such as bronchospasm, angioedema, and urticaria have also been associated with fluoxetine administration. Although a specific underlying immunologic basis for these reactions has not been determined, current recommendations suggest that fluoxetine should be discontinued if a rash or other possible allergic manifestation occurs during fluoxetine administration (Stokes 1993).

Fluoxetine has also been found to be relatively safe in overdose. Deaths attributed to fluoxetine overdose have been extremely rare and most have been associated with the ingestion of multiple medications (Wernicke 1985). There has been a report of seizures in a patient who ingested 3000 mg of fluoxetine, but there were no further adverse events and the patient had a full recovery (Stokes 1993). The most prominent symptoms reported after fluoxetine overdose are nausea, vomiting, agitation, restlessness, and hypomania (Stokes 1993). There is no specific antidote for fluoxetine overdose, so general supportive measures are recommended for suspected overdose.

Some attention has been focused on the hepatic cytochrome P450 system, which is composed of more than 30 distinct isoenzymes. Fluoxetine appears to significantly inhibit the P450 isoenzymes 2C, 2D6, and 3A4 (Crewe et al. 1992; DeVane 1994; Gelenberg 1995; Pollack 1994). Numerous medications are metabolized by these isoenzymes. Coadministration of fluoxetine with these medications may result in significant changes in metabolism and possible important drug interactions. The TCAs, neuroleptics, type IC antiarrhythmics, codeine, and beta-blockers are all metabolized by the 2D6 isoenzyme (DeVane 1994; Gelenberg 1995; Pollack 1994). Because these medications have a narrow therapeutic index, drug interactions can be particularly important. The degree of cytochrome P450 2D6 inhibition, at least as measured in vitro, suggests that paroxetine is the most potent inhibitor followed by fluoxetine, norfluoxetine, sertraline,

and fluvoxamine (Crewe et al. 1992; see Chapter 1 for details). Most of the SSRIs have some inhibitory effects on certain P450 enzymes, particularly 1A2, 2C, 2D6, and 3A4. Fluoxetine has marked inhibition at 2D6.

Several reports have implicated fluoxetine as the cause of increased plasma TCA concentrations (Aranow et al. 1989; Downs et al. 1989; Vaughan 1989); this interaction can occur when two antidepressants are used concurrently or when a patient is being transferred from one antidepressant to fluoxetine. Both increases and decreases in lithium have been reported with coadministered fluoxetine; thus, monitoring of serum lithium levels is recommended. Fluoxetine may reduce the clearance of diazepam (Rowe et al. 1985), although the clinical significance, if any, of this interaction is unknown.

Treatment Duration and Discontinuation

Several open studies have also supported the continued maintenance of efficacy for fluoxetine when administered long term in patients with OCD (Frenkel et al. 1990; Levine et al. 1989). In addition, patients who were enrolled in the Tollefson et al. (1994b) controlled, multicenter trial of fluoxetine in OCD and completed the acute phase (13 weeks) were eligible to enter a double-blind extension phase. Most of the 76 patients with OCD who completed and responded during the acute phase maintained symptom improvement during the 24-week continuation phase. Patients who were judged to be nonresponders after the core study were also eligible for entry into an open-label extension study, and over one-half of the 198 nonresponders had a 25%–50% reduction in their Y-BOCS score during the 24-week open-label extension phase. Adverse effects during the long-term extension phase were rarely associated with discontinuation and were similar to those noted during the acute treatment phase.

In comparison with the Y-BOCS scores obtained at the end of the core treatment phase, no significant additional reductions were found in the Y-BOCS scores of the patients who received placebo, 20 mg/day of fluoxetine, or 40 mg/day of fluoxetine during the double-blind extension phase. The group that received 60 mg/day of fluoxetine, however, showed significant additional improvement on Y-BOCS scores at the end of the extension phase (Tollefson et al. 1994b). These results suggest that fluoxetine is safe and effective for the long-term treatment of OCD. Moreover, there are at least preliminary data suggesting that higher doses (60 mg/day) of fluoxetine may be associated with more OCD symptom reduction in the long-term treatment of OCD.

A large discontinuation study with fluoxetine has been conducted, but findings are not yet available. The small studies that have been done—Pigott et al. 1990, Dominguez 1992—appear to indicate that relapse often occurs when medication is discontinued. However, because of fluoxetine's long half-life, this relapse may take several months or even half a year before it will become apparent.

Summary

Both open and controlled trials of fluoxetine have confirmed its efficacy in the treatment of OCD. Similar to other antiobsessive agents, fluoxetine treatment is associated with only partial improvement (40%–60%) in OCD symptoms. As with other antiobsessionals, an adequate trial of at least 8–12 weeks is necessary to fully evaluate antiobsessive efficacy, and continued efficacy appears to require continuation of medication.

Preliminary data suggest that most patients with OCD who respond to clomipramine will also respond to fluoxetine therapy. Fluoxetine has relatively few side effects in comparison with clomipramine and represents a welcome alternative to clomipramine therapy for patients with OCD because of its superior side effect profile, absence of associated weight gain, and safety in overdose.

Case Examples

Case 1

In contrast to the smiling, 6-month-old infant securely cradled in her lap, Mary looked haggard as she sat beside her beleaguered husband. As soon as the psychiatrist appeared, she vehemently exclaimed, "You've got to help me! I know I'll hurt my child!" Absently rocking her infant, she continued the self recriminations for several minutes, "I haven't slept for days...My husband doesn't understand how careful you must be as a mother." Subdued by repeated reassurances, Mary gradually stopped her diatribe and began responding to questions.

At the time of this visit Mary was 28 years old, and this child was her first. Her pregnancy had been complicated by a severe depressive episode, but she had responded well to antidepressant medication, which was successfully discontinued prior to the birth of her daughter. Initially, Mary seemed to revel in her new role as a mother. Then, at 3 months postpartum, recurrent worries that something terrible would happen to her daughter emerged. At first Mary was able to discount them as "little normal doubts about being a good mother." However, the worries rapidly intensified and elicited convoluted checking rituals. She also developed

endless cleaning rituals to prevent the "transfer of germs" to her daughter. Despite these safety measures, Mary became more convinced that she was neglecting her child. She began doubting every one of her actions and required constant reassurance from her husband. She had not slept in 3 days because she could not be "absolutely sure" that she had not harmed the baby.

Mary had not had other depressive episodes besides that which occurred during her pregnancy. However, she described at least one previous episode of "preoccupation." During her adolescence, she recalled being excessively concerned about "heaven and hell"; in fact, she kept a journal of her "good versus bad deeds" for several years, but these concerns gradually resolved. Mary also described "nervous habits" such as a compulsion to repeat specific prayers if she sees "66" on a sign or license plate and a need to check that the doors are locked and the lights are off "three times" before leaving the house for "as long as I can remember."

Mary's obsessions about harming her daughter, pathologic doubt, and checking and cleaning rituals supported a diagnosis of OCD. She was subsequently prescribed clomipramine for her symptoms. After several months, she reported that her "preoccupation" had substantially decreased and her checking and cleaning rituals were also diminished. Despite her undeniable improvement, she remained discouraged. Troubled by weight gain, hand tremor, and sedation, Mary was adamant about changing medication. She was subsequently placed on fluoxetine therapy. Within 8 weeks of beginning fluoxetine at 40 mg/day, there was considerable progress. After 6 months on fluoxetine (80 mg/day), Mary was approximately 80% improved. She denied significant side effects including weight gain and reported, "I finally think I am myself again."

Mary eventually achieved a good treatment response, but it was a lengthy and often frustrating process. Despite data supporting similar efficacy for clomipramine and fluoxetine in direct comparative trials in OCD, sequential trials are still necessary to determine the best agent for the individual OCD patient.

Case 2

Joanne, a 48-year-old divorced woman, complained of an approximately 12-year history of OCD. At the time of her initial visit, she complained of various compulsive behaviors, most notably, repeated checking, hoarding of trash, and obsessions concerning fears of contamination, with subsequent rituals. She was seriously incapacitated in her job as a secretary because of pervasive obsessive-compulsive symptoms, such as repeatedly checking her typing and spelling for errors and being unable to perform any task at work without first wiping her glasses a circumscribed number of times to "remove dirt." She estimated that she spent approximately four times as long as other coworkers on letters because she would have to check each line she typed at least five times "for correctness." She had great difficulty sorting through the mail, because she was often unable to throw away any paper: "I am always afraid that I will throw some-

thing away that will be very important or that letters might contain money or checks that I missed." She noted that she often stayed hours longer than her coworkers because she would feel obliged to check and recheck everything that she had typed that day and would also feel compelled to recheck the trash for "important items." She readily noted that these behaviors were irrational, but felt unable to resist them without overwhelming anxiety.

Joanne's behaviors were not confined to her workplace; she described a similar world of private torment at home. She was very concerned with germs and contamination at her home, yet paradoxically was forced to live in relatively squalid surroundings because she feared contamination by washing dirty clothes or dishes and because she was hoarding trash. In fact, her house was filled with overflowing trash bags containing papers and other items that she had been unable to throw away. Interestingly, she related that her mother had similar behaviors, although her mother refused psychiatric treatment. Joanne recalled that her family moved to another house when she was an adolescent because her mother had collected "so many bags of trash and paper that there was no room for us to live there. "

Joanne had been receiving imipramine and perphenazine for several years before her entry into protocol. She felt that these medications were helpful in treating some of her depressive symptoms and anxiety, but denied any demonstrable antiobsessive effects. After 5 months of clomipramine treatment, her scores on the rating scales indicated that her OCD symptoms were reduced by approximately 60% from her pretreatment baseline ratings. She was spending much less time checking and proofreading at work and had begun to leave work at the same time as her coworkers. She continued to be fairly symptomatic at home, although she was able to do several loads of laundry for the first time in 6 months. She was also able to throw away approximately 30% of the trash bags in her home—the first time in 10 years that she had been able to throw anything away at home. She did have some side effects from the clomipramine, most notably dry mouth, constipation, and a significant decrease in libido. Most troubling to her, however, was the presence of a significant fine tremor in her hands that occurred daily and was fairly disruptive at her workplace.

Because of this persistent tremor it was mutually decided to attempt to taper Joanne off clomipramine and institute a trial of fluoxetine. She was stabilized on a daily dose of fluoxetine at 80 mg/day administered over a 6-week period. After approximately 8 weeks of treatment, she reported that fluoxetine was also significantly effective in reducing her OCD symptoms. By 6 months of fluoxetine treatment, her OCD symptoms were reduced by approximately 60%–70% from her pretreatment baseline ratings. She reduced her cleaning compulsions at work and was able to further reduce the amount of trash bags in her home. She did not experience any substantial side effects from the fluoxetine except for some complaints of vague lethargy. Joanne reported an antidepressant and antianxiety response comparable to her response on clomipramine.

She has remained on fluoxetine at 80 mg/day for approximately 9 months; several attempts to decrease her dose resulted in an exacerbation of her OCD symptoms and reemergence of depressive affect.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised. Washington, DC, American Psychiatric Association, 1987

Aranoff G, Bergstrom R, Pottrat S, et al: Fluoxetine kinetics and protein binding in normal and impaired renal function. Clin Pharmacol Ther 36:138–144, 1984

Aranow R, Hudson J, Pope H, et al: Elevated antidepressant plasma levels after addition of fluoxetine. Am J Psychiatry 146:911–913, 1989

Bergstrom R, Lemberger L, Farid N, et al: Clinical pharmacology and pharmacokinetics of fluoxetine. Br J Psychiatry 153:47–53, 1988

Berken G, Weinstein D , Stern W: Weight gain: a side effect of tricyclic antidepressants. J Affect Disord 7:133–138, 1984

Blier P, Chaput Y, DeMontigny C: Long-term 5-HT reuptake blockade, but not monoamine oxidase inhibition, decreases the function of terminal 5-HT autoreceptors: an electrophysiological study in the rat brain. Archives of Pharmacology 337:246–254, 1988

Crewe H, Lennard M, Tucker G, et al: the effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 activity in human liver microsomes. Br J Clin Pharmacol 34:262–265, 1992

DeVane C: Pharmacogenetics and drug metabolism of newer antidepressant agents. J Clin Psychiatry 55:38–45, 1994

Dominguez R: Serotonergic antidepressants and their efficacy in OCD. J Clin Psychiatry 53:56–59, 1992

Downs J, Downs A, Rosenthal T, et al: Increased plasma tricyclic antidepressant concentrations in two patients concurrently treated with fluoxetine. J Clin Psychiatry 50:226–227, 1989

Feighner J, Boyer W, Tyler D, et al: Adverse consequences of fluoxetine–MAOI combination therapy. J Clin Psychiatry 51:222–225, 1990

Fisch C: Effect of fluoxetine on the electrocardiogram. J Clin Psychiatry 46:42–44, 1985

Fisher S, Kent TA, Bryant SG: Postmarketing surveillance by patient self-monitoring: preliminary data for sertraline versus fluxoetine. J Clin Psychiatry 56:288–296, 1995

Fontaine R, Chouinard G: Fluoxetine in the treatment of OCD. Prog Neuropsychopharmacol 9:605–608, 1985

Fontaine R, Chouinard G: An open clinical trial of fluoxetine in the treatment of OCD. J Clin Psychopharmacol 6:98–101, 1986

Fontaine R, Chouinard G: Fluoxetine in the long-term maintenance treatment of OCD. Psychiatr Ann 19:88–91, 1989

Freeman C, Trimble M, Deakin J, et al: Fluvoxamine versus clomipramine in the treatment of OCD: a multi-center, randomized, double-blind, parallel group comparison. J Clin Psychiatry 55:301–305, 1994

Frenkel A, Rosenthal J, Nezriglu F, et al: Efficacy of long-term treatment of OCD. Mt Sinai J Med 57:23–32, 1990

Gelenberg A: The P450 family. Biol Ther Psychiatry 18:30, 1995

Geller D, Biederman J, Reed E, et al: Similarities in response to fluoxetine in the treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 34:36–44, 1995

Goodman W, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive-Compulsive Scale. Arch Gen Psychiatry 46:36–44, 1989

Grady TA, Pigott TA, L'Heureux F, et al: A double-blind study of adjuvant buspirone hydrochloride in fluoxetine-treated patients with OCD. Am J Psychiatry 150:819–821, 1993

Jenike M: Pharmacologic treatment of OCD. Psychiatr Clin North Am 15:895–919, 1992

Jenike M, Rauch S: Managing the patient with treatment-resistant OCD: current strategies. J Clin Psychiatry 55:11–17, 1994

Jenike M, Buttolph L, Baer L, et al: Fluoxetine in OCD: a positive open trial. Am J Psychiatry 146:909–911, 1989

Jenike MA, Baer L, Greist JH: Clomipramine versus fluoxetine in OCD: a retrospective comparison of side effects and efficacy. J Clin Psychopharmacol 10:122–124, 1990

Jenike M, Baer L, Buttolph L, et al: Buspirone augmentation of fluoxetine in patients with OCD. J Clin Psychiatry 1:13–14, 1991

Lebegue B: Mania precipitated by fluoxetine (letter). Am J Psychiatry 144:1620, 1987

Lemberger L, Bergstrom R, Wolen R, et al: Fluoxetine: clinical pharmacology and physiologic disposition. J Clin Psychiatry 46:14–19, 1985

Levine L, Enas G, Thompson W, et al: Use of fluoxetine, a selective serotonin-reuptake inhibitor, in the treatment of obesity: a dose response study. Int J Obes 13:635–645, 1989

Lopez-Ibor JJ, Saiz J, Cottraux J, et al: Double blind comparison of fluoxetine versus clomipramine in the treatment of obsessive compulsive disorder. Eur Neuropsychopharmacol 6:111–118, 1996

Markovitz P, Stagno S, Calabrese J: Buspirone treatment of fluoxetine in OCD. Am J Psychiatry 147:798-800, 1990

Montgomery S, Bullock T, Fineberg N, et al: Selective serotonin reuptake inhibitors in OCD. Clin Neuropharmacol 15:255–256, 1992

Orzack MH, Friedman LM, Marby DW: Weight changes on fluoxetine as a function of baseline weight in depressed outpatients. Psychopharmacol Bull 26:327–330, 1990

Piacentini J, Jaffer M, Gitow A, et al: Psychopharmacologic treatment of child and adolescent obsessive-compulsive disorder. Psychiatr Clin North Am 15:87–107, 1992

Piccinelli M, Pini S, Bellantuono C, et al: Efficacy of drug treatment in OCD: a meta-analytic review. Br J Psychiatry 166:424–443, 1995

Pigott T: OCD: where the serotonin-selectivity story begins. J Clin Psychiatry 57(suppl):11–20, 1996

Pigott TA, Pato MT, Bernstein SE, et al: Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 47:1543–1550, 1990

Pigott T, L'Heureux F, Bernstein S, et al: A controlled trial of adjuvant clonazepam in clomipramine and fluoxetine treated patients with OCD. APA Annual Meeting Abstracts NR 144:82, 1992

Pigott T, L'Heureux F, Murphy D: Pharmacological approaches to treatment-resistant OCD patients. 1st International OCD Conference Abstracts, Isle of Capri, 1993, pp 123–125

Pollack B: Recent developments in drug metabolism of relevance to psychiatrists. Harv Rev Psychiatry 2:204–213, 1994

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

Riddle M, Leckman J, Hardin M, et al: Fluoxetine treatment of obsessions and compulsions in patients with Tourette's syndrome. Am J Psychiatry 145:1173–1174, 1988

Riddle M, Hardin M, King R, et al: Fluoxetine treatment of children and adolescents with Tourette's and OCD: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry 29:45, 1990

Rowe H, Lemberger L, Bergstrom R, et al: The effect of co-administration of fluoxetine and diazepam on psychomotor and physiologic responses. Pharmacologist 27:196, 1985

Settle E, Settle G: A case of mania associated with fluoxetine. Am J Psychiatry 141:280–281, 1984

Stark P, Fuller R, Wong D: The pharmacological profile of fluoxetine. J Clin Psychiatry 46:7–13, 1985

Sternbach H: Danger of MAOI therapy after fluoxetine withdrawal. Lancet ii:850–851, 1988

Stokes P: Fluoxetine: a five year review. Clin Ther 15:216–243, 1993

Tollefson G, Birkett M, Koran L et al: Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. J Clin Psychiatry 55:69–78, 1994a

Tollefson G, Rampey A, Potvin J, et al: A multi-center investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 51:559–567, 1994b

Turner S, Jacob R, Beidel D, et al: Fluoxetine treatment of OCD. J Clin Psychopharmacol 5:207–212, 1985a

Turner S, Jacob R, Beidel D, et al: A second case of mania associated with fluoxetine (letter). Am J Psychiatry 142:274–275, 1985b

Vaughn D: Interactions of fluoxetine with tricyclic antidepressants. Am J Psychiatry 145:1478, 1989

Welner S, DeMontigny C, Desroches J, et al: Autoradiographic quantification of serotonin 1A receptors in rat brain following antidepressant drug treatment. Synapse 4:347–352, 1989

Wernicke J: The side effect profile and safety of fluoxetine. J Clin Psychiatry 46:59–67, 1985

Wong D, Bymaster F, Reid L, et al: Fluoxetine and two other serotonin uptake inhibitors without affinity for neuronal receptors. Biochem Pharmacol 32:1287–1293, 1983

CHAPTER 4

Fluvoxamine

Wayne K. Goodman, M.D.
Lawrence H. Price, M.D.
Dan J. Stein, M.B.

Efficacy studies and the weight of clinical experience suggest that the potent inhibitors of serotonin (5-hydroxytryptamine [5-HT]) reuptake should be the mainstay of drug treatment for obsessive-compulsive disorder (OCD). Several studies have shown that the potent serotonin reuptake inhibitor (SRI) clomipramine is more effective than placebo (DeVeaugh-Geiss et al. 1989; Montgomery 1980), other tricyclic antidepressants (TCAs) that are not so selective for 5-HT (Ananth et al. 1981; Leonard et al. 1988), and monoamine oxidase inhibitors (DeVeaugh-Geiss et al. 1989).

Together, these drug response data support the hypothesis that the serotonin reuptake properties of an antidepressant drug are relevant to its efficacy as an anti-obsessive-compulsive agent. Nevertheless, because clomipramine also binds to muscarinic, histaminergic, alpha-adrenergic receptors (McTavish and Benfield 1990), it may have dopamine D2 receptor binding (Austin et al. 1991), and its primary metabolite (desmethylclomipramine) inhibits noradrenaline reuptake (Träskman et al. 1979), it is unclear whether its efficacy was related solely to its effects on serotonin transport.

In recent years, trials have confirmed the efficacy of the selective serotonin reuptake inhibitors (SSRIs) in the treatment of OCD. Unlike clomipramine, these medications do not lose their selectivity for blocking serotonin reuptake in vivo (Fuller and Wong 1987). Also, in contrast with TCAs, the SSRIs lack significant affinity for cholinergic, alpha-adrenergic, and histaminic receptors; this, presumably, explains the relatively lower

incidence of anticholinergic and cardiovascular side effects and sedation with the SSRIs. In this chapter we focus on the use of fluvoxamine in OCD.

History of Use in Obsessive-Compulsive Disorder

Fluvoxamine was originally developed in Europe as an antidepressant. In most published double-blind trials in patients with depression, fluvoxamine has been shown to be significantly better than placebo and to be equal in efficacy to both TCAs and other SSRIs. Studies were also conducted with fluvoxamine in patients with OCD on the basis of its serotonin reuptake–blocking properties. The results of these studies led to U.S. Food and Drug Administration (FDA) approval for fluvoxamine in the treatment of OCD. Fluvoxamine was the first non-TCA to receive this approval.

Preliminary evidence for the antiobsessional effect of fluvoxamine dates back to small-scale trials conducted in the late 1980s. In a single-blind study of fluvoxamine (up to 300 mg/day), 6 of 10 inpatients with severe OCD were considered "responders" on the basis of a clinical rating of "much improved" or "very much improved" on a modified version of the Clinical Global Impression (CGI) Improvement scale (McNair 1974; Price et al. 1987). Most of the patients in this study were previously refractory to adequate trials of other antidepressant medications.

These encouraging findings were further supported by two double-blind studies comparing fluvoxamine with placebo. In a study conducted by Perse et al. (1988), 16 patients with OCD completed a 20-week randomized crossover trial that compared fluvoxamine with placebo. Treatment was administered over two 8-week periods using a fluvoxamine dose of 300 mg/day, with a 2-week single-blind placebo period before the start of treatment and between treatment periods. Fluvoxamine was found to be effective on several different measures of OCD. For example, marked clinical improvement was associated only with the active drug phase, with 9 of 16 (56%) patients classified as "better" during fluvoxamine treatment.

Similarly good results were obtained in a larger placebo-controlled study conducted by Goodman et al. (1989) in which 42 patients were randomly assigned to 6 or 8 weeks of treatment with fluvoxamine (up to 300 mg/day) or placebo. Approximately 50% of patients in each group had coexisting major depression. Significant and sustained separation between fluvoxamine and placebo was noted on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score from as early as week 2 onward. No significant changes were recorded in the mean Y-BOCS score of the placebo group at any time. Analysis of response category data showed

that fluvoxamine was effective in reducing the severity of obsessive-compulsive symptoms. In the fluvoxamine group, 9 of 21 patients were responders (as defined previously according to CGI scores), whereas none of the 21 patients in the placebo group were rated as responders. This remarkably low placebo response rate seemed characteristic of patients with OCD in early clinical trials (Mavissakalian et al. 1990) and contrasted with a much higher placebo rate typically seen in drug trials in depressed outpatients. Fluvoxamine was equally effective in patients with and without secondary depression, and the response did not correlate with the severity of baseline depression. A similar lack of correlation between baseline depression scores and improvement on the Y-BOCS score has also been noted in other clinical trials (Goodman et al. 1989, 1990; Perse et al. 1988). Thus, it appears that the anti-obsessive-compulsive effects of fluvoxamine can be differentiated from its antidepressant action.

The most convincing evidence for the therapeutic efficacy of fluvoxamine in OCD was obtained from two pivotal multicenter, double-blind, placebo-controlled, parallel-group studies performed in the United States (Goodman et al. 1996; Greist et al. 1995). Each study collected data from 160 outpatients with OCD who were recruited in four study centers. The study protocols were of an identical design, thus permitting pooling of data (Rasmussen et al., in press). Fluvoxamine was flexibly titrated to 100–300 mg/day (twice-daily regimen) with a 10-week treatment duration. Patients had to meet the DSM-III-R (American Psychiatric Association 1987) criteria for OCD of at least 12 months' duration and had to have a minimum score of 7 on the National Institute of Mental Health Obsessive-Compulsive (NIMH-OC; Insel et al. 1983) scale plus a maximum score of 19 on the 17-item Hamilton Depression Scale (Ham-D; Hamilton 1960). Thus, the sample consisted of severely ill patients with primary OCD. Assessments were made every 2 weeks, commencing at baseline using the Y-BOCS and NIMH-OC scale as the primary ratings and the CGI scale as a secondary rating. Responders were defined as patients who were "much" or "very much" improved on the CGI scale.

No significant differences were found between the fluvoxamine and placebo groups in terms of baseline demographics and clinical characteristics. A total of 121 (76%) fluvoxamine-treated patients and 139 (87%) placebo-treated patients completed the study. The mean dose of fluvoxamine at week 10 was 249 mg/day. There was a significantly greater mean improvement in the fluvoxamine group than in the placebo group as assessed by both the Y-BOCS and NIMH-OC scale. By the end of week 10, the Y-BOCS score had fallen by 23% in the fluvoxamine group compared with 7% in the placebo group; a statistically significant ($P<0.001$) differ-

ence between the two groups was first observed at week 6. Response was achieved in 43% of patients in the fluvoxamine group compared with 11% in the placebo group.

Comparative Efficacy

The role of serotonin in the etiology and treatment of OCD was well demonstrated in a study comparing fluvoxamine with the noradrenaline reuptake inhibitor desipramine (Goodman et al. 1990). In this double-blind trial, 21 patients received fluvoxamine and 19 received desipramine (both at dosages of 100–300 mg/day) for 8 weeks. In terms of change in Y-BOCS total score over time, desipramine had no therapeutic effect on obsessive-compulsive features, whereas fluvoxamine showed a significant improvement relative to baseline from week 3 onward and significant superiority over desipramine at weeks 7 and 8 ($P< 0.05$). Also, significantly more patients responded ("much" or "very much" improved on the CGI Improvement scale) to fluvoxamine than to desipramine (11/21 versus 2/19; $P<0.01$).

A more robust comparator, however, is the SRI clomipramine. A double-blind, multicenter study conducted in the United Kingdom compared fluvoxamine with clomipramine in 66 patients with OCD (Freeman et al. 1994). Doses of each medication were titrated between 100–250 mg/day according to clinical response and administered over 10 weeks. The functioning of these patients improved during treatment, and the response was similar with fluvoxamine and clomipramine. Y-BOCS scores were reduced by 8.6 (33%) and 7.8 (31%) points with fluvoxamine and clomipramine, respectively. The two treatments also had similar effects in terms of the proportion of responders ("much" or "very much" improved on the CGI Improvement scale [59% with fluvoxamine and 53% with clomipramine]) and the reduction in NIMH-OC scores (-2.6 points with fluvoxamine and -2.5 points with clomipramine) at the end of the study. The only significant difference between treatments was a longer obsession-free interval on the Y-BOCS with fluvoxamine than with clomipramine in patients with a disease duration of more than 12 months ($P=0.026$). As expected, adverse event profiles of the agents differed; fluvoxamine was associated with fewer anticholinergic side effects and less sexual dysfunction than clomipramine, but with more reports of headache and insomnia.

A similar double-blind multicenter study was performed in the United States by Koran et al. (1996) in which 79 patients with OCD were treated with fluvoxamine (100–300 mg/day) or clomipramine (100–250 mg/day) for 10 weeks. Both treatments again resulted in a steady improvement throughout the study, with no significant differences between

them at any time. At the end of the study, 56% of patients had responded to fluvoxamine and 54% to clomipramine (defined as a 25% or more decrease in total Y-BOCS score). The mean reductions in Y-BOCS scores were 7.7 (30%) and 7.3 (30%) points with fluvoxamine and clomipramine, respectively.

These findings have been confirmed in a larger, more recent 10-week double-blind study carried out in 227 patients with OCD (Mundo et al., in press) Again, both fluvoxamine (150–300 mg/day) and clomipramine (150–300 mg/day) were equally effective, with no significant differences between them at any time. The mean Y-BOCS scores fell by 12.2 points in the fluvoxamine group and 12.0 points in the clomipramine group at the end of the study. Similarly, the percentage of patients who responded to treatment (defined as a 35% or more decrease in total Y-BOCS score) was 62% with fluvoxamine and 65% with clomipramine.

Although an early response to treatment is seen in some cases, evidence indicates that at least 10–12 weeks may be needed for an adequate treatment trial in OCD (Goodman et al. 1997). In general, a steady linear improvement in symptoms appears to occur over many weeks, without the response plateau that is characteristic of depression.

Interestingly, the use of fluorine-19 magnetic resonance spectroscopy has shown that steady-state brain concentrations of fluvoxamine are achieved within 30 days in patients with OCD treated with doses of 100–300 mg/day (Strauss et al. 1997). This is faster than previously reported for fluoxetine (Karson et al. 1993).

There has been considerable interest in developing treatment strategies for partial responders or intractable cases. The principal pharmacologic approaches adopted in the patient with treatment-refractory OCD include changing to a different SRI or augmenting treatment with another medication. In the pivotal placebo-controlled studies of fluvoxamine (Rasmussen et al., in press), a history of nonresponse to previous SRIs was associated with an approximately 50% reduction in response rate to fluvoxamine. However, it may clearly be beneficial to try a different SRI if there has been no response to one SRI or if there have been problems with tolerability.

One approach to treating nonresponders or partial responders has been to add agents that may modify serotonergic function, such as lithium, L-tryptophan, fenfluramine, buspirone, or pindolol, to the existing SRI treatment. However, little benefit has been achieved with augmenting fluvoxamine in this way. Early promising findings with lithium or buspirone augmentation were not confirmed in subsequent double-blind studies (McDougle et al. 1991, 1993). Similarly, pindolol, a 5-HT_{1A} antagonist that

has been used to accelerate or augment the actions of antidepressants in patients with depression, does not appear to shorten the latency of anti-obsessive-compulsive responses to fluvoxamine (300 mg/day) (Mundo et al. 1998). L-tryptophan has been linked to eosinophilia-myalgia syndrome, which may be fatal. This agent is therefore not recommended.

Another option is to give a combination of clomipramine and an SSRI; SSRIs inhibit the metabolism of clomipramine to its less serotonergic metabolites. In a study of 21 patients with depression or OCD, a combination of fluvoxamine and clomipramine resulted in a good response in most patients, with an increase in plasma clomipramine levels and a corresponding decrease in the metabolite levels (Szegedi et al. 1996). However, caution is advised when employing such regimens, especially in light of the risk of a reduced seizure threshold with high plasma levels of clomipramine and cardiac toxicity secondary to atrioventricular block from elevated clomipramine levels.

Although antipsychotics alone are not effective in OCD, several studies have shown beneficial effects when these agents are given in conjunction with an SRI. In an open case series conducted in 17 nonpsychotic patients with fluvoxamine-resistant OCD, beneficial effects were achieved after low doses of antipsychotic medication (haloperidol or pimozide) were added to the fluvoxamine treatment (McDougle et al. 1990). These results were further supported by a subsequent double-blind placebo-controlled study carried out in 34 patients with fluvoxamine-refractory OCD (McDougle et al. 1994). Patients treated with fluvoxamine and haloperidol (mean dose 6.2 mg/day) for 4 weeks showed a significantly better response than those given fluvoxamine and placebo. A response was achieved in 11 of the 17 patients (65%) given fluvoxamine and haloperidol compared with none of the patients given fluvoxamine and placebo. The greatest benefits of haloperidol augmentation were seen in patients who also had chronic tic disorder. In another fluvoxamine and antipsychotic (sulpiride) combination study, synergistic effects were seen in both OCD and tic symptoms (George et al. 1993). Marked improvement after the addition of risperidone has also been reported in three patients with primary OCD that was unresponsive to fluvoxamine alone (McDougle et al. 1995), and subsequent reports of SRI augmentation with this agent and other atypical antipsychotics also seem promising.

Dosing

The usual adult dose of fluvoxamine for the treatment of OCD is between 100 and 300 mg/day. Patients rarely respond to doses of less than 100 mg/

day. Starting initial titration at 25–50 mg/day and increasing by 50 mg/day every 3–4 days may help to minimize early side effects. Based on clinical experience, we recommend a target dose of 200 mg/day and an increase to 300 mg/day after 4 weeks if there is no significant improvement.

Prescribing guidelines for fluvoxamine in children and adolescents recommend a starting dose of 25 or 50 mg/day, rising gradually in small increments (25–50 mg) until there is sustained symptom relief, adverse events become problematic, or the maximum dose of 300 mg/day is reached (Riddle 1998).

The dose of fluvoxamine should be titrated more slowly in the elderly and should be reduced in patients with hepatic impairment.

Treatment Duration and Discontinuation

OCD is recognized as a chronic condition that requires long-term treatment (Montgomery 1996). Unfortunately, the relapse rate among patients with OCD is very high, with a return of symptoms likely to occur in approximately 90% of patients within only a few weeks of treatment discontinuation (Leonard et al. 1991; Pato et al. 1988).

In most patients, fluvoxamine-induced improvement in OCD seems to be maintained during long-term treatment (Cottraux et al. 1990; Mallya et al. 1992). There is also evidence that lower doses may be effective for maintenance therapy. For example, in a 2-year open follow-up study of 281 patients with OCD who had received acute fluvoxamine, fluoxetine, or clomipramine therapy, half-dose maintenance therapy was equal in efficacy to full-dose therapy for all three treatments (Ravizza et al. 1996). Similarly, in a double-blind study conducted in 30 patients with OCD who had responded to fluvoxamine or clomipramine treatment, the relapse rate over a follow-up period of 102 days did not differ significantly between those patients maintained on their original doses and those who had their doses reduced by up to two-thirds (Mundo et al. 1997).

Use in Children and Adolescents

The onset of OCD frequently occurs during childhood or adolescence; indeed, it is estimated that at least 80% of adults with OCD experienced their first symptoms before age 18 (Pauls et al. 1995). It is therefore important that safe and effective treatment is available for children and adolescents with OCD.

The efficacy and safety of fluvoxamine has been demonstrated in chil-

dren and adolescents, and it was the first SSRI to gain FDA approval for the treatment of OCD in children and adolescents. Initial evidence was obtained from an open study conducted in 14 adolescents (aged 13–18 years) with OCD (Apter et al. 1994). Fluvoxamine (100–300 mg/day) significantly reduced the mean Y-BOCS total score from 28.0 to 19.8 after 8 weeks ($P<0.0001$).

A subsequent 10-week double-blind study carried out in 120 children or adolescents (aged 8–17 years) with OCD showed that fluvoxamine (50–200 mg/day) was significantly superior to placebo ($P<0.05$) as assessed by an adapted Y-BOCS scale for children (CY-BOCS; Riddle et al. 1996). Significant differences between fluvoxamine and placebo were seen as early as 1 week after the start of treatment and persisted to the end of the study. This profile was supported by several secondary variables. A 1-year follow-up study was then carried out in 98 of these patients, all of whom received fluvoxamine (200 mg/day) (Walkup et al. 1999). At the end of long-term treatment, the mean decrease in CY-BOCS score was 10.2 points (42%). Patients who were given placebo in the short-term study showed a marked improvement with long-term fluvoxamine treatment; the mean decrease in CY-BOCS score at endpoint was 11.5 points (48%). Moreover, patients who had responded to fluvoxamine in the short-term study continued to improve with long-term treatment. Fluvoxamine was well tolerated in both the short- and long-term studies, and side effects were generally mild.

Side Effects

In general, fluvoxamine is well tolerated. Moreover, the tolerability profile in patients with OCD is similar to that seen in depressed patients. The most commonly reported side effects with fluvoxamine are nausea, drowsiness, asthenia, headache, dry mouth, and insomnia (Wagner et al. 1995), a profile similar to that seen with the other SSRIs. Most patients receiving fluvoxamine develop a tolerance to nausea. If nausea is severe, however, it may be necessary to maintain the patient at the lowest possible daily dose until signs of tolerance develop. Administration with food, which does not affect the absorption of the drug, may also help reduce gastrointestinal side effects. Potential drug–drug interactions with fluvoxamine should also be borne in mind (see Goodman et al. 1997 for details).

Summary

In summary, the potent SSRI fluvoxamine has been found to be an effective treatment for OCD. Comparative studies suggest that fluvoxamine has

equivalent efficacy to the TCA clomipramine but is better tolerated. Response to the anti-obsessive-compulsive effects of fluvoxamine is independent of severity of depression at baseline. At least 10–12 weeks of treatment at a sufficient dose are required for an adequate trial. Long-term treatment with fluvoxamine is effective and there is evidence that lower doses are suitable for maintenance therapy. Fluvoxamine is also effective and safe in children and adolescents with OCD. Patients who are refractory to fluvoxamine treatment often show an improved response when treatment is augmented with an antipsychotic. However, augmentation strategies with agents that may modify serotonergic function, such as lithium and pindolol, have proved less successful. Fluvoxamine is well tolerated and any early side effects can be minimized by dose titration. Most patients require a target dose of 200–300 mg/day to achieve a good response. Fluvoxamine also appears effective in several OCD-related disorders (Goodman et al. 1997); such findings are discussed in Chapter 11.

Case Example

Ms. A., a 39-year-old divorced mother of two, was admitted to the research unit with the chief complaint that "I am constantly washing my hands and changing my clothes…for fear of…getting people sick by spreading contamination." The patient dated the onset of her current symptoms to approximately 8 months before admission, at which time she had learned that she had made an error at work. She had forgotten to place a stamp on an envelope containing a $10.00 filing fee, and as a result the fee was late and an important business deal fell through. After this incident, she began checking and rechecking all of her current and past work. In the process, she discovered some minor mistakes that reinforced her compulsion to check. She experienced difficulty falling asleep, dysphoric mood, marked anxiety, insomnia, a diminished appetite, and a 5–10-lb weight loss. A psychiatrist prescribed clorazepate (7.5 mg, four times daily), which was initially helpful in reducing symptoms of anxiety and insomnia. Further worsening of her obsessive-compulsive and depressive symptoms and deterioration in her level of functioning led to several psychiatric hospitalizations, during which she received trials of diazepam (up to 20 mg/day), alprazolam (dose unknown), thioridazine (150 mg/day), amitriptyline (150 mg/day) alone and in combination with perphenazine (16 mg/day), and trazodone (600 mg/day). After showing no improvement, she was transferred to our facility for a trial of fluvoxamine.

At the time of admission, Ms. A.'s obsessions primarily involved the fear that she would be responsible for inadvertently harming others. She feared that germs might be spread by her bodily wastes and secretions. Her compulsions principally involved cleaning rituals and checking. She washed her hands, on average, 12 times a day (5–10 minutes per washing), and she restricted her dietary intake to avoid urinating or moving

her bowels. She inspected reflective spots on the floor for evidence of metal fragments or slivers of glass out of concern that they might be accidentally transferred into someone's food. She spent more than 8 hours a day scanning her environment for potential hazards or reviewing instances in which she may have caused harm to others. Pathologic doubt was a prominent feature of her presentation; staff reassurance only momentarily allayed her anxiety. The patient readily acknowledged the irrationality of her fears and excessiveness of her behaviors, except during times of extreme anxiety. She made little effort to actively resist her compulsive behaviors and exhibited no control over them. Depressive symptoms were prominent.

Fluvoxamine was administered at a starting dose of 50 mg at bedtime and subsequently increased in divided doses (up to 300 mg/day by the end of week 2), with the bulk of the dose given in the late evening. Mild nausea was reported during the first week of treatment, and some sedation persisted throughout treatment. After 6 weeks of fluvoxamine (300 mg/day for 4 weeks), the patient experienced a marked improvement in obsessive-compulsive symptoms. An approximately 60% reduction in severity was noted in obsessive-compulsive symptoms with respect to the time they occupied, the distress and interference they produced, and the patient's willingness and ability to control them. However, Ms. A. continued to have occasional intrusive thoughts that were similar in intensity to those experienced at the outset of treatment. Depressive symptoms were nearly absent except for dysphoric mood when obsessive-compulsive symptoms were present. Because of these persistent symptoms, lithium carbonate (900 mg/day) was added to fluvoxamine. After 2 weeks of combination treatment, obsessive-compulsive symptoms were present for less than 1 hour per day and were no longer significantly interfering with functioning. Depression was resolved. The patient was discharged on this combination treatment.

At 1-year follow-up, she was receiving only fluvoxamine (300 mg/day). Discontinuation of lithium 6 months earlier did not result in apparent worsening of symptoms. There was no evidence of either obsessive-compulsive or depressive symptoms. The patient had returned to gainful employment. She reported carbohydrate craving and a 10–15-lb weight gain compared with her premorbid baseline. She also complained of mild daytime drowsiness, particularly when in a nonstimulating environment (e.g., a boring business meeting) or while driving long distances. No laboratory abnormalities were noted. Out of fear of losing her excellent response, she declined a recommendation to begin a slow taper of the medication.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised. Washington, DC, American Psychiatric Association, 1987

Ananth J, Pecknold JC, Van Den Steen N, et al: Double-blind comparative study of clomipramine and amitriptyline in obsessive neurosis. Prog Neuropsychopharmacol Biol Psychiatry 5:257–262, 1981

Apter A, Ratzoni G, King RA, et al: Fluvoxamine open-label treatment of adolescent inpatients with obsessive-compulsive disorder or depression. J Am Acad Child Adolesc Psychiatry 33:342–348, 1994

Austin LS, Lydiard RB, Ballenger JC, et al: Dopamine blocking activity of clomipramine in patients with obsessive-compulsive disorder. Biol Psychiatry 30:225–232, 1991

Cottraux J, Mollard E, Bouvard M, et al: A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. Int Clin Psychopharmacol 5:17–30, 1990

DeVeaugh-Geiss J, Landau P, Katz R: Treatment of obsessive compulsive disorder with clomipramine. Psychiatr Ann 19:97–101, 1989

Freeman CPL, Trimble MR, Deakin JFW et al: Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. J Clin Psychiatry 55:301–305, 1994

Fuller RW, Wong DT: Serotonin reuptake blockers in vitro and in vivo. J Clin Psychopharmacol 7:36S–43S, 1987

Goodman WK, Price LH, Rasmussen SA, et al: The efficacy of fluvoxamine in obsessive compulsive disorder: a double-blind comparison with placebo. Arch Gen Psychiatry 46:36–44, 1989

Goodman WK, Price LH, Delgado PL, et al: Specificity of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 47:577–585, 1990

Goodman WK, Kozak MJ, Liebowitz M, et al: Treatment of obsessive-compulsive disorder with fluvoxamine: a multicentre, double-blind, placebo-controlled trial. Int Clin Psychopharmacol 11:21–29, 1996

Goodman WK, Ward H, Kablinger A, et al: Fluvoxamine in the treatment of obsessive-compulsive disorder and related conditions. J Clin Psychiatry 58(suppl):32–49, 1997

Greist JH, Jenike MA, Robinson D, et al: Efficacy of fluvoxamine in obsessive-compulsive disorder: results of a multicentre, double-blind, placebo-controlled trial. Eur J Clin Res 7:195–204, 1995

George MS, Trimble MR, Robertson MM: Fluvoxamine and sulpiride in comorbid obsessive-compulsive disorder and Gilles de la Tourette syndrome. Hum Psychopharmacol 8:327–334, 1993

Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–66, 1960

Insel T, Murphy D, Cohen R, et al: Obsessive compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 40:605, 1983

Karson CN, Newton JE, Livingston R, et al: Human brain fluoxetine concentrations. J Neuropsychiatry Clin Neurosci 5:322–329, 1993

Koran LM, McElroy SL, Davidson JRT, et al: Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol 16:21–29, 1996

Leonard H, Swedo S, Rapoport JL et al: Treatment of childhood obsessive-compulsive disorder with clomipramine and desmethylimipramine: a double-blind crossover comparison. Psychopharmacol Bull 24:93–95, 1988

Leonard HL, Swedo SE, Lenane MC, et al: A double-blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive-compulsive disorder. Arch Gen Psychiatry 48:922–927, 1991

Mallya GK, White K, Waternaux C, et al: Short- and long-term treatment of obsessive-compulsive disorder with fluvoxamine. Ann Clin Psychiatry 4:77–80, 1992

Mavissakalian MR, Jones B, Olson S: Absence of placebo response in obsessive-compulsive disorder. J Nerv Ment Dis 178:268–270, 1990

McDougle CJ, Goodman WK, Price LH, et al: Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 147:652–654, 1990

McDougle CJ, Price LH, Goodman WK, et al: A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. J Clin Psychopharmacol 11:175–184, 1991

McDougle CJ, Goodman WK, Leckman JF, et al: Limited therapeutic effect of addition of buspirone in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 150:647–649, 1993

McDougle CJ, Goodman WK, Leckman JF, et al: Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: a double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 51:302–308, 1994

McDougle CJ, Fleischmann RL, Epperson CN, et al: Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 56:526–528, 1995

McNair D: Original investigations: self-evaluations of antidepressants. Psychopharmacology 37:281, 1974

McTavish D, Benfield P: Clomipramine: an overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. Drugs 39:136–153, 1990

Montgomery SA: Clomipramine in obsessional neurosis: a placebo-controlled trial. Pharmaceutical Medicine 1:189–192, 1980

Montgomery SA: Long-term management of obsessive-compulsive disorder. Int Clin Psychopharmacol 11(suppl):23–29, 1996

Mundo E, Bareggi SR, Pirola R, et al: Long-term pharmacotherapy of obsessive-compulsive disorder: a double-blind controlled study. J Clin Psychopharmacol 17:4–10, 1997

Mundo E, Guglielmo E, Bellodi L: Effect of adjuvant pindolol on the antiobsessional response to fluvoxamine: a double-blind, placebo-controlled study. Int Clin Psychopharmacol 13:219–224, 1998

Mundo E, Rouillon F, Figuera ML, et al: Fluvoxamine in obsessive-compulsive disorder: similar efficacy but superior tolerability in comparison with clomipramine. J Clin Psychopharmacol, in press

Pato MT, Zohar-Kadouch R, Zohar J, et al: Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. Am J Psychiatry 145:1521–1525, 1988

Pauls DL, Alsobrook JP, Goodman W, et al: A family study of obsessive-compulsive disorder. Am J Psychiatry 152:76–84, 1995

Perse TL, Greist JH, Jefferson JW, et al: Fluvoxamine treatment of obsessive-compulsive disorder. Am J Psychiatry 144:1543–1548, 1988

Price LH, Goodman WK, Charney DS, et al: Treatment of severe obsessive-compulsive disorder with fluvoxamine. Am J Psychiatry 144:1059–1061, 1987

Rasmussen SA, Goodman WK, Greist JH: Fluvoxamine in the treatment of obsessive-compulsive disorder: a multicenter double-blind placebo-controlled study in outpatients. Am J Psychiatry, in press

Ravizza L, Barzega G, Bellino S, et al: Drug treatment of obsessive-compulsive disorder (OCD): long-term trial with clomipramine and selective serotonin reuptake inhibitors. Psychopharmacol Bull 32:167–173, 1996

Riddle M: Obsessive-compulsive disorder in children and adolescents. Br J Psychiatry 173(suppl):91–96, 1998

Riddle M, Claghorn J, et al: A controlled trial of fluvoxamine for OCD in children and adolescents. Presented at the 36th annual meeting of the NCDEU, Boca Raton, FL, June, 1996

Strauss WL, Layton ME, Hayes CE, et al: ^{19}F Magnetic resonance spectroscopy investigation in vivo of acute and steady-state brain fluvoxamine levels in obsessive-compulsive disorder. Am J Psychiatry 154:516–522, 1997

Szegedi A, Wetzel H, Leal M, et al: Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety and tolerability data. J Clin Psychiatry 57:257–264, 1996

Träskman L, Åsberg M, Bertilsson L, et al: Plasma levels of chlorimipramine and its demethyl metabolite during treatment of depression. Clin Pharmacol Ther 26:600–610, 1979

Wagner W, Zaborny BA, Gray TE: Fluvoxamine: a review of its safety profile in world-wide studies. Int J Psychopharmacol 9:223–227, 1995

Walkup J, Reeve E, Yaruyura-Tobias J, et al: Fluvoxamine in childhood OCD: long-term treatment. Eur Neuropsychopharmacol 9(suppl):S307, 1999

This page intentionally left blank

CHAPTER 5

Sertraline

Joseph Zohar, M.D.
Michele Tortora Pato, M.D.

Sertraline is a selective serotonin reuptake inhibitor (SSRI) that, like other SSRIs, provides antiobsessional activity without the anticholinergic and cardiotoxic side effects associated with clomipramine. Its pharmacologic characteristics include linear pharmacokinetics, a relatively low risk for interactions with concomitant medications, and a half-life of 25–26 hours, which permits the attainment of steady-state plasma levels within approximately 1 week of starting treatment. This chapter provides a profile of sertraline and a review of the clinical experience with this agent in treating obsessive-compulsive disorder (OCD).

Pharmacology

Sertraline, a naphthylamine derivative, is a potent and selective inhibitor of presynaptic serotonin (5-hydroxytryptamine [5-HT]) reuptake in the central nervous system (Koe 1990). In vitro studies using rat brain synaptosomes have shown sertraline to be twice as potent as clomipramine, nine times more potent than fluvoxamine, and five times more potent than fluoxetine in inhibiting the reuptake of serotonin (Koe 1990). The increase in synaptic serotonin levels promotes serotonergic activity and, in the long term, the adaptive downregulation of 5-HT receptors.

Although its precise mechanism of action has yet to be fully defined, the inhibitory effects of sertraline on serotonin reuptake are believed to be mediated by its effects on the 5-HT transport mechanism, similar to other antiobsessional agents, rather than through direct effects on 5-HT recep-

tors (Goodwin 1996; Grimsley and Jann 1992). Indeed, sertraline has been shown to possess high affinity for the serotonin transporter, the effect of which is to inhibit the uptake of serotonin through cell membranes. Moderate-to-high affinity for eight receptors thought to be involved in various cerebral physiologic functions has, however, been shown by sertraline in rat brain receptor binding studies (Narita et al. 1996). Although sertraline is specific for serotonin reuptake in vitro and has demonstrated only weak inhibition of noradrenaline reuptake, it has been suggested that its therapeutic effects may be mediated not only by serotonergic activity but also by effects on other biogenic amines and possibly via the γ-aminobutyric acid (GABA) neuronal pathway (Giardino et al. 1996).

In contrast to some SSRIs, such as fluoxetine, fluvoxamine, and paroxetine, sertraline (like citalopram) has linear, dose-proportional pharmacokinetics for doses up to 200 mg/day. Sertraline is absorbed slowly after oral administration, reaches peak plasma concentrations in 4–8 hours independently of dose, and has a half-life of 25–26 hours. The time to reach peak plasma concentration and sertraline area under curve (AUC) values have been reported to be approximately 25% less in young (age 18–45 years) men than in young women or in healthy elderly (age 65 years or older) men and women volunteers (Ronfield et al. 1997). Steady-state concentrations of sertraline are attained after approximately 1 week of daily administration.

Like other SSRIs, sertraline has a large volume of distribution in the tissues (Catterson and Preskorn 1996). It is extensively protein bound (98%–99%), chiefly to α_1-acid glycoprotein and albumin (Catterson and Preskorn 1996; Preskorn 1997). It is eliminated mainly by oxidative metabolism; extensive first-pass hepatic metabolism by CYP3A3 and CYP3A4 isoenzymes produces the dominant metabolite N-desmethylsertraline, which is clinically inactive (Sprouse et al. 1996). Desmethylsertraline is converted through oxidative deamination and hydroxylation to an α-hydroxy ketone and an alcohol metabolite. Sertraline metabolites are clinically unimportant with respect to serotonin reuptake inhibition (Hyttel 1994; Sprouse et al. 1996). Sertraline is eliminated in approximately equal proportions in the urine (conjugated metabolites) and in the feces (unconjugated metabolites) (Murdoch and McTavish 1992).

Because sertraline, like other SSRIs, is metabolized in the liver, impairment in hepatic function can have an impact on its rate of clearance. One study showed that after oral administration of a single dose of sertraline, 100 mg (capsule formulation), peak plasma concentrations and AUC values were increased 1.7-fold and fourfold, respectively, and the elimination half-life was increased 3.2-fold in 10 patients with chronic stable liver cir-

rhosis compared with values measured in 10 healthy volunteers (Demolis et al. 1996). With multiple-dose administration (sertraline 50 mg/day for 21 days), 24-hour AUC and peak plasma concentrations were threefold greater and the mean elimination half-life was 1.7-fold greater in 10 patients with varying degrees of hepatic impairment as compared with values in 10 healthy volunteers (Wilner et al. 1996). The slower rate of elimination in patients with hepatic disease means that the dose of sertraline should be reduced or the dosage interval prolonged in such patients.

Studies evaluating the effects of renal impairment on sertraline pharmacokinetics have shown that the single- and multiple-dose pharmacokinetics are similar in healthy volunteers and patients with mild or moderate to severe renal impairment (Van Harten 1993; Warrington 1991; Wilner et al. 1996). Dose adjustment of sertraline is, therefore, not necessary in patients with mild-to-moderate renal impairment. Although an earlier study showed no effect of severe renal impairment on sertraline pharmacokinetics (Van Harten 1993; Warrington 1991), this finding was not supported by another study in two patients with end-stage renal disease in which the elimination half-life of sertraline was 42–92 hours, considerably longer than the 25–26 hours reported for healthy volunteers (Schwenk et al. 1995).

Despite its high plasma protein binding and metabolism by cytochrome P450 isoenzymes (Perry and Benfield 1997), sertraline has relatively few clinically significant interactions reported to date. This feature of sertraline has been attributed to its relatively weak inhibitory effects on hepatic isoenzymes. Studies in healthy volunteers have shown no clinically significant interactions between sertraline and digoxin (Rapeport et al. 1996a), lithium (Apseloff et al. 1992), atenolol (Ziegler and Wilner 1996), desipramine, or imipramine (Catterson and Preskorn 1996; Lane 1996; MacKay et al. 1994). Insignificant increases in peak plasma phenytoin levels and phenytoin AUC values were recorded during concomitant phenytoin and sertraline administration over 17 days in volunteers (Rapeport et al. 1996b); a clinically insignificant increase (7.9%) in prothrombin time in healthy male volunteers receiving warfarin and sertraline compared with those receiving warfarin and placebo for 15 days also has been reported (Apseloff et al. 1992).

History of Use in Obsessive-Compulsive Disorder

Sertraline has undergone several large, multicenter trials to establish its efficacy for OCD treatment. Four of these randomized, double-blind multicenter studies have compared sertraline with placebo in the treatment of nondepressed adults with OCD, whereas one has compared sertraline

with clomipramine. Another trial specifically studied children and adolescents with OCD (March et al. 1998). The placebo-controlled studies each found sertraline to be significantly more effective than placebo in terms of symptom improvement, and the clomipramine comparison study showed equal efficacy.

In a study reported by Kronig et al. (1995), 167 patients with mild to severe OCD (Yale-Brown Obsessive Compulsive Scale [Y-BOCS; Goodman et al. 1989a, 1989b] score ≥ 20; National Institute of Mental Health Global Obsessive-Compulsive [NIMH-OC; Insel et al. 1983] scale score ≥ 7) received either sertraline 50 mg/day or placebo. The sertraline patients had their dose titrated to a maximum of 200 mg/day according to response. After 12 weeks of treatment, the sertraline group showed significantly greater improvements in Y-BOCS and NIMH-OC scores than the placebo group, and a significantly greater proportion of sertraline patients were classed as responders in terms of Clinical Global Impression-Improvement (CGI-I; McNair 1974) scale scores ($P=0.003$).

Sertraline was shown to be as effective as clomipramine in a head-to-head double-blind study in which 168 patients with moderate-to-severe OCD as defined by DSM-III-R (American Psychiatric Association 1987) (Y-BOCS score ≥20) were randomized to receive 16 weeks of treatment with sertraline at 50–200 mg/day ($n=86$) or clomipramine at 50–200 mg/day ($n=82$) (Bisserbe et al. 1997). From a mean baseline Y-BOCS score of more than 27 in both treatment groups, patients treated with sertraline and clomipramine showed an improvement. When the results were analyzed for only those patients who completed the trial, however, no significant difference was found between sertraline and clomipramine on the efficacy parameters used. The difference in efficacy in the intent-to-treat analysis favoring sertraline reflects the greater rate of withdrawal because of adverse events in the clomipramine treatment arm than in the sertraline group.

Dosing

A 12-week dose-ranging study in 324 patients (Greist et al. 1995a) established the minimum clinically effective dose of sertraline to be 50 mg/day. Patients in this study were randomly assigned to sertraline doses of 50 mg/day, 100 mg/day, or 200 mg/day or to placebo. There were no significant differences in efficacy between the three sertraline groups, each of which had clinically superior results compared with the placebo group in terms of improvement from baseline in Y-BOCS and NIMH-OC scores at week 12 (the 100 mg/day dose produced significantly greater improve-

ments only on the NIMH-OC scale, not on the Y-BOCS). An intention-to-treat analysis of the data from this study showed that sertraline (all doses combined) was superior to placebo on all efficacy parameters after 12 weeks of treatment. At week 12, Y-BOCS scores had decreased by a mean of 23.4% in the patients receiving sertraline compared with a mean decrease of 14.6% in those who received placebo ($P \geq 0.005$); 52.8% of those receiving sertraline but only 35% of those receiving placebo were clinically "much improved" or "very much improved" on their CGI-I scale scores at week 12. The overall response rates, as defined by CGI-I scores, were 60.4% and 49% for sertraline and placebo recipients, respectively. The relatively high placebo response rate was attributed to the inclusion of patients with less severe OCD in this study as compared with earlier studies.

In this regard, sertraline appears to be different from the other two SSRIs, fluoxetine and paroxetine, in which dose-finding studies were performed. For these two agents, higher doses appear to be more effective than low doses (20 mg). This may not be the case for sertraline, for which both 50 mg and 200 mg were effective. Whether this is related to specific characteristics of sertraline or the specific nature of the subject pool in this study requires further research.

Treatment Duration and Discontinuation

In long-term use, treatment with sertraline is associated with sustained efficacy and a trend toward continued improvement in symptoms. In a long-term extension to the 12-week dose-ranging study, 96 patients who had responded to sertraline and 22 who had responded to placebo continued with double-blind treatment for an additional 40 weeks (Greist et al. 1995b), after which responders entered a 1-year open extension study (Montgomery 1996; Rasmussen et al. 1995). In the sertraline group, there was a trend of increased improvement from week 12 to endpoint on each of the efficacy measures (Y-BOCS, NIMH-OC, CGI-Severity, and CGI-I), whereas the placebo group showed a trend of decreased efficacy on these measures. Sertraline was significantly more effective than placebo on all four of the efficacy measures used, with a response rate of 29%.

Patients classified as responders (51 patients from the sertraline group and 8 from the placebo group) were then entered into a 12-month open extension of the trial. Patients were tapered off their previous medication and treated with sertraline 50–200 mg/day. A mean improvement of 3.6 points on the Y-BOCS was achieved during this open-label treatment period. The overall improvement for those patients ($n=51$) who had received 2 years of treatment with sertraline 50, 100, or 200 mg/day was 15.6 points

from the Y-BOCS baseline score. Patients who switched from placebo to sertraline showed significantly greater improvement on the CGI-I scale than those who had received sertraline in the earlier parts of the trial ($P<0.01$).

Side Effects

For any chronic disorder, compliance is a key consideration in its long-term management, and the favorable tolerability profile of SSRIs compared with that of tricyclic antidepressants (TCAs) has been highlighted as a key advantage for the SSRIs (Montgomery 1994). Many patients are not prepared to tolerate the side effects associated with clomipramine, as illustrated by the results of a comparative study of sertraline and clomipramine (Bisserbe et al. 1997). In contrast to clomipramine and similar to other SSRIs, sertraline exhibits minimal anticholinergic activity and is therefore less likely to cause the anticholinergic adverse effects commonly reported for TCAs (i.e., dry mouth, blurred vision, constipation, sedation, excessive perspiration, and weight gain). Sertraline is also essentially devoid of the adverse cardiovascular effects of TCAs, which lead to postural hypotension, tachycardia, palpitations, and flushing, and does not generally appear to impair psychomotor performance. In the sertraline versus clomipramine study carried out by Bisserbe et al. (1997), adverse events affecting 10% or more of the clomipramine-treated patients were dry mouth (20%), anxiety (17%), constipation (16%), nausea (15%), somnolence (11%) and tremor (11%) and those affecting at least 10% of the sertraline-treated patients were nausea (12%) and diarrhea (12%). Anxiety was the most common reason for discontinuation of treatment (nine patients in the clomipramine group versus two patients in the sertraline group). Adverse events led to treatment discontinuation in 25.6% of clomipramine-treated patients compared with only 10.5% of sertraline-treated patients ($P<0.02$).

Overall, clinical studies have demonstrated sertraline to be generally well tolerated by adults and children with OCD. Sertraline-related adverse events appear to be dose related and to resolve with continued treatment (Greist et al. 1995a, 1995b). In a long-term clinical study of sertraline use for OCD (Greist et al. 1995b), patients who received sertraline at doses of 50–200 mg/day for 2 years reported fewer adverse events during the later stages of the study. In a 12-week double-blind placebo-controlled study of sertraline given at doses of 50–200 mg/day to 240 adults, the most common adverse events (affecting at least 10% more sertraline-treated than placebo-treated patients) were headache, insomnia, nausea, diarrhea, decreased libido, and anorexia (Greist et al. 1995a). Sexual dysfunction is a

side effect of treatment with sertraline as well (as is common with SSRIs) (Lane 1997; Lane et al. 1995).

The wide therapeutic index of sertraline is comparable with that of other SSRIs and translates into a lower risk of toxicity in overdose than is associated with the TCAs. Limited data on the effects of sertraline overdose document tremor, lethargy, and nausea as the most common effects of sertraline in patients receiving up to 30 times the recommended dose, with no reports of serious systemic toxicity (Myers et al. 1993). Because the potentially fatal serotonin syndrome does rarely occur in patients receiving serotonergic drugs, however, vigilance for associated symptoms of fever, diarrhea, mental status changes, and increased neuromuscular activity is warranted in all patients receiving SSRIs (Nierenberg and Semprebon 1993; Sternbach 1991).

Use in Children and Adolescents

Sertraline has been shown to be effective and generally well tolerated in children and adolescents with OCD (March et al. 1998; Wolkow et al. 1996, 1997). In the largest study of sertraline in pediatric OCD to date, the efficacy and safety of sertraline in children and adolescents were evaluated in a 12-week multicenter double-blind placebo-controlled trial in 187 OCD patients ages 6–17 years (Wolkow et al. 1997). After a 1-week placebo washout phase, patients entered randomized double-blind treatment with either sertraline 25–200 mg/day or placebo. The patients receiving sertraline had their doses titrated upward in 25-mg increments on a semiweekly schedule (children aged 6–12 years) starting with 25 mg/day or in 50-mg increments on a weekly basis (adolescents aged 13–17 years) starting with 50 mg/day. Significantly greater improvements from baseline were shown for the sertraline groups than for the placebo groups on the following efficacy parameters: Children's Y-BOCS (mean change, -6.8 versus -3.4 points; $P=0.005$), NIMH-OC (mean change, -2.2 versus -1.3 points; $P=0.019$) and CGI-I (endpoint score 2.7 versus 3.3 points; $P=0.002$) scales. Adverse events associated significantly more frequently with sertraline than with placebo were similar to those observed in adults: insomnia (37% versus 13%), nausea (17% versus 7%), agitation (13% versus 2%), and tremor (7% versus 0%); 11% of patients receiving sertraline and 2% of patients receiving placebo discontinued treatment prematurely because of adverse events. Vital sign, laboratory, and electrocardiographic tests revealed no significant differences between the sertraline and placebo groups.

Studies done with sertraline, combined with studies conducted with fluoxetine and fluvoxamine that specifically examined their effects in chil-

dren and adolescents, suggest that the response of this age group is not different from that of adults with OCD.

Use in Obsessive-Compulsive Spectrum Disorders

The effectiveness of sertraline in the treatment of OCD has led to its evaluation in obsessive-compulsive spectrum disorders because these disorders share several clinical features with OCD and are thought to share a dysfunctional serotonergic system in their pathology. In two small studies of 18 patients with DSM-IV–defined pedophilia (American Psychiatric Association 1994), sertraline 50–200 mg/day reduced signs and symptoms of pedophilia and produced marked improvements from baseline on most sexuality scales (Bradford et al. 1995). Significant improvements from baseline in symptoms were also recorded on the Y-BOCS and CGI scales.

In another small study, sertraline treatment (mean dose 100 mg/day) produced clinically significant improvements from baseline on the Sexual Outlet Inventory and the CGI Outcome scale in 11 of 24 men with paraphilias or paraphilia-related disorders as characterized by Kafka's criteria (Kafka 1994). Several case reports have documented the efficacy of sertraline in treating patients with paraphilias (Bradford and Gratzer 1995) and other OCD-related disorders, including obsessional jealousy (Stein et al. 1994), impulsive aggression in personality disorders (Kavoussi et al. 1994), bulimia nervosa (Roberts and Lydiard 1993), Tourette's syndrome (Frankenburg and Kango 1994), and trichotillomania (Rahman and Gregory 1995).

Summary

Sertraline is yet another SSRI that is effective in the treatment of OCD. Studied and approved for use in adults as well as children and adolescents, it may offer some advantages over other SSRIs. Its easy tolerability and minimal inhibition of the cytochrome P450 enzymes make it one of the safest, except for perhaps citalopram (see Chapter 7), for use with other medications. A fixed-dose study with sertraline, however, had surprising findings. Unlike fixed-dose studies with paroxetine and fluoxetine, which showed higher doses to be more effective, the fixed-dose study with sertraline showed 50 mg and 200 mg to be equally effective, with weaker findings for 100 mg. Thus, clinicians are advised to try 50-mg dosages before moving to higher dosage ranges, but should still pursue treatment up to 200 mg if lower dosages do not bring adequate improvement (see case example below).

Case Example

Ms. A was a 14-year-old girl referred by the eating disorders clinic after aggressive obsessions and compulsive note taking were observed during her therapy for anorexia nervosa. Ms. A arrived with her parent, who noted that she (Ms. A) became agitated and upset unless she was allowed to bring her notebook with her wherever she went. When asked to explain this behavior, Ms. A stated she so feared harming others with her thoughts and actions that whenever she did something that could result in perceived harm, she wrote it down to "log it" so that she would not forget to avoid such behavior in the future. Examples included walking too close to other students on stairwells for fear that she might push them down the stairs or give her anorexia nervosa to others. On her first visit, Ms. A's Y-BOCS score was 26. She had been receiving 150 mg of sertraline for her anorexia nervosa. The dose was increased to 200 mg on this first visit. After 3 months at this higher dose, her Y-BOCS score had dropped to 20. Her pharmacologic treatment was then augmented with behavior therapy, including scripted imagery, and her score dropped to 12. Ms. A, now 17, remained on sertraline for 3 years after the completion of the exposure and response prevention and continued to experience further improvement, eventually scoring a 3 on the Y-BOCS. She tolerated the sertraline well; her only side effect was mild sweating (this case was originally cited in shorter form in Pato et al. 1998).

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised. Washington, DC, American Psychiatric Association, 1987

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

Apseloff G, Wilner KD, von Deutsch DA, et al: Sertraline does not alter steady-state concentrations or renal clearance of lithium in healthy volunteers. J Clin Pharmacol 32:643–646, 1992

Bisserbe JC, Lane RM, Flament M, et al: A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. Eur Psychiatry 12:82–97, 1997

Bradford JM, Gratzer TG: A treatment for impulse control disorders and paraphilia: a case report. Can J Psychiatry 40:4–5, 1995

Bradford JM, Greenberg D, Martindale JJ, et al: Sertraline in the treatment of pedophilia: an open label study. Presented at the annual meeting of the American Psychiatric Association, Miami, FL, May 1995

Catterson ML, Preskorn SH: Pharmacokinetics of selective serotonin reuptake inhibitors: clinical relevance. Pharmacol Toxicol 78:203–208, 1996

Demolis JL, Angebaud P, Grange JD, et al: Influence of liver cirrhosis on sertraline pharmacokinetics. Br J Clin Pharmacol 42:394–397, 1996

Frankenburg FR, Kango JC: Sertraline treatment of attention deficit hyperactivity disorder and Tourette's syndrome. J Clin Psychopharmacol 14:359–360, 1994

Giardino L, Zanni M, Bettelli C, et al: Regulation of glutamic acid decarboxylase mRNA expression in rat brain after sertraline treatment. Eur J Pharmacol 312:183–187, 1996

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Goodwin GM: How do antidepressants affect serotonin receptors? The role of serotonin receptors in the therapeutic and side effect profile of the SSRIs. J Clin Psychiatry 57(suppl):9–13, 1996

Greist J, Chouinard G, DuBoff E, et al: Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 52:289–295, 1995a

Greist JH, Jefferson JW, Kobak KA, et al: A 1-year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol 10:57–65, 1995b

Grimsley SR, Jann MW: Paroxetine, sertraline, and fluvoxamine: new selective serotonin reuptake inhibitors. Clin Pharm 11:930–957, 1992

Hyttel J: Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). Int Clin Psychopharmacol 9(suppl):19–26, 1994

Insel T, Murphy D, Cohen R, et al: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 40:605, 1983

Kafka MP: Sertraline pharmacotherapy for paraphilias and paraphilia-related disorders: an open trial. Ann Clin Psychiatry 6:189–195, 1994

Kavoussi RJ, Liu J, Coccaro EF: Aggression and sertraline. J Clin Psychiatry 55:137–141, 1994

Koe BK: Preclinical pharmacology of sertraline: a potent and specific inhibitor of serotonin reuptake. J Clin Psychiatry 51(suppl):13–17, 1990

Kronig MH, Apter J, Asnis G, et al: A multicenter trial of sertraline for obsessive-compulsive disorder (poster). Presented at the American College of Neuropsychopharmacology meeting, San Juan, Puerto Rico, December 1995

Lane RM: Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 11(suppl):31–61, 1996

Lane RM: A critical review of selective serotonin reuptake inhibitor-related sexual dysfunction: incidence, possible aetiology and implications for management. J Psychopharmacol 11:89–99, 1997

Lane R, Baldwin D, Preskorn S: The SSRIs: advantages, disadvantages and differences. J Psychopharmacol 9(suppl):163–178, 1995

MacKay ES, Carson SW, Grimsley S, et al: Effects of sertraline on steady-state serum concentrations of imipramine and its metabolites (abstract). Pharmacotherapy 14:368, 1994

March JS, Biederman J, Wolkow R, et al: Sertraline in children and adults with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA 280:1752–1756, 1998

McNair D: Original investigations of self-evaluations of antidepressants. Psychopharmacology 32:281, 1974

Montgomery SA: Pharmacological treatment of obsessive-compulsive disorder, in Current Insights in Obsessive-Compulsive Disorder. Edited by Hollander E, Zohar J, Marazziti G, et al. Chichester, England, John Wiley, 1994, pp 215–225

Montgomery SA: Long-term management of obsessive-compulsive disorder. Int Clin Psychopharmacol 11(suppl):23–29, 1996

Murdoch D, McTavish D: Sertraline: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in depression and obsessive-compulsive disorder. Drugs 44: 604-624, 1992

Myers LB, Dean BS, Krenzelok EP: Sertraline (Zoloft): overdose assessment of a new antidepressant (abstract). Vet Hum Toxicol 35:341, 1993

Narita N, Hashimoto K, Tomitaka S-1, et al: Interactions of selective serotonin reuptake inhibitors with subtypes of *s* receptors in rat brain. Eur J Pharmacol 307:117–119, 1996

Nierenberg DW, Semprebon M: The central nervous serotonin syndrome. Clin Pharmacol Ther 53:84–88, 1993

Pato MT, Pato CN, Gunn SA: Biological treatment for obsessive-compulsive disorder, in Obsessive Compulsive Disorder: Theory, Research, and Treatment. Edited by Swinson RP, Antony MM, Bachman S, et al. New York, Guilford, 1998, pp 327–348

Perry CM, Benfield P: Sertraline: an overview of its pharmacological properties and a review of its therapeutic efficacy in obsessive-compulsive disorder. CNS Drugs 7:480–500, 1997

Preskorn SH: Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet 32(suppl):1–21, 1997

Rahman MA, Gregory R: Trichotillomania associated with HIV infection and response to sertraline. Psychosomatics 36:417–418, 1995

Rapeport WG, Coates PE, Dewland PM: Absence of a sertraline-mediated effect on digoxin pharmacokinetics and electrocardiographic findings. J Clin Psychiatry 57(suppl):16–19, 1996a

Rapeport WG, Muirhead DC, Williams SA, et al: Absence of effect of sertraline on the pharmacokinetics and pharmacodynamics of phenytoin. J Clin Psychiatry 57(suppl):24–28, 1996b

Rasmussen S, Hackett E, DuBoff J, et al: Long-term sertraline in the treatment of obsessive-compulsive disorder: a 2-year study (abstract). Euro Neuropsychopharmacol 5:373, 1995

Roberts JM, Lydiard RB: Sertraline in the treatment of bulimia nervosa (letter). Am J Psychiatry 150:1753, 1993

Ronfield RA, Tremaine LM, Wilner KD: Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers. Clin Pharmacokinet 32(suppl):22–30, 1997

Schwenk MH, Verga MA, Wagner JD: Hemodialyzability of sertraline. Clin Nephrol 44:121–124, 1995

Sprouse J, Clarke T, Reynolds L, et al: Comparison of the effects of sertraline and its metabolite desmethylsertraline on blockade of central 5-HT reuptake in vivo. Neuropsychopharmacology 14:225–231, 1996

Stein DJ, Hollander E, Josephson SC: Serotonin reuptake blockers for the treatment of obsessional jealousy. J Clin Psychiatry 55:30–33, 1994

Sternbach H: The serotonin syndrome. Am J Psychiatry 148:705–713, 1991

Van Harten J: Clinical pharmacokinetics of selective serotonin reuptake inhibitors. Clin Pharmacokinet 24:203–220, 1993

Warrington SJ: Clinical implications of the pharmacology of sertraline. Int Clin Psychopharmacol 6(suppl):11–21, 1991

Wilner KD, Everson G, Foulds GH, et al: Multiple dose pharmacokinetics of sertraline in subjects with varying degrees of hepatic impairment (abstract). Eur Neuropsychopharmacol 6(suppl):40–41, 1996

Wolkow R, Alderman J, Johnston H, et al: Sertraline treatment of children and adolescents with obsessive-compulsive disorder or depression (poster). Presented at the World Congress of Psychiatry, Madrid, Spain, August 1996

Wolkow R, March J, Biederman J, Safferman A: Sertraline in pediatric obsessive compulsive disorder: a multicenter controlled trial (poster). Presented at the European Congress of Neuropsychopharmacology, Vienna, Austria, September 1997

Ziegler MG, Wilner KD: Sertraline does not alter the β-adrenergic blocking activity of atenolol in healthy male volunteers. J Clin Psychiatry 57(suppl):12–15, 1996

CHAPTER 6

Paroxetine

José A. Yaryura-Tobias, M.D.

Obsessive-compulsive disorder (OCD) occupies a preferential site in the psychiatric nosology (Yaryura-Tobias 1998). Its symptomatology is vast and complex because it comprises a substantial number of symptoms found in other conditions. Its symptoms are divided into two groups: primary (obsessions, compulsions, doubting, disperceptions, and motor disturbances) and secondary (anxiety, depression, phobias, and others). There is also a group of latent symptoms attached to this clinical cluster that can be awakened during the evolution of the disorder. When these symptoms emerge, they express themselves as a continuum of the primary disorder—OCD (Yaryura-Tobias 1998)—or as a comorbid or interrelated condition (Yaryura-Tobias and Neziroglu 1983, 1997).

Currently, the role of serotonin (5-hydroxytryptamine [5-HT]) in the mechanism of OCD is generally accepted. However, the mediation of 5-HT for OCD pathology was first postulated in 1973 in studies of clomipramine, a tricyclic antidepressant (TCA) with potent inhibitor properties of serotonin reuptake (Yaryura-Tobias and Neziroglu 1975). At that time it was said that clomipramine was an anti-obsessive-compulsive agent. Further confirmation of its efficacy in OCD was reported later on (Yaryura-Tobias et al. 1976).

Within a few years, observations narrating the clinical implications of OCD and its overlap with other disorders were presented. In our own work, we have clinically documented the efficacy of clomipramine for several related disorders such as Tourette's syndrome (Yaryura-Tobias 1975, 1977), Tourette's and primary anorexia nervosa (Yaryura-Tobias 1979), compulsion, aggression, and self-mutilation (Yaryura-Tobias et al. 1995).

It has been suggested that OCD symptoms are caused by supersensi-

tive 5-HT_1–type receptors and that serotonin uptake inhibitors such as clomipramine, fluoxetine, and the nonselective 5-HT antagonist metergoline owe their efficacy to their ability to reduce the activity of these receptors (Zohar et al. 1997). Finally, because the striatum in humans has been correlated to OCD pathology and its receptors are 5-HT_{1D} and 5-HT_2, it has been proposed that these receptor subtypes are implicated in OCD (Baxter et al. 1987).

This chapter focuses on paroxetine for the treatment of OCD and its spectrum. However, as noted elsewhere in this book (Chapters 1, 11, and 12) the psychiatrist must be knowledgeable about the issues of the diagnosis of OCD or its spectrum in order to implement the optimal treatment strategy. Treatment choices include drug therapy, behavioral therapy, or cognitive therapy. Most clinicians prefer a combined strategy.

Pharmacology

Selective serotonin reuptake inhibitors (SSRIs) endorse serotonin uptake inhibition over that of noradrenaline. The most selective serotonin reuptake inhibitor is citalopram, whereas paroxetine is the most potent. However, one should remember that selectivity and potency are different. With this basic concept in mind, we may discuss the administration of paroxetine specifically for the treatment of OCD.

Paroxetine hydrochloride is an orally administered anti-obsessive-compulsive or antidepresssant agent. Paroxetine hydrochloride is one of the SSRIs, but its chemical structure is unrelated to other SSRIs or to tricyclic, tetracyclic, or other available antiobsessive or antidepressant compounds. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans 4R-(4'-fluorphenyl)--3S-(3'4'-methylenedioxyphenoxy)methyl piperidine hydrochloride.

In contrast with clomipramine, which is a potent serotonin reuptake inhibitor and a milder norepinephrine inhibitor, paroxetine strongly inhibits the neuronal reuptake pump for 5-HT. Studies in humans show that paroxetine blocks the uptake of 5-HT in platelets. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic alpha-1, alpha-2, beta-adrenergic, dopamine (D2), 5-HT_1, 5-HT_2, and histamine (H_1) receptors. Antagonism of muscarinic, histaminergic, and alpha-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs, thus giving paroxetine a potentially more favorable side effect profile.

Furthermore, paroxetine has minimal effects on other neuroreceptors and fast sodium channels. Fluoxetine, sertraline, fluvoxamine, citalopram,

and paroxetine have remarkably similar clinical characteristics in the treatment of OCD. However, recent observations indicate that subreceptor activity differs from drug to drug. Therefore, the validity of using one common therapeutic denominator for all these drugs to equally treat OCD is questionable. It should be expected that the exchange or substitution of one SSRI for another will not necessarily bring identical results.

Paroxetine is equally bioavailable in oral suspension and tablet form. The drug is completely and slowly absorbed by the gut after oral administration. Paroxetine is distributed throughout the body, including the central nervous system, with only 1% in the plasma; about 93% is bound to plasma protein at 100 ng/mL, and its half-life is 21 hours.

Paroxetine metabolism requires oxidation and cytochrome P450 enzymes mediation in two steps for its elimination. P450 2D6 seems to be the major P450 enzyme involved in this reaction. Paroxetine inhibits 2D6 in a concentration-dependent manner. The metabolism of paroxetine is affected by two factors, age and gender. Plasma concentrations of paroxetine are 100% higher in the elderly than in the young. Cytochrome P450 enzymes are responsible for most drug-metabolizing activity (Gonzalez 1992) in humans, and 2D6 intervenes in the metabolism of several antidepressants, including SSRIs (e.g., fluoxetine, N-dimethylcitalopram, and paroxetine), TCAs (e.g., amitriptyline, clomipramine, desipramine, imipramine, nortriptyline), and other antidepressants (e.g., venlafaxine). Thus, all SSRIs, with the possible exception of fluvoxamine, have active metabolites inhibited by CYP2D6. Pharmacologic reviews of SSRIs with an accent on pharmacokinetics have been published elsewhere (Grimsley and Jann 1992; Preskorn 1993).

Paroxetine is metabolized by the cytochrome P450 2D6 and thus may significantly inhibit the activity of the 2D6 isoenzyme. Therefore, administration of paroxetine with other drugs that are metabolized or inhibited by this isoenzyme (e.g., terfenadine, astemizole, disapride, triazolam, and cyclosporin) should be approached with caution. Paroxetine inhibits TCA metabolism and thus may increase the concentration of these agents in plasma. Concomitant administration of paroxetine and a TCA (e.g., desipramine) requires monitoring (Preskorn 1997).

Paroxetine is also highly bound to plasma protein; thus, its administration with other protein-bound drugs may cause an increase in the concentration of the other drug, potentially resulting in side effects. Conversely, the other drug may affect paroxetine concentration. Caution is advised when administering lithium, diazepam, beta-blockers, procyclidine, and theophylline in conjunction with paroxetine, although no formal research is available. Alcohol should be avoided as a precautionary measure

given the general effects of alcohol on the liver and the importance of a well-functioning liver for the metabolism of paroxetine. The administration of paroxetine in combination with tryptophan may result in complaints of headache, nausea, sweating, and dizziness. The combination of paroxetine and warfarin may cause bleeding diathesis and should be used with caution; this is also applicable for other SSRIs. Sumatriptan in combination with paroxetine may cause weakness, hyperreflexia, and incoordination. Cimetidine and the anticonvulsants phenobarbital and phenytoin may affect the hepatic metabolism of paroxetine. Finally, at least a 2-week washout period should be allowed between the administration of a monoamine oxidase inhibitor and that of paroxetine; myoclonus, hypertermia, rigidity, vital sign changes, and extreme agitation followed by progressive delirium and coma have been observed with monoamine oxidase inhibitors and SSRIs (such as paroxetine) in combination. An even longer washout period of 5 weeks is required for fluoxetine because of its long half-life (see Chapter 3).

History of Use in Obsessive-Compulsive Disorder

It is of value to review the available research literature pertaining to paroxetine use in OCD. Three short-term trials studying paroxetine efficacy and safety in OCD were performed (SmithKline Beecham Pharmaceuticals, unpublished, data on file; Zohar and Judge 1996). Patients with at least a 6-month history of OCD (DSM-III-R; American Psychiatric Association 1987) and a baseline score of at least 16 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989a, 1989b) were included in the study. These trials included patients 16 years of age or older; the mean age ranged from the upper 30s to lower 40s. Overall male-to-female ratio was 3:2. Exclusion criteria were comorbid condition such as major depression, any Axis I disorder other than OCD, and participation in behavioral therapy (exposure and response prevention).

In the Wheadon (1993) and SmithKline Beecham (unpublished, data on file) studies, 263 patients were divided into four groups and received either placebo or paroxetine in equal doses of 20, 40, and 60 mg over a 12-week period. Results indicated significant improvement with 40 mg and 60 mg ($P < 0.05$) when compared with placebo. No clear differences in side effects were noticed among the different dose groups. However, diarrhea, nervousness, and somnolence were slightly more prominent with the 60-mg dose.

Another unpublished SmithKline Beecham study (data on file) compared paroxetine, clomipramine, and placebo. The 241 patients who par-

ticipated were divided into groups and each group received one of the three treatments. Patients receiving paroxetine were given 20–60 mg/day, and those receiving clomipramine were given 25–250 mg/day. No significant differences were reported between paroxetine and clomipramine; however, placebo response was high for all of the parameters. A multinational randomized study by Zohar and Judge (1996) compared paroxetine, 20–60 mg/day (N=201); clomipramine, 25–250 mg/day (N=99), and placebo (N=99) over a 12-week trial. Paroxetine and clomipramine were equally effective in three efficacy parameters for OCD (Y-BOCS; National Institute of Mental Health Obsessive-Compulsive Scale [NIMH-OC; Insel et al. 1983]; Clinical Global Impression [CGI; McNair 1974]), but for depression, paroxetine was more effective than clomipramine or placebo on the Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg 1979) at week 12.

A 12-week Italian study compared the efficacy of paroxetine, fluvoxamine, and citalopram in a blind, randomized sample of patients with OCD without comorbid Axis I. No significant differences were found between the three groups (Mundo et al. 1997). One protocol investigated long-term treatment and OCD relapse prevention with paroxetine after a short-term study of paroxetine and placebo. This study consisted of a 6-month open-label phase followed by a 6-month double-blind phase with paroxetine at a flexible dose (20–60 mg/day) and placebo. The results of this study demonstrated the efficacy of paroxetine in maintaining a therapeutic response (Steiner et al. 1995).

Before pharmacologic treatment for OCD is initiated, a complete physical examination and a complete blood count, urinalysis, and routine chemistries, including a liver profile, should be performed. In addition, an electrocardiogram and an electroencephalogram should be a habitual request. A clinical baseline is important to rule out any other medical conditions that may interfere with the treatment. Moreover, paroxetine requires a healthy liver and kidney to be properly metabolized.

Patients receiving paroxetine should be educated about the dosage, duration of treatment, and side effects as well as the possibility of neurologic and psychiatric side effects. This preliminary approach to treatment will cement the doctor–patient relationship. Furthermore, because family participation in the treatment of OCD is fundamental, members of the immediate family should be invited to this introductory meeting.

Paroxetine should be administered as a single oral dose during the morning. The recommended dose for the treatment of OCD is 40–60 mg/day (Dunner and Dunbar 1992). Paroxetine should be given in gradual increments, starting with 10 mg/day and stepping up in weekly increments

of 10 mg. It is advisable not to exceed a dose of 60 mg/day. For those interested in a slow, gradual administration, a liquid form of the drug that provides 10 mg per 5-mL dose is available.

In general, the recommended starting dose of paroxetine for OCD is twice that for the treatment of depression. This higher dose of medication applies to the other SSRIs as well. The rationale behind this empirical approach is unavailable.

Although there are no robust data regarding how long paroxetine should be prescribed to prevent relapse, one limited, long-term study has shown paroxetine to be effective in maintaining a therapeutic response over periods of 1 year in depression (Gunasekara et al. 1998). It is generally agreed that patients should receive anti-obsessive-compulsive agents for at least 6 months (March et al. 1997).

For elderly patients and children, the advisable dose should be one-third of the adult dose. In 700 elderly patients 65 years of age or older, the clearance of paroxetine slowed down; thus, a lower starting dose is advisable in this population. In children, a gradual weekly increase in dose is recommended.

Use in Pregnancy

One important issue involved in the treatment of OCD is pregnancy. Patients either present pregnant or are curious about whether they can continue medication if they become pregnant. For women who are contemplating pregnancy, three issues should be raised. First, will her OCD symptoms allow her to become a mother and then have time to rear a child? Patients with OCD can be dependent and self-absorbed with their symptoms; thus, the capacity to raise a child must be questioned. Second, is the presence of OCD affected by pregnancy? One report has indicated that pregnancy may precipitate or modify the evolution of OCD (Neziroglu et al. 1992). Third, is the OCD medication going to affect the pregnancy? The pros and cons of OCD medication and pregnancy must be considered because of the risk–benefit ratio involved for both the patient and the unborn child. In spite of the large numbers of women of childbearing age who have taken SSRIs, not much data exist on the safety and risk of these agents for the human fetus.

Most of the studies investigating fertility, mutagenesis, and teratologic effects have been performed in animal experimentation. A reduced fertility rate in rats receiving 2–4 times the manufacturer's recommended highest dose for OCD on a mg/m^2 basis was recorded. Reproduction studies were performed in rats and rabbits given doses averaging 10 times the

equivalent given to humans with OCD. No teratogenic effect was noticed, although there was an increase in the death of pups.

A study to assess the safety and risks of paroxetine, fluvoxamine, and sertraline in the fetus was conducted by Kulin et al. (1998). In a group of 297 women exposed to an SSRI, no associated increased risk for major malformations was found when compared with control subjects. Of the 297 exposed patients, 49 received the drug during pregnancy. Those receiving paroxetine received an average dose of 30 mg/day (10–60 mg/day). This study confirms animal experimentation results, which showed that, when used in the recommended doses, the new SSRIs do not seem to increase the risk of congenital malformation.

The effect of paroxetine on labor, delivery, and breastfeeding has not been studied. I recommend nonpharmacologic interventions, especially behavior therapy; if the obsessionality is intense, I recommend cognitive therapy.

Side Effects

When studying side effects, it is convenient to divide the body by systems. In this way, the repercussions of a drug acting on other bodily structures can be seen beyond cerebral parameters. Within this context, paroxetine affects every system. It affects the body as a whole primarily through asthenia (22%), the cardiovascular system with vasodilation (4%), the gastrointestinal system with nausea (23%), and the urogenital system with abnormal ejaculation (23%) and impotence (8%). Of interest is the possibility of weight loss, but in general this loss amounts to no more than a pound or so. This possibility of weight loss is in contrast with clomipramine, a TCA, which can result in significant weight gain.

When present, treatment-emergent neuropsychiatric side effects are important because they directly modify treatment aim. Moreover, patients may misinterpret these side effects and report worsening of the original symptoms, which may result in an undue switch to other medications in the mistaken belief that the drug has failed to improve symptoms. Clinicians must remember that symptoms may worsen initially before the onset of a therapeutic efficacy (see Chapter 1).

Common neuropsychiatric side effects are insomnia, somnolence, dizziness, tremor, nervousness, decreased libido, agitation, anxiety, abnormal dreams, impaired concentration, despersonalization, myoclonus, and amnesia. The most frequent symptoms are sleep disturbances, nervousness, and tremor. A case of akathisia was reported in a female patient (Olivera 1996). On one occasion, the evolution of a paroxetine-induced psychosis was observed in a 49-year-old man with primary OCD but without prior

psychotic comorbidity. This side effect started after 3 weeks of paroxetine, 40 mg/day, and disappeared very rapidly after discontinuation. A case of paroxetine-induced manic psychosis in a male patient has also been reported (Christensen 1995).

If the medication is efficacious but the patient presents with side effects, a conflict ensues. Should the medication be changed or should the dose be decreased? The most common adverse events (greater than or equal to 10%) associated with paroxetine during short- and long-term therapy studies in patients with OCD included insomnia, asthenia, somnolence, dizziness, dry mouth, nausea, and abnormal ejaculation. Sometimes side effects are dose dependent, or they appear early with the onset of treatment. If medication adjustment is insufficient, a reduced dose and combination with a coadjuvant drug (e.g., lithium, L-tryptophan, pindolol) may be tried. A consortium of experts has put forward a series of recommendations to tailor the treatment of OCD (March et al. 1997). It has been agreed that side effects are dose and time dependent. More severe side effects are related to larger doses and faster increases, resulting in a shorter time to maximum dose. However, tolerance may develop within 6–8 weeks and is likely to occur with some side effects (e.g., nausea) but not with other side effects (e.g., akathisia). Tolerance is less likely to occur with TCAs.

Serotonin syndrome is caused by an excessive increase of blood serotonin that could theroetically be brought on by excessive dosing or by mixing more than one serotonergic agent. It is not often diagnosed, perhaps because many of its subjective and objective symptoms are similar to some of the adverse effects seen with serotonin reuptake inhibitors in general. The syndrome includes diaphoresis, nausea, diarrhea, abdominal cramps, hyperreflexia, myoclonus, insomnia, psychosis, bleeding, and flushing (Metz and Shader 1990). Clinicians should be aware of this potentially more dangerous constellation of symptoms and be ready to provide close monitoring and physiologic supportive therapy if it presents.

Treatment Duration and Discontinuation

Paroxetine discontinuation symptoms are similar to those reported in other serotonin reuptake inhibitors and may not be time or dose related. These symptoms develop soon after discontinuation or dose reduction. The classic symptoms are sensations of general malaise, asthenia, dizziness, instability, vertigo, headaches, myalgia, loss of appetite, nausea, vomiting, diarrhea, and abdominal cramps. A syndrome of pseudoinfluenza has also been reported. In general, treatment consists of restarting the medication and then, on disappearance of the discontinuation symptoms,

gradually reducing the dose. The literature accounting for these findings is inadequate and consists of anecdotal reports (Barr et al. 1994; Bryois et al. 1998; Dominguez and Goodnick 1995; Keuthen et al. 1994).

Summary

The nosology of OCD involves diagnostic symptoms, course of the disorder over time, and therapeutic response. Therefore, to try to offer a comprehensive treatment by using one or more form of therapy may be short sighted and prone to failure. The clinician must become acquainted with the individual patient's phenomenology, which provides a window to explore intuitively and empirically the mental state or experiences of the patient's life. Paroxetine is just one of many agents that a clinician should consider for the pharmacotherapy of OCD. Its unique secondary binding properities and potency may make it particularly useful in some patients.

Case Example

The patient was a 28-year-old woman, married, with one daughter, who worked as a computer analyst. She developed OCD at the age of 16 and had been able to control her symptoms for about 2 years until she enrolled in college. At that point, morbid thoughts, rituals to ward off her distressing thoughts, and double-checking occupied about 8 hours of her day. After a program of clomipramine, 125 mg, and 2 months of intensive behavior therapy in 90-minute sessions each day, 6 days per week, she improved. It took about 6 months to observe this therapeutic effect. However, while receiving clomipramine she gained 15 pounds and complained of diminished libido and anorgasmia. Nonetheless, she was able to graduate from college, work, and get married. After 2 years of marriage, she became pregnant. After the delivery of her daughter, she relapsed. Symptom content postpartum included fears of tragedy involving her family and of contamination. These two thoughts controlled her life. She developed a deep depression with slowness that practically paralyzed her. She refused a new trial of clomipramine because of the side effects experienced in the past. Paroxetine was then considered. She was placed on paroxetine with a gradual increase of 10 mg/week until a level of 50 mg/day was reached. Four months later, she began to improve. She recovered enough to take care of her baby daughter and eventually considered a return to work.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised. Washington, DC, American Psychiatric Association, 1987

Barr LC, Goodman WK, Price LH: Physical symptoms associated with paroxetine discontinuation (letter). Am J Psychiatry 151:289, 1994

Baxter LR, Phelps ME, Mazziotta TC: Local cerebral glucose metabolic rates in obsessive compulsive disorder. Arch Gen Psychiatry 44:211–218, 1987

Bryois C, Rubin C, Zbinden JD, et al: Withdrawal syndrome caused by selective serotonin reuptake inhibitors: apropos of a case. Schweiz Rundsch Med Prax 87:345–348, 1998

Chada DR, Dasilva L: The placebo in clinical psychopharmacology. Curr Ther Res Vol 5, 1977

Christenson RC: Paroxetine-induced psychotic mania. Am J Psychiatry 152:1399–1400, 1995

Dominguez RA, Goodnick PJ: Adverse events after the abrupt discontinuation of paroxetine. Pharmacotherapy 15:778–780, 1995

Dunner DL, Dunbar GC: Optimal dose regimen for paroxetine. J Clin Psychiatry 53(suppl):21–26, 1992

Gonzalez FJ: Human cytochrome P450: problems and prospects. Trends Pharmacol 13:346–352, 1992

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Grimsley SR, Jann MW: Paroxetine, sertraline, and fluvoxamine: new selective serotonin reuptake inhibitors. Clinical Pharmacy 11:930–957, 1992

Gunasekara NS, Noble S, Benfield P: Paroxetine: an update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. Drugs 55:85–120, 1998

Hyttel J: Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). Int Clin Psychopharmacol 9(suppl)1:19–26, 1994

Insel T, Murphy D, Cohen R, et al: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 40:605, 1983

Keuthen NJ, Cyr P, Ricciarde JA, et al: Medication withdrawal symptoms in obsessive-compulsive disorder patients treated with paroxetine (letter). J Clin Psychopharmacol 14:206–207, 1994

Kulin NA, Pastuszak A, Sage S, et al: Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 279:609–610, 1998

March J, Frances A, Carpenter D, et al: The expert consensus guideline series: treatment of obsessive compulsive disorder. J Clin Psychiatry 58:4, 1997

McNair D: Original investigations of self-evaluations of antidepressants. Psychopharmacology 32:281, 1974

Metz A, Shader R: Adverse reaction encountered when using trazodone to treat insomnia associated with fluoxetine. Int Clin Pharmacol 5:191–194, 1990

Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389, 1979

Mundo E, Bianchi L, Bellodi L: Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. J Clin Psychopharmacol 17:267–271, 1997

Neziroglu F, Anemone R, Yaryura-Tobias JA: Onset of obsessive compulsive disorder in pregnancy. Am J Psychiatry 149:947–950, 1992

Olivera AA: A case of paroxetine-induced akathisia. Biol Psychiatry 39:910, 1996

Preskorn SH: Pharmacokinetics of antidepressants: why and how they are relevant to treatment. J Clin Psychiatry 54(suppl):14–34, 1993

Preskorn SH: Clinically relevant pharmacology of selective serontonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. Clin Pharmacokinet 32(suppl):1–21, 1997

Steiner M, Bushnell WD, Gergel IP, et al: Long-term treatment and prevention of relapse of OCD with paroxetine. Presented at the annual meeting of the American Psychiatric Association, Miami, FL, May 1995

Wheadon DE, Bushnell WD, Steiner M: A fixed dose comparison of 20, 40, or 60 mg paroxetine to placebo in the treatment of obsessive compulsive disorder. Proceedings from the American College of Neuropsychopharmacology meeting, Honolulu, HI, 1993

Yaryura-Tobias JA: Chlorimipramine in Gilles de la Tourette's disease. Am J Psychiatry 132:1221–1225, 1975

Yaryura-Tobias JA: Gilles de la Tourette syndrome: a new clinico-therapeutic approach. Prog Neuropsychopharmacol 1:335–338, 1977

Yaryura-Tobias JA: Gilles de la Tourette syndrome: interactions with other neuropsychiatric disorders. Acta Psychiatr Scand 59:9–16, 1979

Yaryura-Tobias JA: The unified theory of obsessive-compulsive disorder. CNS Spectrums 3:54–60, 1998

Yaryura-Tobias JA, Neziroglu F: The action of chlorimipramine in obsessive compulsive neurosis: a pilot study. Curr Ther Res 17:111–116, 1975

Yaryura-Tobias JA, Neziroglu FA: Obsessive compulsive disorder spectrum. Pathogenesis, Diagnosis and Treatment. 5:37–50, 1983

Yaryura-Tobias JA, Neziroglu FA: Obsessive compulsive disorder spectrum. Pathogenesis, Diagnosis and Treatment. 13:255–302, 1997

Yaryura-Tobias JA, Neziroglu F, Bergman L: Chlorimipramine for obsessive compulsive neurosis: an organic approach. Curr Ther Res 20:541–548, 1976

Yaryura-Tobias JA, Neziroglu FA, Kaplan S: Self-mutilation, anorexia, and dysmenorrhea in obsessive compulsive disorder. Int J Eat Disord 17:33–38, 1995

Zohar J, Judge R: Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. Br J Psychiatry 169:468–474, 1996

Zohar J, Mueller EA, Insel TR, et al: Serotonergic responsivity in obsessive compulsive disorder. Arch Gen Psychiatry 44:946–951, 1997

This page intentionally left blank

CHAPTER 7

Citalopram

Margaret A. Richter, M.D.

Citalopram is the most recent selective serotonin reuptake inhibitor (SSRI) to be released in North America and at present is indicated for use only in depression. However, it is beginning to undergo systematic trials in obsessive-compulsive disorder (OCD) and has a long history of effective use in Europe for depression and anxiety conditions. Based on emerging data, it is therefore likely that citalopram will emerge as an alternative to currently marketed medications in this class for the management of OCD. Thus, in this chapter, available data on the clinical utility of citalopram in the treatment of OCD is discussed along with information on its pharmacologic profile, side effects, dose, and potential drug interactions.

Pharmacology

Citalopram is the most selective reuptake inhibitor of serotonin (Baumann 1996). Citalopram's very low affinity in vitro for serotonin receptors, similar to that of the other SSRIs, supports the role of reuptake inhibition as opposed to direct agonist effects for therapeutic response. Chemically, it is a bicyclic phthalane derivative. It is available as a racemic mixture. Although both the S (+) and R (-) enantiomers of citalopram and its metabolites are SSRIs, the S-enantiomer appears to be the main pharmacologically active compound based on in vitro and in vivo studies in rodents (Hytell et al. 1992). Like all of the SSRIs, it has low affinity for adrenergic, muscarinic, and histaminic receptors (Hytell 1984; Milne and Goa 1991). Thus, cardiotoxicity, sedation, and anticholinergic effects associated with the older tricyclic antidepressant (TCA) class of medications, such as constipation and impaired visual accommodation, are largely avoided.

Citalopram is highly lipophilic, resulting in excellent absorption orally. Peak plasma concentrations are reached within 3 hours. Its elimination half-life is about 33 hours in healthy adults, making once-daily dosing sufficient; steady state is reached in about 1 week (Baumann and Larsen 1995). Citalopram follows first-order (linear) kinetics in the usual dose range; however, there is significant interindividual variability. There is no clear correlation between plasma citalopram concentration and therapeutic effect (Milne and Goa 1991). Bioavailability is high (80%–95%) (Baumann 1996), as is the volume of distribution, suggesting extensive tissue binding (Milne and Goa 1991). Citalopram is about 50% protein bound in plasma.

Relative to the TCAs, citalopram has very low first-pass elimination. Approximately 13% of a given dose is excreted unchanged in the urine (Kragh-Sorensen et al. 1981). Hepatic metabolism of citalopram is principally mediated by two isoenzymes in the cytochrome P450 system, CYP3A4 and CYP2C19; CYP2D6 plays a lesser role (Rochat et al. 1997; Sindrup et al. 1993). Citalopram has two principal metabolites: demethylcitalopram and didemethylcitalopram. Both are only weakly active in comparison with their parent compound, are present in low concentration in plasma, and enter the brain less easily; thus, they are considered unlikely to significantly contribute to the clinical effect (Baumann 1996; Luo and Richardson 1993). In recent years, attention has been focused on the role of the cytochrome P450 system in drug interactions. In comparison with the other SSRIs, citalopram has little impact on this hepatic enzyme system; it is a relatively weak inhibitor of CYP2D6 as compared with fluoxetine, norfluoxetine, and paroxetine (Stahl 1998). Only fluvoxamine causes significant inhibition of CYP1A2. CYP2C19 is moderately inhibited by fluoxetine and fluvoxamine. The fluoxetine metabolite, norfluoxetine, is the most substantive inhibitor of CYP3A4 (Brosen 1996; Jeppesen et al. 1996). This favorable profile means that citalopram has minimal effect on the metabolism of other coadministered medications.

History of Use in Obsessive-Compulsive Disorder

Citalopram has been subjected to extensive investigation in depression over the past decade. It has been repeatedly shown to be significantly better than placebo (see Montgomery and Djarv 1996 or Noble and Benfield 1997 for recent reviews). Citalopram has also been compared extensively with numerous other antidepressants, including the tricyclic compounds imipramine and clomipramine and the SSRIs fluoxetine, fluvoxamine, and sertraline, and has been found to have comparable efficacy (Ekselius et al.

1997; Fuglum 1996; Haffmans et al. 1996; Patris et al. 1996). Interestingly, one study has suggested a more rapid onset of action for citalopram than for fluoxetine, based on a significantly greater improvement in depression scores after 2 weeks (Bougerol et al. 1997).

The efficacy of citalopram in OCD has only recently become a subject of interest. Thus, the first large multisite double-blind studies using fixed-dose and flexible-dose strategies have only recently been completed; results of these studies are not available as yet beyond preliminary reports. However, there are several published case reports, open trials, and small double-blind studies available (see Pato 1999 for review). The first report of citalopram use in OCD was published by White et al. (1986). They described the case of a 31-year-old man with long-standing OCD who responded within 5 weeks to treatment with 80 mg of citalopram daily. Bejerot and Humble (1991) described a response in two of six severely ill patients with OCD to citalopram 60 mg/day. Koponen et al. (1995) reported that two men in their 20s with lengthy histories of OCD symptoms obtained a good clinical response with citalopram after receiving doses of 30 and 60 mg/day, respectively. The first patient maintained his improvement for 6 months without significant side effects, after which medication was discontinued. The other patient was reported as doing well on medication 9 months later but experienced side effects, including lack of appetite and orgasmic dysfunction, that resolved after the first 2 months of therapy. A recent case report by Bejerot and Bodlund (1998) is particularly interesting. The patient, a 43-year-old woman, had shown no response after 3 months of citalopram, 80 mg/day. However, within days of raising her dose to 220 mg/day, her OCD had markedly improved. This benefit was subsequently maintained on a once-daily dose of 160 mg. The medication was generally well tolerated, aside from palpitations and episodes of tachychardia. It should be noted, however, that this dose far exceeds the recommended range of 20–60 mg.

The first open-label treatment study of citalopram in OCD involved a 12-week trial with doses of up to 60 mg; mean dose at completion was 44.2 mg. Of the 12 patients who completed treatment, 8 were deemed "responders" (Stein et al. 1996a, 1996b). Overall, the mean Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989a, 1989b) score declined by greater than 40%, from 25.6 to 14.2. Subjects experienced only minimal side effects. Koponen et al. (1997) also reported a 24-week open pilot study of 29 patients meeting DSM-III-R criteria (American Psychiatric Association 1987) for OCD. Individuals with a concurrent diagnosis of major depression or marked depressive symptoms (scoring more than 21 on the Montgomery-Åsberg Depression Rating Scale [Montgomery and

Åsberg 1979]) were excluded, as were those with psychoses, organic brain disease, personality disorders, alcohol or drug abuse, or previous history of resistance to SSRI treatment. The mean score at entry on the Y-BOCS was 20.1; this declined to 5.7 ($P = 0.042$) at study conclusion. Overall, 76% of the patients (22 of 29) benefited according to a conservative definition of a greater than 50% reduction on Y-BOCS score. Patients also showed significant improvement on scores of depression and quality of life (assessed with the Psychological Well-Being Schedule). Most patients were receiving 40–60 mg/day by the study conclusion; only two had remained on 20 mg. Compliance was monitored by serum drug levels at two time points. All but two patients completed: one refused further treatment and one was discontinued because of noncompliance. The medication was generally well tolerated. Nausea and vomiting were the most commonly reported side effects, and they subsided during the study. Up to 10% of the patients reported sleep disturbance (increased dreaming or decreased sleep), and 5% experienced decreased sexual desire. Eight percent also reported orgasmic dysfunction.

The first published double-blind study involving citalopram compared the efficacy of fluvoxamine, paroxetine, and citalopram during 10 weeks of treatment (Mundo et al. 1997). Thirty psychiatric inpatients meeting DSM-III-R criteria on a structured interview (Diagnostic Interview Schedule–Revised [DIS-R]) were randomized to one of the three treatment groups, after which treatment was administered in single-blind fashion (raters were blinded, patients were not). Patients could not meet criteria for any other Axis I condition aside from tic disorders. All patients completed the study. Mean daily dose of medication in the three groups was 290 mg (fluvoxamine), 53.3 mg (paroxetine), and 50.9 mg (citalopram). All drugs achieved a similar magnitude of therapeutic response. When response was defined as improvement of greater than 35% in Y-BOCS score, no significant difference was found between groups, with 60% considered responders to fluvoxamine, 45% to paroxetine, and 40% to citalopram. The Y-BOCS scores of the 11 individuals who received citalopram dropped from a mean of 29.3 at baseline to 19.8 at the endpoint, for a mean reduction of 32% in symptom severity.

Pidrman and Tuma conducted a double-blind clomipramine-controlled study of citalopram in OCD for which preliminary results for the first 14 individuals were published in 1997. They have subsequently reported on a total of 34 patients (Pidrman and Tuma 1998). Patients met International Classification of Diseases (ICD)-10 diagnostic criteria for OCD; individuals with significant depression on the Hamilton Depression Rating Scale (Ham-D; Hamilton 1960), substance abuse, seizures or other

organic brain disorder were excluded. Treatment was initiated at 20 mg citalopram or 75 mg clomipramine, which could be titrated up to double that amount after the third week. Unfortunately, the trial was only 6 weeks long, limiting the possible degree of response to the medication. Nonetheless, significant improvement (defined as a greater than 20% reduction in Y-BOCS score) was observed in 14 of the 15 citalopram subjects and 13 of the 16 clomipramine subjects. No significant difference in efficacy was found between the two groups, although side effects were more marked in the clomipramine group. The authors reported low levels of side effects, including tremor, akathisia, dry mouth, nausea, dizziness, and tachycardia; all of these diminished by the fourth week of treatment.

The results of a more definitive double-blind placebo-controlled multicenter trial have not been fully analyzed as yet; however, preliminary results in a sample of 401 patients were similar to those for other SSRIs (Montgomery 1998). Subjects were randomized to receive 12 weeks of citalopram at 20, 40, or 60 mg/day after a 1-week single-blind placebo run-in. The individuals receiving citalopram obtained a statistically significant greater improvement on their Y-BOCS score than did the placebo group, with observed decreases of 9.4, 9.5, and 11.4 points for the three medication dose levels and 6.7 points in the placebo group. Thus, as with fluoxetine and paroxetine, trends indicate that higher doses of citalopram may be more effective than lower ones. Similar results were seen on secondary outcome measures, including the Montgomery-Åsberg Depression Rating Scale, National Institute of Mental Health Obsessive Compulsive scale (Insel et al. 1983; Murphy et al. 1982), and the Sheehan Disability Scale (Sheehan et al. 1996). As in previous studies, the medication was described as well tolerated at all dose levels; nausea, headache, and insomnia were the most commonly reported side effects.

Dosing

Most patients easily tolerate an initial dose of 20 mg, administered once daily. This dose can be taken in the morning or at night depending on the individual's side effect profile, because some patients may develop insomnia or other sleep disturbance in contrast to the more commonly reported somnolence. It is not necessary to take citalopram with food. Because there are only limited published data on dosing in OCD, no optimal dose has been established for this condition. However, based on the studies reviewed above, 40–60 mg/day appears reasonable. Moreover, this dose range is consistent with data on other SSRIs for which fixed-dose studies in OCD have typically found the best response at the higher end of the

dose range (Tollefson et al. 1994; Wheadon et al. 1993). Based on the same reasoning, patients should probably be treated for a minimum of 10 weeks, including at least 4–6 weeks at a maximum dose, before being considered "nonresponders" to citalopram or any other SSRI agent (March et al. 1997). A case report by Bejerot and Bodlund (1998) raised the possibility of increased efficacy with considerably higher doses, suggesting that higher doses may represent an alternative in individuals with otherwise treatment-resistant OCD.

Citalopram is also available in parenteral form, although this form is not currently approved for use in the United States. A double-blind trial of oral dose after an initial infusion period compared citalopram favorably with viloxazine, a noradrenergic antidepressant (Bouchard et al. 1997). One study has compared oral dosing with an initial slow-drop infusion for 10 days followed by oral form in a group of moderately to severely depressed patients. Although no significant differences were found between the groups, a trend was observed toward faster response (defined as a greater than 50% reduction in Ham-D score) in patients who received the infusion initially (33.3%) compared with those receiving the oral treatment (17.9%) (Baumann et al. 1998). Intravenous administration is generally well tolerated and may prove in the future to be a valuable alternative in some populations. No studies of intravenous use in OCD are yet available, although one might assume similar positive responses as seen with clomipramine (see Chapter 2).

Use in Children and Adolescents

There have been some reports of efficacy of citalopram in children. Maud and Stein (1996) described one case of a prepubertal girl with OCD who responded to 40 mg citalopram within 10 weeks and remained well for an additional 3 months thereafter. More significant is an open-label trial of citalopram in children and adolescents (Thomsen 1997). In this naturalistic treatment study, 23 subjects (mean age 13 years) meeting DSM-III-R criteria for OCD were treated over the course of 10 weeks with a combination of citalopram and inpatient or outpatient cognitive-behavioral therapy. Exclusion criteria included psychosis, neurologic or medical disorders, and alcohol or substance abuse. Citalopram was started at 10 mg/day and increased gradually as tolerated. The mean daily dose of citalopram was 37.0 mg, with 20 of the 23 patients maintained on 40 mg, 2 patients on 20 mg, and 1 patient on 10 mg/day. Y-BOCS scores (either adult version or children's version in subjects younger than 15 years) dropped from a mean at entry of 30.1 to 20.9 at the study conclusion ($P<0.001$), representing a

reduction of 29% overall. This included 4 children who experienced a reduction of greater than 50% and 14 children with "moderate improvement," liberally defined as greater than 20% reduction in Y-BOCS score. The medication was generally well tolerated. Of the 23 children, 13 experienced mild side effects that remitted within the first few weeks, including dry mouth, headaches, and tremor. Two subjects experienced some agitation necessitating dose reduction, and one individual developed erectile difficulty.

Use in the Elderly

Citalopram appears to be extremely well tolerated by elderly subjects. Several meta-analyses have been conducted on data from open and double-blind studies. These studies have suggested that young patients experience equal or perhaps even higher frequency of adverse events than do the elderly. Dencker and Hopfner Petersen (1989) found that reduced sleep duration and reduced salivation were significantly more common in younger subjects in their analyzed sample of 800 depressed patients. In contrast, Elsborg (1991) found side effect profiles to be essentially the same when controlled for age, with the exception of significantly more dizziness in the older subjects. However, notwithstanding the benign profile, serum concentrations of citalopram and metabolites increase linearly with age (Leinonen et al. 1996). Similarly, clearance decreases and half-life is increased by up to 50% (Overo et al. 1985). Allowing for this difference, a daily dose of 20 mg is considered sufficient for elderly patients, adjusting upward to a maximum of 30 mg daily if necessary.

Side Effects

Like the other SSRIs, citalopram is very well tolerated in general. It has a side effect profile markedly different from the older TCAs in that it is generally lacking significant anticholinergic effects. The most commonly reported adverse events (in comparison with placebo) include nausea (8% versus placebo), dry mouth (7.4%), somnolence (7.6%), increased sweating (3.9%), tremor (3%), diarrhea (3.2%), and ejaculation failure (3.3%), based on Lundbeck's accumulated database of more than 1,000 subjects (Forest Pharmaceuticals Inc. 1998; Muldoon 1996). When compared with the TCAs, only nausea and ejaculation failure are more common with citalopram. Citalopram, therefore, appears to be similar to fluoxetine and sertraline and perhaps superior to fluvoxamine in terms of its side effect profile (Ekselius et al. 1997; Haffmans et al. 1996; Patris et al. 1996). A recent article

comparing tolerability of antidepressants based on the *Physicians' Desk Reference* along with other published sources suggests that citalopram may in fact have the most favorable side effect profile of the available SSRIs (Dewan and Anand 1999). Most adverse events have been shown to diminish in frequency during the first few weeks of therapy (Gravem et al. 1987). Sexual dysfunction is typically underestimated because patients may fail to spontaneously report these symptoms. In a recent clinical trial of 475 patients with panic disorder, 10% of individuals receiving 40 mg/day or more of citalopram reported anorgasmia (Wade et al. 1997). Three cases of transient clitoral priapism have been reported during the second week of treatment with citalopram (Berk and Acton 1997). However, there have also been reports of lack of sexual impairment in patients who experienced difficulty with other SSRIs (Pallanti and Koran 1999).

Citalopram does not seem to be associated with cardiovascular toxicity in the normal dose range. A small and clinically insignificant bradycardia of 5–9 beats per minute has been shown to occur early in treatment (Muldoon 1996). There is no evidence of citalopram-related QT or other interval changes, suggesting a lack of effect on cardiac conduction and repolarization (Rasmussen and Overo 1999). Hematologic, hepatic, and renal functions are essentially unchanged. Moreover, no pattern of unexplained sudden deaths has been reported so far, after use in more than 600,000 patients in Europe (Baldwin and Johnson 1995). Similarly, citalopram is not normally associated with any increased risk of seizures. Although discontinuation reactions have been increasingly observed after sudden discontinuation of some of the SSRIs, two studies in which 116 patients were abruptly switched from citalopram to placebo did not apparently result in this difficulty (Muldoon 1996).

Based on the small number of documented cases in which patients have overdosed on citalopram alone, it appears to be very safe. Of the almost 70 reported overdoses, only 4 involving citalopram alone were lethal, despite consumed amounts estimated up to 5,200 mg (Noble and Benfield 1997). According to a recent review, only five fatal overdoses involving citalopram in combination with other drugs, such as moclobemide and barbiturates, have been reported (Muldoon 1996). Generalized seizures and widened QRS complexes have been observed in some overdoses (Power 1998). Thus, overdoses should be managed with prompt gastric lavage, administration of activated charcoal, and symptomatic management of residual overdose effects, which should probably entail medical observation including electrocardiographic monitoring for at least 24 hours.

In individuals with renal insufficiency, the half-life of citalopram may be somewhat raised. However, this does not ordinarily translate into a

need for dose adjustment (Joffe et al. 1998). Little is known about the impact of severe renal impairment. Hepatic impairment reduces drug clearance, potentially resulting in a doubling of steady-state concentrations. In individuals with poor liver functioning, therefore, the dose should be kept at the lower end of the range (i.e., 20 mg/day).

Use in Pregnancy

As with all psychotropic agents, there is relatively little information available on safety during pregnancy. Because all antidepressants cross the placenta, the potential for teratogenicity and fetal and neonatal toxicity is present for all available agents. Thus, the decision to use any antidepressant during pregnancy must be made with extreme caution, after careful consideration of treatment alternatives and potential risks and benefits. When antidepressant treatment is warranted, the favorable side effect and safety profile of the SSRIs render them a good choice. Currently, fluoxetine is the best-studied agent; several studies suggest no associated increase in major birth defects with fluoxetine, although there may be elevated rates of spontaneous abortions and perinatal complications (Goldstein 1995; Pastuzak et al. 1993). Given the lesser state of knowledge on citalopram exposure, the need for use should be carefully evaluated on the merits of each case. There are two reports of excessive somnolence, decreased feeding, and weight loss in two infants exposed to citalopram during lactation (Forest Pharmaceuticals Inc. 1998). There are two published reports on the excretion of citalopram in breast milk; these suggest that nursing infants receive no more than 5% of the maternal dose, adjusting for weight (Jensen et al. 1997; Spigset et al. 1997). Infant serum level was 1/15 the maternal trough concentration in the one case in which this was directly studied (Jensen et al. 1997). Thus, available data suggest that the relative dose of citalopram ingested by a nursing infant is comparable with that of fluoxetine and higher than those of fluvoxamine, sertraline, and paroxetine (as calculated by Spigset et al. 1997). Taken together, citalopram is probably a poorer choice than some of the other SSRIs for nursing mothers.

Summary

Although definitive conclusions should await peer-reviewed results of large double-blind trials, it seems clear that citalopram appears to help OCD in adults as well as children and adolescents. The small comparative study by Mundo et al. (1997), which reported efficacy for subjects receiving citalopram comparable with that for subjects receiving the SSRIs flu-

voxamine and paroxetine, indicates that citalopram may well represent a valid alternative to current first-line treatments for OCD. Moreover, it may offer some advantages as compared with other agents in its class in terms of tolerability and low capacity for drug–drug interactions. It appears that the therapeutic dose range will likely be comparable with, or slightly higher than, that reported for depression, but the absence of published data from fixed-dose trials makes it premature to come to any conclusions as yet. There are as yet no data on longer-term outcomes. This problem plagues our knowledge of all of the available first-line drugs but will hopefully be addressed in the years to come.

Case Example

Mr. K. was a 42-year-old single man with an approximately 15-year history of OCD with comorbid chronic depression and panic disorder. He had previously received trials of all available serotonin reuptake inhibitors (clomipramine, fluoxetine, fluvoxamine, sertraline, and paroxetine) but had either not responded or had been unable to tolerate therapeutic trials of all these agents. A large number of other psychotropic medications had also been tried without success over the years, including several benzodiazepines, neuroleptics, TCAs, and phenelzine. At presentation, he was being maintained on high-dose clonazepam with partial alleviation of panic attacks.

Mr. K's principal OCD symptoms consisted of almost constant intrusive, vague thoughts that he would be responsible for something terrible happening. This resulted in ongoing repetition rituals of virtually all actions to avoid harm. Additionally, he described avoidance of certain bad numbers and subsequently would feel unable to do anything at all for extended periods until the clock would show it was a "safe" time. For example, getting out of bed could take an hour or more because he would repeatedly swing his legs off and back onto the bed, initially waiting for it to "feel right" and then until it was a "safe" time. He would try to avoid moving or doing anything for hours at a time to avoid rituals, sitting in front of the television regardless of what was shown. As a result, he was severely disabled, with rituals occupying or immobilizing him for most of his waking time. He would leave his apartment as little as possible, going out only twice per week for groceries and doctor appointments. He was extremely dysphoric, anhedonic, and quite hopeless, and he had longstanding complaints of poor concentration and lack of energy. He also reported constant passive suicidal ideation.

After being seen at the Anxiety Disorders Clinic, Mr. K. was initially treated with venlafaxine but had severe dose-limiting insomnia and no clinical benefit on a low dose of 37.5 mg twice daily. Attempts to treat the insomnia with imovane, chloral hydrate, and several benzodiazepines (in addition to his usual dose of clonazepam) were ineffective. He was switched to nortryptiline, which after 6 weeks at 150 mg/day resulted in

remission of depression and further reduction in frequency and severity of panic symptoms. Obsessions and compulsions were unsurprisingly unchanged. The decision was made to add citalopram to the tricyclic agent. After 2 weeks of citalopram, 20 mg/day, he reported some reduction in the intensity of obsessional fears and was able to occasionally limit rituals after only a few repetitions. He experienced insomnia, which responded to an increase in his late-evening dose of clonazepam. However, complaints of frequent headaches led to a decrease to 10 mg with loss of benefit. His nortryptiline was subsequently decreased to 50 mg and the citalopram increased back to 20 mg. He reported some nausea, diminishing with time. After 10 weeks on this combination, he had achieved an approximately 30% reduction in his OCD symptoms. Clinically, this translated to a marked reduction in periods of total immobilization from several times per day to only a few times per week. Although he still reported occasional lengthy rituals, he would generally only repeat actions for 5–30 minutes at a time. He had also begun to leave his apartment on a more regular basis.

At 1-year follow-up, Mr. K. continued to benefit from this combination of medications. Several attempts had been made to further increase the citalopram or decrease the nortryptiline dose, but these attempts resulted in complaints of severe headaches and recurrence of depression, respectively. OCD symptoms continued to occupy at least half of his waking time, but were, in his own estimation, "manageable." He had become involved in a committed, caring relationship for the first time in more than 15 years and was living with his partner. After some discussion, the decision was made to continue on this medication regimen indefinitely, in view of his lengthy history of treatment resistance.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised. Washington, DC, American Psychiatric Association, 1987

Baldwin D, Johnson FN: Tolerability and safety of citalopram. Reviews in Contemporary Pharmacotherapy 6:315–325, 1995

Baumann P: Pharmacology and pharmacokinetics of citalopram and other SSRIs. Int Clin Psychopharmacol 11(suppl):5–11, 1996

Baumann P, Larsen F: The pharmacokinetics of citalopram. Reviews in Contemporary Pharmacotherapy 6:287–295, 1995

Baumann P, Nil R, Bertschy G, et al: A double-blind double-dummy study of citalopram comparing infusion versus oral administration. J Affect Disord 49:203–210, 1998

Bejerot S, Bodlund O: Response to high doses of citalopram in treatment-resistant obsessive-compulsive disorder. Acta Psychiatr Scand 98:423–424, 1998

Bejerot S, Humble M: Citalopram treatment of obsessive-compulsive disorder: pilot study of antiobsessive efficacy. Biol Psychiatry 29:443–446, 1991

Berk M, Acton M: Citalopram-associated clitoral priapism: a case series. Int Clin Psychopharmacol 12:121–122, 1997

Bouchard JM, Bellazanz D, Charbonnier JF, et al: Citalopram and viloxazine in the treatment of depression by means of slow drop infusion: a double-blind comparative trial. J Affect Disord 46:51–58, 1997

Bougerol T, Scotto JC, Patris M, et al: Citalopram and fluoxetine in major depression: comparison of two clinical trials in a psychiatrist setting and in general practice. Clin Drug Invest 14:77–89, 1997

Brosen K: Are pharmacokinetic drug interactions with the SSRIs an issue? Int Clin Psychopharmacol 11(suppl):23–27, 1996

Dencker SJ, Hopfner Petersen HE: Side effect profile of citalopram and reference antidepressants in depression, in Citalopram: A New Antidepressant from Lundbeck Research. Proceedings of the XXII Nordiske Psykiater-Kongres, Reykjavik, Iceland, August, 1988. Edited by Montgomery SA. Amsterdam, The Netherlands, Excerpta Medica, 1989, pp 31–42

Dewan MJ, Anand VS: Evaluating the tolerability of the newer antidepressants. J Nerv Ment Dis 187:96–101, 1999

Ekselius L, von Knorring L, Eberhard G: A double-blind multicenter trial comparing sertraline and citalopram in patients with major depression treated in general practice. Int Clin Psychopharmacol 12:323–331, 1997

Elsborg L: Safety aspects of treatment of the elderly with dementia and/or depression: side effect profile of a specific 5HT uptake inhibitor. Nord J Psychiatry 45(suppl):29–35, 1991

Forest Pharmaceuticals Inc: Celexa: Citalopram HBr. St Louis, MO, Warner-Lambert Company, 1998

Fuglum E: Screening and treating depressed patients: a comparison of two controlled citalopram trials across treatment settings: hospitalized patients vs. patient treated by their family doctors. Acta Psychiatr Scand 94:18–25, 1996

Goldstein DF: Effects of third trimester fluoxetine exposure on the newborn. J Clin Psychopharmacol 15:417–420, 1995

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Gravem A, Amthor KF, Astrup C, et al: A double-blind comparison of citalopram (Lu 10-171) and amitriptyline in depressed patients. Acta Psychiatr Scand 75:478–486, 1987

Haffmans PMJ, Timmerman L, Hoogduin CAL, et al: Efficacy and tolerability of citalopram in comparison with fluvoxamine in depressed outpatients: a double-blind, multicentre study. Int Clin Psychopharmacol 11:157–164, 1996

Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–66, 1960

Hytell J: Experimental pharmacology of selective 5-HT reuptake inhibitors: differences and similarities, in Proceedings of the 14th CINP Congress. Edited by Racagni G, Paoletti R, Kielhotz P. Clin Neuropharmacol 7(suppl):866–867, 1984

Hytell J, Bges KP, Perregaard J, et al: The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J Neural Transm 88:157–160, 1992

Insel T, Murphy D, Cohen R, et al: Obsessive-compulsive disorder: a double-blind trial of clomipramine and clorgyline. Arch Gen Psychiatry 40:605, 1983

Jensen PN, Olesen OV, Bertelsen A, et al: Citalopram and desmethylcitalopram concentration in breast milk and in serum of mother and infant. Ther Drug Monit 19:236–239, 1997

Jeppesen U, Gram LF, Vistisen K, et al: Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. Eur J Clin Pharmacol 51:73–78, 1996

Joffe P, Larsen FS, Pedersen V, et al: Single-dose pharmacokinetics of citalopram in patients with moderate renal insufficiency or hepatic cirrhosis compared with healthy subjects. Eur J Clin Pharmacol 54:237–242, 1998

Koponen H, Lepola H, Leinonen E: Citalopram in the treatment of obsessive-compulsive disorder: a report of two cases. Eur Psychiatry 10:209–210, 1995

Koponen H, Lepola H, Leinonen E, et al: Citalopram in the treatment of obsessive-compulsive disorder: an open pilot study. Acta Psychiatr Scand 96:343–346, 1997

Kragh-Sorensen P, Over KF, Petersen OL, et al: The kinetics of citalopram: single and multiple dose studies in man. Acta Pharmacol Toxicol 48:53–60, 1981

Leinonen E, Lepola U, Koponen H, et al: The effect of age and concomitant treatment with other psychoactive drugs on serum concentration of citalopram measured with a non-enanitioselective method. Ther Drug Monit 8:111–117, 1996

Luo H, Richardson JS: A pharmacological comparison of citalopram, a bicyclic serotonin selective uptake inhibitor, with traditional tricyclic antidepressants. Int Clin Psychopharmacol 8:3–12, 1993

March JS, Frances A, Carpenter D, et al (eds): Treatment of obsessive-compulsive disorder. J Clin Psychiatry 58(suppl):10–72, 1997

Maud C, Stein DJ: Treatment of childhood obsessive-compulsive disorder with citalopram. South Am Med J 86:746–747, 1996

Milne RJ, Goa KL: Citalopram: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 41:450–477, 1991

Montgomery S: Citalopram treatment of obsessive-compulsive disorder: results from a double-blind, placebo-controlled trial. Abstract presented at the 37th American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, December 1998

Montgomery SA, Åsberg M: A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389, 1979

Montgomery SA, Djarv L: The antidepressant efficacy of citalopram. Int Clin Psychopharmacol 11(suppl):29–33, 1996

Muldoon C: The safety and tolerability of citalopram. Int Clin Psychopharmacol 11(suppl):35–40, 1996

Mundo E, Bianchi L, Bellodi L: Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. J Clin Psychopharmacol 17:267–271, 1997

Murphy DL, Pickan N, Alertman IS: Methods for the evaluation of depressive and manic behavior, in The Behavior of Psychiatric Patients. Edited by Burock EL, Sudilovsky A, Gershon S. New York, Marcel Dekker, 1982, pp 35–342

Noble S, Benfield P: Citalopram: a review of its pharmacology, clinical efficacy and tolerability in the treatment of depression. CNS Drugs 8:410–431, 1997

Overo KF, Toft B, Christophersen L, et al: Kinetics of citalopram in elderly patients. Psychopharmacology 86:253–257, 1985

Pallanti S, Koran L: Citalopram and sexual side effects of selective serotonin reuptake inhibitors. Am J Psychiatry 156:5, 1999

Pastuszak A, Schick-Boschetto B, Zuber C, et al: Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). JAMA 269:2246–2248, 1993

Pato MT: Beyond depression: citalopram for obsessive-compulsive disorder. Int Clin Psychopharmacol 14(suppl):S19–S26, 1999

Patris M, Bouchard J-M, Bougerol T, et al: Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. Int Clin Psychopharmacol 11:129–136, 1996

Pidrman V, Tuma I: Fenfluramine challenge test in obsessive-compulsive disorder: first results. Acta Medica 40:99–102, 1997

Pidrman V, Tuma I: Citalopram versus clomipramine in double-blind therapy of obsessive-compulsive disorder. 11th Annual Meeting of the European College of Neuropsychopharmacology (ECNP), Paris, France, November 1998

Power A: Citalopram in overdose may result in serious morbidity and death. BMJ 316:306–307, 1998

Rasmussen SL, Overo KF: Cardiac safety of citalopram: prospective trials and retrospective analyses. J Clin Psychopharmacol 19:407–415, 1999

Rochat B, Amey M, Baumann P: Identification of three cytochrome P450 isozymes involved in N-demethylation of citalopram enantiomers in human liver microsomes. Pharmacogenetics 7:1–10, 1997

Sheehan DV, Harnett-Sheehan K, Raja B: The measurement of disability. Int Clin Psychopharmacol 11:89–95, 1996

Sindrup SH, Brsen K, Hansen MGJ, et al: Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. Ther Drug Monit 15:1–17, 1993

Spigset O, Carieborg L, Ohman R, et al: Excretion of citalopram in breast milk. Br J Clin Pharmacol 44:295–298, 1997

Stahl SM: Not so selective serotonin reuptake inhibitors. J Clin Psychiatry 59:343–344, 1998

Stein D, Maud C, Bouwer MB: Use of citalopram, a serotonin selective reuptake inhibitor, in obsessive-compulsive disorder (abstract). Eur Neuropsychopharmacol 6(suppl):70, 1996a

Stein DJ, Maud CM, Bouwer C: Use of the selective serotonin reuptake inhibitor citalopram in obsessive-compulsive disorder. Journal of Serotonin Research 1:29–33, 1996b

Thomsen PH: Child and adolescent obsessive-compulsive disorder treated with citalopram: findings from an open trial of 23 cases. J Child Adolesc Psychopharmacol 7:157–166, 1997

Tollefson GD, Rampey AH, Potvin JH, et al: A multicenter investigation of fixed dose fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 51:559–567, 1994

Wade AG, Lepola U, Koponen HJ, et al: The effect of citalopram in panic disorder. Br J Psychiatry 170:S49–S53, 1997

Wheadon D, Bushnell W, Steiner M: A fixed-dosed comparison of 20, 40, or 60 mg paroxetine to placebo in the treatment of obsessive-compulsive disorder. Presented at the annual meeting of the American College of Neuropsychopharmacology, Honolulu, HI, December 1993

White K, Keck PE, Lipinski J: Serotonin-uptake inhibitors in obsessive-compulsive disorder: a case report. Compr Psychiatry 27:211–214, 1986

This page intentionally left blank

CHAPTER 8

Diagnosis and Treatment in Children and Adolescents

Joseph V. Penn, M.D.
Henrietta L. Leonard, M.D.

> The individual may recognize the obsession to be foolish, but he nevertheless cannot control it, and feels compelled to do so. For instance, an obsessed child may feel that he has to touch doorknobs. So he will touch every doorknob he sees. The obsession might grow so that in addition to touching every doorknob, he must also quite uncontrollably have to tap his right foot as he touches the doorknob. The obsession might continue until it becomes quite an elaborate ritual with the individual not only touching the doorknob and tapping his right foot, but perhaps also turning his head three times in alternate directions.
>
> *Berkowitz and Rothman 1960, p. 61*

It is estimated that perhaps as many as 1 million children and adolescents in this country may have obsessive-compulsive disorder (OCD). In the past, psychiatrists saw few such patients, perhaps because those afflicted with the disorder concealed it or because their symptoms were not appropriately recognized by others. With the increase in both professional and media interest in this disorder and the greater sensitivity to its diagnosis, however, many patients are now being recognized and receiving effective treatments. In this chapter we review the phenomenology, neurobiology, and treatment of OCD in children and adolescents. Pediatric pharmacologic treatment and cognitive-behavioral therapy (CBT) of OCD will be emphasized as well as recommendations for other treatments.

Phenomenology

As recently as 1990, the perception existed that OCD in childhood was a rare condition. The disorder is now thought to be a common neuropsychiatric syndrome that affects more than 1 million children and adolescents in the United States (Flament et al. 1988; Rapoport 1989). Underestimates of the rate of OCD have been attributed, in part, to the fact that individuals with OCD may often disguise or be secretive about their symptoms, may be embarrassed by their "irrationality," and may wait until the symptoms are severe before seeking treatment. Children with OCD, like adults with the disorder, often have symptoms for quite a while before they receive assessment and treatment. Families may turn first to nonpsychiatric specialists who have a varying degree of experience with the disorder (Rapoport 1989; Rasmussen and Tsuang 1986; Zohar et al. 1992), which may further delay recognition and treatment.

As in DSM-III-R (American Psychiatric Association 1987), OCD in DSM-IV and DSM-IV-TR (American Psychiatric Association 1994, 2000) is characterized by recurrent obsessions and/or compulsions that cause marked distress or interference in one's life. To meet diagnostic criteria for OCD, an affected child or adolescent must have either obsessions or compulsions, although the great majority seem to have both, especially now that DSM-IV-TR makes a clear distinction between mental rituals and compulsions. Furthermore, DSM-IV-TR also specifies that affected individuals recognize at some point in the illness that their obsessions are not simply excessive worries about real problems and that their compulsions are excessive or unreasonable. The requirement that insight be preserved is waived for children, although people of all ages who lack insight receive the added specification *poor insight type*. Finally, the specific content of the obsessions cannot be related to another Axis I diagnosis, such as thoughts about food that result from an eating disorder or guilty thoughts (ruminations) that result from major depression.

Children and adolescents with OCD typically have both obsessions and compulsions (Flament et al. 1988; Judd 1965; Riddle et al. 1990b; Swedo et al. 1989a). In contrast to other forms of severe psychopathology, the specific symptoms of the OCD are virtually identical in children and adults (Rapoport 1989; Rettew et al. 1992; Swedo et al. 1989a). Berkowitz and Rothman (1960) described obsessions as varying greatly and ranging from an ideational wish that misfortune or death befall a parent to bizarre, unrealistic persistent thoughts. The most commonly reported obsessions focus on germs and contamination, fears about harm or danger, and worries about right and wrong. The major presenting ritual symptoms (beginning with the most frequently seen) include washing, repeating, checking, touching, counting, arranging,

and hoarding (Flament et al. 1988; Judd 1965; Rettew et al. 1992; Riddle et al. 1990b; Swedo et al. 1989a). The specific types of obsessions and compulsions have been reported to change in content and severity over time in most individuals (Rapoport 1989; Rettew et al. 1992; Swedo 1989a).

There is some disagreement over the gender distribution of children and adolescents with OCD. There is a preponderance of boys in most studies of children and adolescents with OCD; however, two epidemiologic studies of OCD in adolescents and two studies of referred children and adolescents with OCD found an approximately equal number of boys and girls with the disorder (see Hanna 1995). This is most likely due to the fact that, in the prepubertal years, the male:female ratio is increased, whereas this ratio reverses postpubertally. At least one-third of adults with OCD had onset in childhood (Black 1974), often very early. The usual age of onset can range from 3 to 18 years (Riddle et al. 1990) but has been reported as 9 to 11 years (Last and Strauss 1989) and 7 to 18 years with a mean age at onset of 12.8 years (Flament et al. 1988). Several studies suggest that boys have an earlier age at onset than girls (Flament et al. 1988; Last and Strauss 1989), that younger boys have more severe symptoms than younger girls (Flament et al. 1988), and that boys are more likely than girls to have a comorbid tic disorder (Leonard et al. 1992).

The disorder is typically characterized by a waxing and waning course, often with some worsening attributed to psychosocial stress. Initially, children often disguise their rituals (Swedo et al. 1989a). For example, "hand washers" may conceal their actions from their families; thus, only when the disorder has progressed to the point that they have raw, chapped, and bleeding hands do their families "discover" the extent of their illness. One 16-year-old girl's hand washing was detected because she used two bottles of liquid hand-washing soap every day and began carrying around a carton of hand wipes. In another family, the child's extensive showering became apparent when the utility bills for hot water skyrocketed, dozens of towels began to appear in the laundry every day, and all of the soap in the house disappeared. An 8-year-old boy hid his elaborate 2-hour bedtime ritual of arranging until it turned into a contamination fear of his bed and he began sleeping on the floor of his bedroom. (Case examples at the end of this chapter describe the specific presentations and course of treatment of patients in more detail.)

Obviously, severely incapacitated children and adolescents with classic symptoms are more readily diagnosed. However, the less severely ill patients, those with unusual symptoms (such as "a tune in the head"), and those who hide their symptoms are more difficult to recognize. "Red flags" for OCD may include unproductive hours spent on homework,

holes erased into test papers and homework, retracing over letters or words, unusually high utility bills, a dramatic increase in laundry, toilets stopped up from too much paper, exaggerated requests for reassurance, requests for family members to repeat phrases, a preoccupying fear of harm coming to self or others, a persistent fear of contracting an illness, very long bedtime rituals, difficulty leaving the house, hoarding of useless objects, or peculiar patterns for walking, breathing, or sitting.

Several rating scales are available to assess OCD severity. The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) has been specifically adapted for children and is the most widely used (Goodman et al. 1992; Scahill et al. 1997). It can document baseline severity of symptoms and changes over time that otherwise might not be reported unless specifically assessed. Part of this scale, the Y-BOCS Symptoms Checklist, is particularly useful in a clinical interview to elicit all of the symptoms, including the more "minor" ones that might go unnoticed.

The differential diagnosis of OCD is broad and includes the depressive and anxiety disorders (e.g., separation anxiety, social phobia, panic disorder, and generalized anxiety) with obsessional features; stereotypies seen in mental retardation, pervasive developmental disorders, autism, and brain damage syndromes; obsessive-compulsive personality disorder; anorexia and bulimia; tic disorders; and, more rarely, childhood schizophrenia. The anorexic or bulimic patient's consuming interest in calories, exercise, and food certainly bears resemblance to an obsession. Although the two illnesses can coexist, a distinction usually can be made between OCD and a primary eating disorder.

Repetitive formalized behaviors such as stereotypies seen in autism and pervasive developmental disorders are, superficially, somewhat like OCD rituals; however, OCD rituals are typically well organized, complex, and ego-dystonic, whereas in autism, the rituals seem reassuring, lack egodystonicity, and are not associated with an obsession. Other features of autism, such as peculiar speech patterns and severely impaired interpersonal relationships, are not seen in OCD (Swedo and Rapoport 1989). With the increasing work clarifying Asperger's syndrome, it is clear that the rigid and repetitive behaviors look very similar to that seen in OCD. A careful assessment of developmental history and social relationships may be helpful in making the distinction.

Comorbidity

There is frequent association of OCD and tic disorders (Holzer et al. 1994; Leckman et al. 1994; Leonard et al. 1992; Pauls et al. 1986). Thus, it is im-

portant to distinguish carefully between rituals and tics because each require different treatments. In general, patients with OCD have more complex ritualistic compulsions that occur in response to an obsession. Although motor tics can be complex, and many dispel an "urge" or tension, they are not typically initiated by a thought or accompanied by anxiety. On rare occasions, a complex motor tic preceded by a cognition, sensation, or urge may be difficult to distinguish from a compulsive ritual (Leckman et al. 1994). These experiences may include premonitory feelings or urges that are relieved with the performance of the act and a need to perform tics or compulsions until they are felt to be "just right." (For a review of Tourette's syndrome, see Cohen and Leckman 1994.)

Assessment of comorbidity is crucial for effective treatment planning because other diagnoses are common in children and adolescents with OCD (Geller et al. 1996; Swedo et al. 1989b). In the 70 consecutive children with OCD studied at the National Institute for Mental Health (NIMH), comorbidity was common, with only 18 (26%) having no other psychiatric diagnosis (Swedo et al. 1989b; Thomsen 1995). Geller et al. (1996) studied 30 consecutively referred pediatric patients with OCD and found even higher rates of comorbidity: only 1 patient (3%) in the study had no other psychiatric diagnosis. Diagnoses shown to commonly co-occur with OCD include major depression and other mood disorders, multiple anxiety disorders, tic disorders, and disruptive behavioral disorders, particularly attention-deficit/hyperactivity disorder (ADHD) and oppositional defiant disorder. Of these, only tic disorders are thought to have a shared genetic etiology with OCD (Leonard et al. 1992; Pauls et al. 1995), and the relationship with ADHD merits further study (Pauls et al. 1995). Thus, comorbidity in OCD is common but often requires its own diagnostic and treatment interventions.

Intriguing links have been found between tic disorders (including Tourette's syndrome) and OCD. Patients with Tourette's syndrome frequently have obsessive-compulsive features, and patients with OCD have an increased incidence of tic disorders (DeGroot and Bornstein 1994; Pauls et al. 1986). Since the initial systematic family study of probands with Tourette's syndrome (Pauls et al. 1986), others have demonstrated increased rates of OCD in families of probands with the syndrome and increased rates of tic disorders in families of probands with OCD (Leonard et al. 1992; Pauls et al. 1995). Several studies have demonstrated a familial relationship among OCD, tics, and Tourette's syndrome (see Pauls et al. 1995). OCD probands often have a family history of tic disorders and OCD, and Tourette's syndrome probands often have a family history of tic disorders and OCD. Lenane et al. (1988) found that 20% of personally in-

terviewed first-degree relatives of children and adolescents with OCD also met lifetime history criteria for OCD. Of note, the primary OCD symptoms in the affected family member were usually different, suggesting against a modeling theory for OCD and against familial symptom subtypes. Thus, there appears to be a relationship between Tourette's syndrome and OCD (Pauls et al. 1986).

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection (PANDAS)

The clinical description of a subgroup of children and adolescents with OCD characterized by an episodic course in which periods of dramatic and acute symptom exacerbations are interspersed with periods of relative symptom quiescence (Allen et al. 1995; Leonard et al. 1993; Leonard et al. 1999; Swedo 1994; Swedo et al. 1989b, 1993, 1994, 1998) led to the proposal that a distinctive subgroup of patients with neuropsychiatric disorders exists that could be identified by the following criteria: 1) presence of OCD or a tic disorder, 2) prepubertal onset of symptoms, 3) episodic course of symptom severity, 4) association with group A beta-hemolytic streptococcal (GABHS) infection, and 5) association with neurologic abnormalities (Swedo et al. 1997, 1998). These criteria reflect an underlying hypothesis that autoimmunity mediates the neuropsychiatric symptoms; hence, this group was designated as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (Swedo et al. 1997, 1998).

Patients with PANDAS are characterized by an especially early age at onset of symptoms (nearly 3 years younger than that of previously described groups of childhood-onset OCD and tic disorders) (Swedo et al. 1989b); abrupt (often "overnight") onset and exacerbation of symptoms; and a saw-toothed episodic course characterized by periods of remissions and dramatic acute worsening of symptoms. Additionally, the comorbid symptoms of emotional lability, acute separation anxiety, motoric hyperactivity, impulsivity, and distractibility were often episodic and temporally related to GABHS infections (Swedo et al. 1998). The frequency of such symptoms and their strong association with exacerbations have supported the speculation that some or all of these symptoms may be manifestations of the pathophysiology underlying PANDAS. The working diagnostic criteria appear to define a meaningful subgroup of patients with childhood-onset OCD and tic disorders; with further study, other neuropsychiatric symptoms may also be included in the PANDAS spectrum.

Treatment

Children and adolescents with OCD vary significantly among individuals with respect to the specific nature of the OCD and its impact. Furthermore, there are often unique psychosocial and family issues that may influence compliance and treatment response. Thus, each child or adolescent requires a comprehensive individualized assessment of symptoms, comorbidity, and psychosocial factors. (For a general reference on clinical assessment in child psychiatry, see King 1995.) An individualized treatment plan should be developed, and whenever possible both the patient and family should participate in this process.

Two valuable resources provide guidelines for the assessment and treatment of children and adolescents with OCD. March et al.'s (1997) "Expert Consensus Guidelines on the Treatment of Obsessive Compulsive Disorder" and the American Academy of Child and Adolescent Psychiatry's (1998) "Practice Parameters for the Assessment and Treatment of Children and Adolescents with Obsessive Compulsive Disorder" both present detailed reviews of the literature and expert advice on a broad range of practical clinical issues.

Psychodynamic Psychotherapy

It is debatable whether specific OCD symptoms represent specific intrapsychic conflicts. Esman (1990) described how OCD can be understood as having both biologic and psychodynamic components. Psychodynamic psychotherapy may play a limited role in overall treatment because it has generally not been an effective treatment for younger or older patients with OCD (Hollingsworth et al. 1980). Thus, this therapy would no longer be considered the treatment of choice.

Individual and Family Therapy

Psychotherapy may play a significant role in teaching coping skills, addressing comorbid diagnoses and family issues, treating the accompanying anxiety and depressive symptoms of OCD, and helping improve peer and family relationships. Because families affect and are affected by OCD, family members often need assistance and direction in how to effectively participate in pharmacologic and behavioral treatment (Lenane 1989). Specific family therapy and/or marital therapy may be appropriate when family dysfunction or marital discord impedes OCD treatment (see Chapter 9).

Behavioral Treatment

Cognitive-behavioral treatments in the form of exposure and response prevention (ERP) have been well developed and studied in adults with OCD (Baer 1992; Foa and Emmelkamp 1983; Greist 1992; Marks 1987) but have not been as systematically studied in children and adolescents. It is only more recently that the effectiveness of these treatments for children and adolescents has been more carefully reviewed and studied (March 1995; Piacentini 1999). In adults diagnosed with OCD, ERP is considered the behavior treatment of choice (Dar and Greist 1992). Available reports suggest that techniques employed with adults (Marks 1987) are also generally applicable and can be modified for children (for reviews see Berg et al. 1989; March 1995; Wolff and Rapoport 1988; Wolff and Wolff 1991). In addition to ERP, the clinician should consider incorporating relaxation techniques, with overall modification of both behavioral treatments for children (March et al. 1994).

Some clinicians have many misconceptions about CBT and ERP in children and adolescents with OCD, including those about time, effort, expense, and associated patient anxiety. Clinicians often complain that pediatric patients do not comply with behavioral treatments, and parents complain that clinicians are not specifically trained in CBT for OCD (March et al. 1994). Often, behavioral treatment may be prematurely discontinued. Mental health practitioners experienced in the behavioral treatment of OCD are in short supply (March et al. 1994). The involvement of family members is often an important consideration in such treatment because familial overinvolvement, marital stress, and psychopathology can interfere with the success of behavior modification.

Based on clinical reports, CBT using ERP appears to be an important treatment intervention to consider in children and adolescents with OCD. Exposure-based treatments include gradual (sometimes termed graded) exposure or flooding, with the exposure targets under patient and/or therapist control. For example, a child with contamination fears must come into, and remain in, contact with a particular OCD phobic stimulus. Response prevention operates under the principle that adequate exposure depends on blocking rituals or avoidance behaviors (Dar and Greist 1992). Thus, aside from touching "contaminated" objects, the patient must refrain from rituals to dispel the anxiety. Thus, the patient and therapist develop a "tolerable" hierarchy of increasingly anxiety-producing stimuli, and these stimuli are assigned subjective units of discomfort scores (SUDS) to quantify the increasing exposure. Eventually, through repeated exposure and response prevention, there is a substantial reduction in pre-

viously overwhelming anxiety when confronted with the stimulus and the anxiety reduction can occur without performing compulsions (Francis and Gragg 1996).

In addition to ERP, there are various other CBT techniques such as anxiety management training, which consists of relaxation and breathing control training, and cognitive restructuring. There are also additional cognitive therapies, such as satiation, thought stopping, and habit reversal, that have been employed to support ERP (see March 1995; March et al. 1994).

Behavioral treatment of OCD should be developmentally sensitive to address the unique issues of each age group. Children may often view their symptoms or experience distress and interference very differently than do their parents (Berg et al. 1989). Because of these differences and the often secretive nature of OCD, it is paramount for the therapist to gain the child's cooperation and willingness and to individualize the particular behavioral treatment. Thus, in general, there are attempts to facilitate a sense of mastery and accomplishment and to minimize massive initial anxiety (such as in flooding). Unlike behavioral treatment for adults with OCD, in which the therapist usually selects the treatment plan, hierarchy of exposure targets, and SUDS scores, the treatment plan and particularly the SUDS hierarchy for children must be established by the child and therapist in collaboration. March and Mulle (1993) developed a protocol-driven treatment manual (*How I Ran OCD Off My Land*) based on a framework of cognitive interventions and ERP. It is explicitly designed to facilitate patient and parental compliance, exportability to other clinicians, and empirical evaluation (March 1995; March and Mulle 1998). In particular, the child is in charge of the choice of exposure targets and the selection of metaphors.

It should be emphasized that empirical evidence of the efficacy of CBT in children with OCD remains limited, especially when contrasted with the literature on pharmacotherapy (Rapoport et al. 1992). March (1995) reviewed 32 investigations, most of which were single case reports with varying degrees of terminology, theoretical framework, and methodologic limitations (i.e., outcomes by self-report), and found that all but one showed benefit for CBT interventions. Because most of the reports were not designed to specifically test the effect of a single behavioral procedure, it was difficult to draw generalized conclusions. Additionally, in most of these studies behavioral treatment was only one part of the multimodal approach and sometimes had only a secondary role. Future research in this area should use controlled trials with standardized diagnostic definitions, baseline observations or established treatment time course, and objective

rating scales to compare medications, behavior therapy, combination treatment, and follow-up studies.

There are several prognostic indicators for successful response to behavioral treatment of OCD; namely, a motivated patient, the presence of overt rituals and compulsions, an ability to monitor and report symptoms, an absence of complicating comorbidities, and a willingness to cooperate with treatment (Foa and Emmelkamp 1983). Furthermore, the ERP technique appears to be more successful for patients with compulsions than for patients with obsessions only or those with obsessional slowness. Clinically, children with primary obsessional slowness generally respond poorly to both behavioral and medication treatment (Wolff and Rapoport 1988). Because ERP has not proven particularly helpful with obsessional slowness, modeling and shaping procedures may be the CBT of choice with this OCD subtype (Ratnasuriya et al. 1991). Future investigations using diverging subjects and clinical settings will be necessary to see if children and adolescents with difficult-to-manage OCD will respond to manualized CBT.

The systematic comparison of drug versus behavioral therapy is as limited for children and adolescents with OCD as it is for adults. There are few guidelines suggesting which treatment to start with (American Academy of Child and Adolescent Psychiatry 1998; March et al. 1997). The decision remains a complex clinical balance between the availability of behavioral treatment, cooperation on the part of the child, and the child's specific symptom pattern. Baer and Minichello (1990) suggested that medication and behavioral therapy actually complement each other and that the use of antiobsessional agents may help improve compliance with behavioral treatment. Potential advantages of behavioral therapy alone may include avoiding the adverse reactions from medications, particularly because the medications have received limited pediatric study. It is also hypothesized that booster behavior therapy may prevent relapse when medications are discontinued (March 1995). Furthermore, in patients treated with medication, concurrent CBT (including booster treatments during medication discontinuation) may improve short- and long-term outcome in medication-responsive patients, including those for whom ongoing pharmacotherapy proves necessary (March 1995). Pharmacotherapy and CBT work well together, and many children with OCD require or would benefit from this combination (Piacentini et al. 1992).

There is abundant clinical and emerging empirical evidence that CBT alone or in combination with pharmacotherapy is an important, safe, acceptable, and effective treatment for OCD in children and adolescents (March 1995; March et al. 1994). A proposed trial of CBT should be pre-

sented and discussed with each individual patient and his or her family. Obviously, each child requires an individual recommendation, but ideally, young persons with OCD should first receive CBT either with or without medication. If not rapidly responsive, or if experiencing marked depression, then concurrent medication treatment should be given. It is crucial to gain the child's cooperation and willingness to participate because he or she has to tolerate the significant stress of implementing the program (American Academy of Child and Adolescent Psychiatry 1998; March et al. 1997).

Pharmacologic Treatment

Clomipramine

Clomipramine, a tricyclic antidepressant (TCA) and potent serotonin reuptake inhibitor, was used in the first controlled pharmacologic treatment trial in children and adolescents for OCD. Nineteen pediatric patients (mean age, 14.5 ± 2.3 years) were studied in a 12-week double-blind placebo-controlled crossover study (5 weeks of active medication) (Flament et al. 1985, 1988). Doses of clomipramine targeting 3 mg/kg/day were used, with a mean dose of 141 mg/day. In the 14 patients with OCD who completed the trial, clomipramine was significantly better than placebo in decreasing obsessive-compulsive symptoms at week 5. An improvement in symptoms could usually be seen as early as week 3, and 75% of the patients had a moderate to marked improvement. This hallmark study led the way for subsequent trials, including those of the newer selective serotonin reuptake inhibitors (SSRIs).

Clomipramine is unique among the TCAs because it significantly inhibits serotonin reuptake. Interestingly, its primary metabolite, desmethylclomipramine, is a potent noradrenergic reuptake inhibitor (Ross 1975); thus, clomipramine has both noradrenergic and serotonergic action. Leonard et al. (1989) noted that clomipramine was clearly superior to desipramine (a selective noradrenergic reuptake inhibitor) in a double-blind crossover comparison of 48 children and adolescents with OCD. The comparison drug desipramine was used because of its similar side effect profile and antidepressant efficacy. Thirty-one boys and girls with a mean age of 13.9 years (range, 7–19 years) and a mean age at onset of 10.2 years (range, 5–16 years) were studied using an average dose of 150 mg/day. Clomipramine was significantly better than desipramine in ameliorating OCD symptoms at week 5. Desipramine was no more effective in improving obsessive-compulsive symptoms than placebo had been in a previous study by Flament et al. (1985). In fact, when desipramine was given as the

second active medication, 64% of the patients had some degree of relapse within several weeks of crossover.

Subsequently, a large 8-week multicenter double-blind parallel comparison of clomipramine versus placebo was completed that led to U.S. Food and Drug Administration (FDA) approval of clomipramine for the treatment of OCD in children and adolescents (aged 10 years or older) (DeVeaugh-Geiss et al. 1992). Clomipramine was generally well tolerated in these studies and in clinical experience. Long-term clomipramine maintenance has not revealed any unexpected adverse reactions (DeVeaugh-Geiss et al. 1992; Leonard et al. 1991, 1995).

There are anticholinergic, antihistaminic, and alpha-blocking side effects associated with clomipramine. The most common side effects reported by children and adolescents include (in order of decreasing frequency) dry mouth, somnolence, dizziness, fatigue, tremor, headache, constipation, anorexia, abdominal pain, dyspepsia, and insomnia, and they are comparable with (but anecdotally are reported as milder than) those seen in adults (DeVeaugh-Geiss et al. 1992; Leonard et al. 1989). One recent report indicated that clomipramine did not have any unexpected cardiotoxic effects. Leonard et al. (1995) suggested that baseline and periodic electrocardiographic monitoring is advisable. Several adolescents who discontinued clomipramine abruptly (during long-term maintenance) experienced withdrawal symptoms of gastrointestinal distress, which appeared to be a cholinergic rebound syndrome like those reported with other antidepressants (Leonard et al. 1989). Thus, abrupt discontinuation of clomipramine is not recommended.

Selective Serotonin Reuptake Inhibitors

The SSRIs have been studied extensively over the past decade. Currently, the medications with an FDA-approved indication for OCD in children include clomipramine (in children 10 years or older), sertraline (children 6 years or older), and fluvoxamine (children 8 years or older). The SSRIs are considered selective inhibitors of serotonin because of their limited effect on other monoamines (Warrington 1992). They represent a new class of agents with distinct advantages in their side effect profile and their broad therapeutic index over those of the TCAs.

A multisite study of fluvoxamine in 8–17-year-olds with OCD demonstrated safety and efficacy (Riddle et al. 1996) and led to an FDA indication (for OCD in children 8 years or older) in 1997. The most common side effects of fluvoxamine include sedation, nausea, anorexia, tremor, and sexual dysfunction, and its side effect profile is clearly less anticholinergic than those of the TCAs.

Similarly, a recent multicenter randomized placebo-controlled trial of sertraline in 187 children and adolescents demonstrated safety and efficacy (March et al. 1998) and led to an FDA indication (for OCD in children 6 years or older). Sertraline was titrated to a maximum of 200 mg/day during the first 4 weeks of double-blind therapy, after which patients continued to receive this dose for 8 more weeks. The most common side effects of sertraline include nausea, dyspepsia, agitation, and tremor.

Riddle et al. (1990a, 1992) concluded that fluoxetine appeared to be safe, effective, well tolerated, and superior to placebo in a small controlled trial of children and adolescents with OCD. The most common side effects included nervousness, insomnia, and restlessness. Two small controlled trials of fluoxetine in children with OCD and Tourette's syndrome reported a modest effect on OCD symptoms (improvement from baseline but not superior to placebo) and no exacerbation of tics (Kurlan et al. 1993; Scahill et al. 1997). A large trial in children is under way. Although no large, systematic studies have been published for children with OCD, fluoxetine is widely used (American Academy of Child and Adolescent Psychiatry 1998) and was the first SSRI commercially available in the United States.

Fluoxetine is reasonably well tolerated in children and adolescents (Riddle et al. 1992). The most common side effects include nervousness, insomnia, and restlessness. To minimize side effects, lower initial doses are used, sometimes 2.5–5.0 mg/day, depending on the child's age and weight. Geller et al.'s (1995) open trial of fluoxetine in children used an average dose of 1 mg/kg/day, and the therapeutic effect was sustained over time (mean follow-up, 19 months). Occasionally, the younger age group may be started on 10 mg (i.e., one-half the usual adult dose) of fluoxetine in the morning; the suspension offers dose flexibility. Given the long half-life of the parent drug and metabolite, steady state is not reached for 2–3 weeks and the drug is not completely eliminated from the system for up to 6 weeks after discontinuation. Thus, clinicians are advised to increase the dose slowly and to monitor for delayed side effects as late as 2 weeks after a dose increase.

A large multisite study of paroxetine in the treatment of OCD in children and adolescents is under way. Citalopram, the most recently introduced SSRI in the United States, has been studied in 23 subjects in an open fashion. Thomsen (1997) reported a generally favorable response with 11 of 23 subjects improving and only 5 having little or no response. Larger trials will be needed to study the safety and efficacy of paroxetine and citalopram in the pediatric population.

The SSRI advantages of few anticholinergic side effects and limited cardiovascular toxicities are particularly relevant for the pediatric popula-

tion (Leonard et al. 1997). There are no defined indications for electrocardiographic monitoring or plasma level monitoring. Most of the side effects reported for SSRIs are from adult studies and include complaints of nausea, headache, nervousness, insomnia, diarrhea, and drowsiness (Stokes 1993).

Clinicians should begin with lower doses of the SSRIs for children and adolescents than would typically be used for adults. Patients should be monitored during SSRI treatment for energizing, activating side effects, behavioral activation/dyscontrol, motor restlessness, and the more common side effects mentioned earlier. There are some case reports of children and adults developing unusual mental status changes (i.e., hallucinations, mania, psychosis, and frank delirium) that highlight the importance of considering concomitant prescription, over-the-counter, or illegal drug use (Leonard et al. 1997). In general, these reports have been rare and it remains unclear whether they were dose related or the result of a drug–drug interaction. Clinicians should inquire about all over-the-counter medications, recreational drugs, and prescription medications used by the patient (especially terfenadine and astemizole [particularly in combination with certain medications, e.g., ketoconozole], which have been shown to prolong the QT interval) (Leonard et al. 1997). Additionally, it has been clearly established that a combination of clomipramine and an SSRI may result in disproportionate clomipramine levels because of competitive inhibition.

Although pharmacologic treatment for each patient with OCD must be individualized, there are a few clinical recommendations. Empirical findings suggest that clomipramine and the SSRIs differ considerably with respect to adverse effects; thus, the choice of a particular agent should be based on the side effect profile, the known efficacy of the agent, and the presence or absence of comorbid diagnoses. SSRIs are preferable to clomipramine for patients with suicidal risk. For patients with OCD and comorbid diagnoses such as ADHD, tic disorders, or anxiety disorders, there is no "head-to-head" evidence that a specific SSRI or clomipramine is more efficacious than another. All of the SSRIs should be used cautiously in patients with lowered seizure thresholds but are preferable antidepressant choices over TCAs.

Clinicians should be aware that during early treatment (first 1 to 2 weeks) with SSRIs, some patients may actually develop a worsening of their OCD symptoms or experience particularly annoying side effects (i.e., insomnia, increased psychomotor activity). This has been referred to as an agitated syndrome and has been well described in patients with some doses. Typically, the exacerbation subsides and a positive clinical response ensues. Thus, the patient and family should be educated about and encouraged to

report worsening or problematic side effects. Initial worsening in the first week usually is not a reason in and of itself to discontinue the medication. As a matter of caution, children should be started at a low dose.

Headaches are commonly reported as a side effect of treatment with the SSRIs, with an incidence up to 15% (Stokes 1993). Because serotonergic dysfunction has been implicated in the pathophysiology of migraine, it is possible that initiation of SSRI treatment may be associated with precipitation of migraine. Thus, the clinician should take a family and personal history of migraines before initiating SSRI pharmacotherapy. If there is a clear history, treatment should begin at lower doses and be increased slowly.

Maintenance and Follow-Up

Because OCD symptoms tend to wax and wane, many patients will experience some continued symptoms that vary in severity over time. Some evidence suggests that long-term maintenance may be required for some medication-responsive patients. Leonard et al. (1991) conducted a double-blind desipramine substitution study of patients maintained on clomipramine long-term in which 8 of the 9 desipramine substitution patients but only 2 of the 11 nonsubstitution patients relapsed. This finding is consistent with that in a study by Pato et al. (1988) in which the majority of adult patients relapsed when taken off maintenance clomipramine. Nevertheless, it is recommended that the medication be periodically tapered to establish whether it is necessary. For a patient who has been symptomatic and who has had a positive clinical response, a slow decrease in medications usually is not attempted in the first year. Often, the patients do not experience an immediate increase in OCD symptoms but rather a gradual insidious return over the subsequent 1–3 months.

Although many patients respond early to one of the serotonin reuptake inhibitors, a substantial minority do not respond until 8 or even 12 weeks of treatment (with therapeutic doses toward the end). Thus, it is important for the clinician to be patient, target a therapeutic dose, and wait at least 10–12 weeks before changing agents or undertaking augmentation regimens. If there is no clinical response after 12 weeks, switching to another SSRI is merited.

In a subpopulation of children with tic disorder, an augmentation of antiobsessional medications with a small dose of haloperidol (1–3 mg/day) or pimozide (0.5–2 mg/day) might be warranted. In a double-blind placebo-controlled study, McDougle et al. (1994), found that this combination (antiobsessive and dopamine blocker) is an effective therapeutic

intervention for obsessive-compulsive symptoms and tics, whereas anti-obsessional medications alone were not effective.

Summary

It is estimated that perhaps as many as 1 million children and adolescents in the United States may have OCD. Childhood OCD presents in a form essentially identical to that seen in adults, and one-third of adult cases have had their onset in childhood. Boys seem to have an earlier age at onset of OCD (prepuberty), whereas girls are more likely to have onset around puberty. Washing, repeating, checking, touching, counting, arranging, hoarding, and scrupulosity are the most commonly seen rituals. Almost all patients reported a change in their principal symptoms over time. Increasing evidence supports a neurobiologic theory for the etiology of OCD, specifically a frontal lobe–basal ganglia dysfunction.

Most recent studies suggest that the early (prepubertal) onset of OCD and/or tic disorders characterized by abrupt onset and acute exacerbations may represent a subtype of pediatric OCD (PANDAS). This group may have environmental triggers and may merit different assessment (e.g., medical illness) and treatment. Childhood OCD appears to have a similar treatment response to that seen in adults with the illness. Behavioral treatment has not been systematically studied in children and adolescents, but reports suggest that response prevention techniques are useful. Flament et al. (1985) found clomipramine to be superior to placebo at week 5 in a double-blind crossover design. Leonard et al. (1989) reported that clomipramine was significantly better than desipramine at week 5 in a double-blind crossover comparison. Fluvoxamine and sertraline were found to be effective, safe, and well tolerated in children with OCD. As for other SSRIs, fluoxetine, paroxetine, and citalopram have been reported in anecdotal cases to be safe and well tolerated in the pediatric population, although systemic studies are needed. Follow-up studies indicate that at least 50% of pediatric patients with OCD are still symptomatic as adults; however, it is hoped that the new treatment modalities available will improve the long-term follow-up outcome.

Case Examples

Case 1: Contamination Fears and Washing

K.W., age 8, was brought to the NIMH by his parents after 2 years of excessive hand washing. He would spend 4 hours or more per day washing

and rewashing his hands, which caused him to be late to school and to stay up late at night. K.W.'s hands were chapped and bleeding from the washing, and he would not allow any lotion to be put on his hands for fear of "contamination." He walked around with his hands up in the air in a "surgeon's position" for fear of contacting anything dirty. He was no longer able to touch doorknobs, flush toilets, touch anyone else, or play with his dog or in any contact sports. K.W. responded to clomipramine (at 3 mg/day) but not to desipramine during the NIMH double-blind study with a dramatic decrease (85%) in his washing and avoidance rituals. He was maintained on clomipramine for 1½ years and spent only 20 minutes per day washing his hands. Although traces of the rituals remained, they did not interfere in his life (e.g., he could play with his dog). When the patient's clomipramine was blindly substituted with desipramine, he relapsed within 3 weeks and was returned to his maintenance clomipramine dose.

Case 2: Repetition

J.R., age 17, would retrace his steps from the car into the house in a very elaborate and specific manner (two steps forward, look to the sky, three steps backward, glance to the left and think a good thought). It took 20 minutes to go a distance that normally should have taken seconds. His complex rituals made him the object of neighborhood curiosity. If interrupted or prevented from completing his elaborate walking ritual, he became enraged and inconsolable. J.R. had a good response (70%) to clomipramine but not desipramine during the NIMH double-blind study. He completely stopped his repeating rituals. He acknowledged that the impulse to perform the rituals remained but that he was able to resist it without much effort. J.R. was maintained on clomipramine (at 3 mg/kg/day) and developed tachycardia and orthostatic hypotension without any electrocardiogram changes. When his dose was dropped (to 2 mg/kg/day) and 1,000 mg/day of L-tryptophan was added to augment the clomipramine the tachycardia resolved, but he was unable to maintain his clinical response. J.R. was switched to fluoxetine, 60 mg/day, and had an excellent response without side effects.

Case 3: Checking

L.S., age 16, had checking rituals as her predominant symptom. Approximately 1 year before presentation, she rather suddenly began to spend an hour at night checking whether the doors and windows were locked and all electrical plugs were pulled out. She could not trust her parents' efforts. Her elaborate pattern of checking the house included many repetitions until she felt "it had been done right." When her symptoms increased and she began to wake her parents up at 3 A.M. to recheck the house, help was sought. L.S. showed a dramatic response to clomipramine at 3 mg/kg/day with minimal side effects (dry mouth, mild tiredness). After 1 year of maintenance, she was tapered off the clomipramine to assess whether it was necessary, and her symptoms returned

3 weeks after discontinuing the medication. L.S. resumed her previous dose of clomipramine, and she regained her clinical response within 3 weeks.

Case 4: Touching

Touching rituals are slightly less common than those of washing and checking. D.D., age 13, felt incapacitated by a need to touch the corners of chairs, refrigerators, doors, and walls. She developed callouses on her hands from touching the walls so many times. She felt compelled to touch them "just the right way" for as long as 2 hours per day. If the ritual was interrupted, she had to start all over again. This behavior was extremely distressing to her, yet she was unable to stop. D.D. had a moderate response (50% reduction in time spent in rituals) to clomipramine at 3 mg/kg/day but not to desipramine in the NIMH double-blind comparison. D.D. felt moderately troubled by the side effects of excessive sweating and daytime tiredness, and she elected not to continue clomipramine maintenance. Currently, the family reports that she is "doing well," but she has not been seen for reevaluation.

Case 5: Arranging

S.E., age 11, was brought for evaluation for needing to "have everything in her room just so." She would spend about 3 hours every day straightening every item in each drawer in her bedroom and every article of clothing in her closet. The rituals increased in time and became so subjectively incapacitating that she refused to go into her room anymore and had to sleep on the floor outside her room to make sure that no one went in to mess anything up. S.E. had a favorable response to clomipramine (75% reduction in time spent in rituals) during the NIMH study. Clomipramine maintenance at 3 mg/kg/day was adequate for continuing the response; however, with an increase of medication to 3.5 mg/kg/day and the addition of behavior therapy, her rituals were decreased 95% to about 5 minutes per day of "making things right."

Case 6: Hoarding

B.W., age 6, had to pick up anything that he might walk over. He began to bring home old pieces of paper, rocks, twigs, and trash that he found on the way home from school. The problem progressed until he was late to school because of having to pick everything up, and he would not allow anything that he had collected to be thrown away. He would go through the house trash and save old coffee envelopes, empty toothpaste tubes, ads, and newspapers. The problem progressed to such a point that his room was full of trash, and his parents felt that it was a health hazard. Whenever they tried to clean his room, B.W. would become agitated and have to be restrained. B.W. had an excellent response to clomipramine (3 mg/kg/day) but was unable to tolerate desipramine, which caused agitation. Unfortunately, B.W.'s coexisting severe ADHD was unchanged by

the clomipramine and remained a continuous problem. When fluoxetine was substituted, he experienced agitation and was unable to tolerate the medication for this reason. During a trial of methylphenidate, the patient developed tics, and the medication was discontinued. Trials of imipramine, desipramine, and clonidine to target the ADHD symptoms were unsuccessful. Other psychopharmacologic interventions are being considered.

Case 7: Scrupulosity

W.S., age 17, prayed about 4 hours per day. Although he came from a very religious family, they became quite concerned about what they perceived as excessive prayer. W.S. would ruminate over past deeds for hours, tortuously reviewing them and wondering if he had done something wrong. He began to go to confession three times per day seeking forgiveness for imagined misdeeds and would repeatedly ask his parents if he had done anything wrong and if he were going to hell. Although W.S. experienced a decrease in symptoms while receiving clomipramine, he chose not to continue on the medication because he was not distressed enough by his praying to want it treated.

Case 8: Somatic Preoccupation

A recent presentation of OCD is the preoccupying fear that one might have AIDS. K.T., age 17, believed that she had contracted AIDS from having touched a sterile, packaged syringe on the ground at a carnival. This conviction that she had AIDS later transformed into fearing that she had herpes and rabies. K.T.'s obsessions about AIDS disappeared while she was receiving clomipramine maintenance over a period of 6 months. When the medication was discontinued, her symptoms did not return. She has been symptom-free for 2 years now.

References

Allen AJ, Leonard HL, Swedo SE: Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 34:307–311, 1995

American Academy of Child and Adolescent Psychiatry: Practice parameters for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 37:27S–45S, 1998

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised. Washington, DC, American Psychiatric Association, 1987

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision. Washington, DC, American Psychiatric Association, 2000

Baer L: Behavioral therapy for obsessive-compulsive disorder and trichotillomania: implications for Tourette's syndrome. Adv Neurol 58:333–340, 1992

Baer L, Minichello WE: Behavior therapy for obsessive-compulsive disorder, in Obsessive Compulsive Disorders: Theory and Management. Edited by Jenike M, Baer L, Minichello W. Chicago, IL, Year Book Medical, 1990, pp 203–232

Berg CZ, Rapoport JL, Wolff RP: Behavioral treatment for obsessive-compulsive disorder in childhood, in Obsessive-Compulsive Disorder in Children and Adolescents. Edited by Rapoport JL. Washington DC, American Psychiatric Press, 1989, pp 169–185

Berkowitz PH, Rothman EP: The Disturbed Child: Recognition and Psychoeducational Therapy in the Classroom. New York, New York University, 1960, pp 61–65

Black A: The Natural History of Obsessional Neurosis in Obsessional States. Edited by Hoch PH, Zubin J. London, England, Methuen, 1974, pp 19–54

Cohen D, Leckman JF: Developmental psychopathology and neurobiology of Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 33:2–15, 1994

Dar R, Griest J: Behavior therapy for obsessive compulsive disorder. Psychiatr Clin North Am 15:885–894, 1992

DeGroot CM, Bornstein RA: Obsessive characteristics in subjects with Tourette's syndrome are related to symptoms in their parents. Compr Psychiatry 35:248–251, 1994

DeVeaugh-Geiss GJ, Moroz G, Biederman J, et al: Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder: a multicenter trial. J Am Acad Child Adolesc Psychiatry 31:45–49, 1992

Esman A: Psychoanalysis in general psychiatry: obsessive-compulsive disorder as a paradigm. J Am Psychoanal Assoc 37:316–319, 1990

Flament MF, Rapoport JL, Berg C, et al: Clomipramine treatment of childhood obsessive-compulsive disorder. Arch Gen Psychiatry 42:977–983, 1985

Flament MF, Whitaker A, Rapoport JL, et al: Obsessive compulsive disorder in adolescence: an epidemiological study. J Am Acad Child Adolesc Psychiatry 27:764–771, 1988

Foa E, Emmelkamp P: Failures in Behavior Therapy. New York, Wiley and Sons, 1983

Francis G, Gragg RA: Childhood Obsessive Compulsive Disorder: Developmental Clinical Psychology and Psychiatry, Vol 35. Thousand Oaks, CA, Sage Publications, 1996

Geller D, Biederman J, Reed ED, et al: Similarities in response to fluoxetine in the treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 34:36–44, 1995

Geller D, Biederman J, Griffin S, et al: Comorbidity of juvenile obsessive-compulsive disorder with disruptive behavior disorders: a review and report. J Am Acad Child Adolesc Psychiatry 35:1637–1646, 1996

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, II: validity. Arch Gen Psychiatry 46:1012–1016, 1992

Griest JH: An integrated approach to treatment of obsessive compulsive disorder. J Clin Psychiatry 53(suppl):38–41, 1992

Hanna GL: Demographic and clinical features of obsessive-compulsive disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry 34:19–27, 1995

Holzer JC, Goodman WK, McDougle CJ, et al: Obsessive-compulsive disorder with and without a chronic tic disorder: a comparison of symptoms in 70 patients. Br J Psychiatry 164:469–473, 1994

Hollingsworth C, Tanguay P, Grossman L: Long-term outcome of obsessive compulsive disorder in childhood. J Am Acad Child Psychiatry 19:134–144, 1980

Judd LL: Obsessive compulsive neurosis in children. Arch Gen Psychiatry 12:136–143, 1965

King RA: Practice parameters for the psychiatric assessment of children and adolescents. J Am Acad Child Adolesc Psychiatry 34:1386–1402, 1995

Kurlan R, Como PG, Deeley C, et al: A pilot controlled study of fluoxetine for obsessive-compulsive symptoms in children with Tourette's syndrome. Clin Neuropharmacol 16:167, 1993

Last CG, Strauss CC: Obsessive-compulsive disorder in childhood. J Anxiety Disord 3:295–302, 1989

Leckman JF, Walker DE, Goodman WK, et al: "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. Am J Psychiatry 151:675–680, 1994

Lenane M: Families and obsessive-compulsive disorder, in Obsessive-Compulsive Disorder in Children and Adolescents. Edited by Rapoport JL. Washington, DC, American Psychiatric Press, 1989, pp 237–252

Lenane M, Swedo S, Leonard H, et al: Obsessive compulsive disorder in first degree relatives of obsessive compulsive disorder in children. Paper presented at the annual meeting of the American Psychiatric Association, Montreal, Canada, May 1988

Leonard HL, Swedo S, Rapoport JL, et al: Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents: a double-blind crossover comparison. Arch Gen Psychiatry 46:1088–1092, 1989

Leonard HL, Swedo SE, Lenane MC, et al: A double-blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive-compulsive disorder. Arch Gen Psychiatry 48:922–927, 1991

Leonard HL, Lenane MC, Swedo SE, et al: Tics and Tourette's disorder: a two to seven year follow-up study of 54 obsessive-compulsive children. Am J Psychiatry 149:1244–1251, 1992

Leonard H, Swedo S, Lenane M, et al: A 2–7-year follow-up study of 54 obsessive-compulsive disorder children and adolescents. Arch Gen Psychiatry 50:429–439, 1993

Leonard H, Swedo S, March J, et al: Obsessive-compulsive disorder, in Treatment of Psychiatric Disorders, 2nd Edition. Edited by Gabbard G. Washington, DC, American Psychiatric Press, 1995, pp 301–313

Leonard HL, March J, Rickler KC, et al: Pharmacology of the selective serotonin reuptake inhibitors in children and adolescents. J Am Acad Child Adolesc Psychiatry 36:725–736, 1997

Leonard HL, Swedo SE, Garvey M, et al: Postinfectious and other forms of obsessive compulsive disorder. Child and Adolescent Psychiatric Clinics of North America 8:497–511, 1999

March J: Cognitive-behavioral psychotherapy for children and adolescents with OCD: a review and recommendations for treatment. J Am Acad Child Adolesc Psychiatry 34:7–18, 1995

March J, Mulle K: How I Ran OCD Off My Land: A Cognitive-Behavioral Program for the Treatment of Obsessive-Compulsive Disorder in Children and Adolescents. Available upon request. Durham, NC, Duke University, 1993

March J, Mulle K: OCD in Children and Adolescents: A Cognitive-Behavioral Treatment Manual. New York, Guilford Press, 1998

March J, Mulle K, Herbel B: Behavioral psychotherapy for children and adolescents with obsessive-compulsive disorder: an open trial of a new protocol-driven treatment package. J Am Acad Child Adolesc Psychiatry 33:333–341, 1994

March J, Leonard H, Swedo S: Obsessive-compulsive disorder, in Anxiety Disorders in Children and Adolescents. Edited by March J. New York, Guilford Press, 1995, pp 251–275

March J, Frances A, Carpenter D, et al: Expert consensus guidelines: treatment of obsessive-compulsive disorder. J Clin Psychiatry 58(suppl):1–72, 1997

March JS, Biederman J, Wolkow R, et al: Sertraline in children and adolescents with obsessive-compulsive disorder: a multi-center randomized controlled trial. JAMA 280:1752–1756, 1998

McDougle C, Goodman W, Leckman JJ, et al: Haloperidol addition in fluvoxamine refractory obsessive compulsive disorder. Arch Gen Psychiatry 51:302–308, 1994

Marks IM: Fears, Phobias and Rituals, Panic Anxiety and Their Disorders. Oxford, England, Oxford University Press, 1987

Pato MT, Zohar-Kadouch R, Zohar J, et al: Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. Am J Psychiatry 145:1521–1525, 1988

Pauls DL, Towbin K, Leckman J, et al: Gilles de la Tourette syndrome and obsessive compulsive disorder: evidence supporting a genetic relationship. Arch Gen Psychiatry 43:1180–1182, 1986

Pauls DL, Alsobrook JP, Goodman W, et al: A family study of obsessive-compulsive disorder. Am J Psychiatry 152:76–84, 1995

Piacentini J, Jaffer M, Gitow A, et al: Psychopharmacologic treatment of child and adolescent obsessive compulsive disorder. Psychiatr Clin North Am 15:87–107, 1992

Piacentini J: Cognitive behavioral therapy of childhood OCD. Child Psychiatr Clin North Am 8:599–616, 1999

Rapoport JL: Obsessive-Compulsive Disorder in Children and Adolescents. Washington, DC, American Psychiatric Press, 1989

Rapoport J, Swedo S, Leonard H: Childhood obsessive compulsive disorder. J Clin Psychiatry 53(suppl):6–11, 1992

Rasmussen SA, Tsuang MT: Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. Am J Psychiatry 143:317–322, 1986

Ratnasuriya R, Marks IM, Forshaw D, et al: Obsessional slowness revisited. Br J Psychiatry 159:273–274, 1991

Rettew DC, Swedo SE, Leonard HL, et al: Obsessions and compulsions across time in 79 children and adolescents with obsessive compulsive disorder. J Am Acad Child Adolesc Psychiatry 29:766–772, 1992

Riddle MA, Hardin M, King R, et al: Fluoxetine treatment of children and adolescents with Tourette's and obsessive compulsive disorders: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry 29:45–48, 1990a

Riddle MA, Scahill L, King R, et al: Obsessive compulsive disorder in children and adolescents: phenomenology and family history. J Am Acad Child Adolesc Psychiatry 29:766–772, 1990b

Riddle MA, Scahill L, King R, et al: Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 31:1062–1069, 1992

Riddle MA, Walkup J, Claghorn J, et al: Fluvoxamine for OCD in children and adolescents: a controlled trial. Poster presented at the annual meeting of the American Academy of Child and Adolescent Psychiatry, Philadelphia, PA, 1996

Ross SB, Renyi AL: Tricyclic antidepressant agents: comparison of inhibition of the uptake of 3H-noradrenaline and 14c-5-hydroxytryptamine in slices and crude synaptosome preparations of the midbrain-hypothalamus region of the rat brain. Acta Pharmacol Toxicol 36:382–394, 1975

Scahill L, Riddle MA, King RA, et al: Fluoxetine has no marked effect on tic symptoms in patients with Tourette's syndrome: a double-blind placebo-controlled study. J Child Adolesc. Psychopharmacol 7:75, 1997

Scahill L, Riddle M, McSwiggin-Hardin M, et al: Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry 36:844–852, 1997

Stokes PE: Fluoxetine: a five year review. Clin Ther 15:216–243, 1993

Swedo SE: Sydenham's chorea: a model for childhood autoimmune neuropsychiatric disorders. JAMA 272:1788–1791, 1994

Swedo SE, Rapoport JL: Phenomenology and differential diagnosis of obsessive-compulsive disorder in children and adolescents, in Obsessive-Compulsive Disorder in Children and Adolescents. Edited by Rapoport JL. Washington, DC, American Psychiatric Press, 1989, pp 13–33

Swedo SE, Rapoport JL, Cheslow DL, et al: High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. Am J Psychiatry 146:246–249, 1989a

Swedo SE, Rapoport JL, Leonard HL, et al: Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry 46:335–341, 1989b

Swedo SE, Leonard HL, Schapiro MB, et al: Sydenham's chorea: physical and psychological symptoms of St. Vitus's dance. Pediatrics 91:706–713, 1993

Swedo SE, Leonard HL, Kiessling LS: Speculations on antineuronal antibody-mediated neuropsychiatric disorders of childhood: commentaries. Pediatrics 93:323–326, 1994

Swedo SE, Leonard HL, Mittleman BB, et al: Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. Am J Psychiatry 154:110–112, 1997

Swedo SE, Leonard HL, Garvey M, et al: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 155:264–271, 1998

Thomsen PH: Obsessive-compulsive disorder in children and adolescents: predictors in childhood for long-term phenomenological course. Acta Psychiatr Scand 92:255–259, 1995

Thomsen PH: Child and adolescent obsessive-compulsive disorder treated with citalopram: findings from an open trial of 23 cases. J Child Adolesc Psychopharmacol 7:157, 1997

Warrington SJ: Clinical implications of the pharmacology of serotonin reuptake inhibitors. Int Clin Psychopharm 7:13–19, 1992

Wolff R, Rapoport JL: Behavioral treatment of childhood obsessive compulsive disorder. Behav Modif 12:252–266, 1988

Wolff RP, Wolff LS Assessment and treatment of obsessive-compulsive disorder in children. Behav Modif 15:372–393, 1991

Zohar AH, Ratzoni G, Pauls DL, et al: An epidemiological study of obsessive-compulsive disorder and related disorders in Israeli adolescents. J Am Acad Child Adolesc Psychiatry 31:1057–1061, 1992

CHAPTER 9

Individual, Group, and Multifamily Cognitive-Behavioral Treatments

Barbara L. Van Noppen, M.S.W.
Gail Steketee, Ph.D.

Since the early 1980s, the psychosocial treatment of choice for obsessive-compulsive disorder (OCD) has been exposure for obsessions and prevention of rituals, or "response prevention," for compulsions conducted mainly in an individual format. This treatment method, based on clinical observations that obsessions increase anxiety and compulsions reduce it, has now been incorporated into the diagnostic criteria for OCD. That is, obsessions "cause marked anxiety or distress" and compulsions "are aimed at preventing or reducing distress" provoked by obsessions (American Psychiatric Association 1994). Not surprisingly, behavioral treatment based on this model includes procedures to reduce anxiety associated with obsessions and to prevent or curtail ritualistic behavior. In this chapter we briefly describe the theoretical model for exposure and response prevention (ERP) and then review the empirical literature supporting the efficacy of this method. In addition, cognitive conceptualizations and interventions have gained considerable recent attention and the limited literature on this method will also be reviewed. Promising alternative treatment strategies to deliver ERP, group, and multifamily formats offer added advantages that may be particularly beneficial to some patients, so we present literature relevant to group and multifamily behavioral treatment as well.

Behavioral Models

Foa and Tillmanns (1980) articulated a definition of OCD based on the functional relationship between obsessions and compulsions—that is, the

thoughts, images, impulses, or actions that generate obsessive anxiety may be prompted by external (environmental) or internal (thoughts, images) triggers for fear. Obsessive fears may be accompanied by fears of potential disaster (e.g., disease, death, going to hell), or they may occur without fears of catastrophic consequences. Most sufferers try to avoid the feared situation or stimuli (passive, phobic-like avoidance), but when this is difficult or impossible, they usually perform overt rituals or covert mental events to restore safety or prevent harm (Rachman 1976). Both behavioral and mental rituals are functionally equivalent in that both are intended to reduce obsessive fear (Rachman 1976; Rachman and Hodgson 1980).

Why obsessions become highly anxiety provoking in the first place is the subject of some debate that remains unresolved. Possible etiologic models include parental teachings and modeling, biologic sources, cultural factors, historical experiences, religious teachings, cognitive beliefs and appraisals, and many other variables. ERP treatment, however, is based on the assumption that thoughts and behaviors are learned responses that have become conditioned and generalized to various contexts despite their seeming irrationality.

Behavioral theorists (e.g., Dollard and Miller 1950; Mowrer 1960) have proposed a two-stage theory of acquisition of fear in which individuals first associate fear or other emotional discomfort with particular situations for various reasons and then find that escaping from or avoiding those contexts reduces discomfort. Because most patients cannot easily avoid many fear-provoking situations (e.g., use of toilets or stoves, perverse religious ideas), they develop ritualistic behaviors such as washing, checking, or praying to prevent or reduce discomfort, even if only minimally or briefly. Such actions are reinforced and repeated precisely because they reduce discomfort. Supporting this hypothesis is substantial evidence from early studies of OCD that obsessions increase both subjective and physiologic anxiety or discomfort and that compulsions reduce it (e.g., Boulougouris et al. 1977; Hodgson and Rachman 1972; Hornsveld et al. 1979; Rabavilas and Boulougouris 1974; Roper et al. 1973). The treatments that logically derive from this learning theory model are exposure to foster habituation of obsessive fears and blocking of rituals to prevent escape and avoidance.

Assessment of Symptoms

Before beginning behavioral (or cognitive) treatment, it is important for the clinician to gain a full picture of the OCD symptoms and their function

for the patient. A complete assessment of symptoms consists of interview data (from the patient and, if possible, from family members or close others), clinician assessment of symptom types and severity, and standardized self-report measures.

In an initial evaluation interview, preparatory to conducting a behavioral treatment, clinicians should assess obsessions and compulsions separately, along with mood state and general functioning. Rating scales include the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989a, 1989b), used either as a rater-administered measure (Woody et al. 1995) or as a self-report (Steketee et al. 1996). Other necessary self-report instruments include a comprehensive list of feared and avoided situations as well as internal thought images and impulses.

Outstanding among standardized clinician ratings of severity is the Y-BOCS, favored because of its detailed assessment of the severity of idiographic symptoms without regard to particular types of obsessions or compulsions. This measure begins with the Y-BOCS Symptom Checklist to determine which obsessions and compulsions occur most frequently for a particular patient and to identify other, less frequent or disturbing OCD symptoms that may prove problematic during behavioral treatment. After administering the Symptom Checklist, the clinician uses the Y-BOCS scale to assess five aspects each of obsessions and compulsions: time spent, distress, interference, resistance, and control. Scores range from 0 to 40. Scores of 16 and above are considered to be in the clinically significant range, with scores above 28 in the severe to extreme range. Positive evidence for the reliability and validity of the Y-BOCS is available in recent studies (e.g., Woody et al. 1995). A self-report version of this measure has demonstrated good reliability and validity in studies of clinical and nonclinical samples (Steketee et al. 1996). However, for patients with very poor insight into the irrationality of their symptoms, the clinician-rated Y-BOCS may be more valid.

Observational measures of the frequency and duration of ritualistic behavior are recommended because these bring the clinician closest to an understanding of the impact and role of obsessions and compulsions in the patient's everyday life. Self-reported minutes spent on compulsive activity have been collected in some studies to provide an independent assessment of symptom severity before and after therapy (Emmelkamp and van Kraanen 1977; Foa et al. 1980b), although the reliability and validity of such measures have not been established.

Behavioral Treatment

Variants of exposure and blocking procedures have been used very successfully for patients with OCD who have covert and overt rituals. Direct

exposure techniques require the patient to directly confront fearful or disturbing ideas or situations and may be accompanied by exposure in imagery to feared catastrophic outcomes. Response prevention or blocking methods halt the patient's ritualistic behaviors. To block "mental compulsions," strategies such as thought stopping or distraction can be useful. These treatment strategies follow from the conceptualization of OCD described earlier; procedures that reduce anxiety (e.g., exposure) are applied specifically to anxiety-provoking obsessional content, whereas blocking strategies (e.g., response prevention) are used to prevent cognitive and behavioral rituals, thus allowing for habituation of obsessive fears. Both interventions are necessary for patients with obsessions accompanied by compulsions, as discussed later (Steketee 1993b; Steketee and White 1990).

The combining of exposure for obsessions with response prevention for compulsions was first employed by Meyer in 1966 in patients with washing and cleaning rituals. In this program, compulsions were prevented while the patient was required to repeatedly touch objects that evoked anxiety about "contamination" and consequent urges to wash (Meyer and Levy 1973; Meyer et al. 1974). Studies using variants of direct exposure techniques were compared with relaxation training, both in conjunction with response prevention. Of the patients treated with ERP, 75% were improved or much improved after 15 sessions and maintained their gains after 2 years; by contrast, relaxation training had no effect (Marks et al. 1975). In two studies from Greece, an average of 11 sessions of in vivo and imaginal exposure plus response prevention produced good results in 85% of patients (Boulougouris and Bassiakos 1973; Rabavilas et al. 1976), but a long-term follow-up indicated that only 60% were still improved (Boulougouris 1977). Several studies by investigators in the Netherlands used 10–15 sessions of in vivo exposure and blocking of compulsions. Overall, about 70%–80% of a large sample of patients with OCD improved and most remained so at follow-up, although some patients required additional treatment sessions (Boersma et al. 1976; Emmelkamp and van Kraanen 1977; Emmelkamp et al. 1980; Hoogduin and Duivenvoorden 1988).

In the initial studies by Foa and Goldstein (1978) in the United States, after 10 sessions of daily imagined and in vivo exposure treatment, 85% of patients were nearly symptom-free on rituals and only one patient failed to show improvement on obsessions, but fewer (57%) were asymptomatic. At follow-up, approximately 15% of patients relapsed. These findings indicated that treatment was somewhat more effective with compulsions than with obsessions, results that have held up in subsequent studies of exposure therapy. Later studies showed very positive gains with 15 sessions of treatment (Foa et al. 1992); most treatment reg-

imens generally provide between 12 and 15 sessions of ERP.

Although "pure obsessionals" (OCD patients without overt rituals) have traditionally been considered more difficult to treat with ERP, studies suggest that careful application of this behavioral treatment may result in substantial improvement for some patients. For instance, Hoogduin et al. (1987) treated 26 obsessive patients with a systematic program of deliberate evoking of obsessional thoughts (exposure) combined with strategies for refraining from neutralizing thoughts and cognitive rituals (response prevention). Nineteen subjects (73%) showed improvement of greater than 30%, and 61% of these maintained their gains at a 1-year follow-up. Salkovskis and Westbrook (1989) outlined some helpful approaches to invoking an ERP treatment paradigm with pure obsessionals, including the use of tape-recorded obsessional thoughts to allow for deliberate exposure.

To date, prolonged ERP has been used to treat hundreds of patients with OCD, with most data derived from group studies. The remarkable convergence of results from studies conducted in many centers attests to the generalizability of the treatment effects. It is not surprising that, at present, ERP is considered the psychologic treatment of choice for OCD.

Although the basic components of ERP have been well established, further work has been done to explore the relative importance of the various components, specifically, the relative need for exposure as well as response prevention, the required duration of the exposure, and the need for a therapist to model the behavior. Meyer's original treatment consisted of two basic components: exposure to discomfort-evoking stimuli and prevention of ritualistic responses. Theoretically, exposure should be necessary to reduce anxiety associated with obsessions, and ritualistic behavior should be blocked because it terminates confrontation with the fearful stimuli, thus preventing extinction of anxiety. The research data support these assumptions. However, both in case studies and in controlled comparisons, obsessive anxiety declined more after prolonged exposure rather than after blocking of rituals, and compulsions were reduced mainly by response prevention but not by exposure (Foa et al. 1980a, 1984; Mills et al. 1973; Turner et al. 1980). Thus, not surprisingly, combined treatment led to the best results. From a clinical standpoint, therapists should gradually expose patients to situations that provoke obsessions while at the same time preventing the rituals that usually occur in these circumstances.

According to clinical studies of patients with OCD, prolonged exposure to fear-provoking stimuli is superior to brief exposure: 80 minutes of continuous direct in vivo exposure proved superior to eight 10-minute segments (Rabavilas et al. 1976). Surprisingly, however, duration of the

imagined exposure did not affect outcome. How quickly the therapist moves up the hierarchy of disturbing stimuli has not proved to be important in the treatment of OCD. Hodgson et al. (1972) exposed some patients gradually and others immediately to the most feared situation. The two procedures were equally effective, although patients reported feeling more comfortable with the gradual approach. We suspect from clinical experience that progressing too slowly will be unhelpful for most patients whose motivation and sense of accomplishment may wane. In general, then, clinicians are advised to extend patients' exposure experiences in the office and at home as long as feasible and to encourage them to confront their fears as rapidly as they can tolerate.

A combination of response prevention and participant modeling, in which the patient copied the therapist's demonstration of exposure, yielded better results than passive modeling in which the patient only observed the therapist (Roper et al. 1975). However, other investigators found that adding modeling did not improve outcome (Boersma et al. 1976; Rachman et al. 1973). Nonetheless, some patients have reported that observing the therapist helped them overcome their resistance and avoidance of exposure. How the therapist models or conducts exposure may influence patients' willingness to continue in treatment. Marks et al. (1975) proposed that ERP treatment requires a good therapeutic relationship and often a sense of humor. The very limited research on the qualities of a good therapist for OCD indicated that therapists who were respectful, understanding, interested, encouraging, challenging, and explicit were able to help patients achieve greater gains than those who gratified dependency needs or were permissive or tolerant (Rabavilas et al. 1979). In practice, a combination of support, encouragement, humor, and firm insistence that the patient follow therapeutic instructions for ERP seems to be optimal.

Although the personal style of the therapist may be important, his or her presence during exposure may not be required, at least in some cases. Emmelkamp and van Kraanen (1977) found no differences in outcome for self-controlled versus therapist-controlled exposure, although subjects in the therapist-led group required more treatment sessions at follow-up than did the other group. The authors suggested that the self-controlled exposure patients may have gained greater independence in handling their fears. Consistent with this earlier study, the addition of therapist-aided exposure after 8 weeks of self-exposure instructions yielded only transient benefits that were lost at week 23 (Marks et al. 1988). Preliminary trials of computer-aided exposure suggest that such treatment may prove very useful for selected individuals with OCD (Greist 1996; Griest et al. 1996). The findings of these studies do not suggest that therapists are dis-

pensable but do indicate that direct exposure may be implemented without their immediate presence. Whether this is especially true for patients with mild to moderate (rather than severe) symptoms remains to be tested.

In conclusion, it seems that both exposure and blocking of mental and overt rituals are needed for successful outcome. Imagined treatment may be especially useful when fears of disasters are prominent features of a patient's OCD symptoms. From a clinical standpoint, research suggests that therapists may begin treatment by conducting prolonged exposure in office and then assigning more exposure as homework between sessions. Only if the patient has serious difficulty with homework should the therapist insist on being present through the process. Most patients are likely to prefer graduated exposure, but some circumstances may require more rapid confrontation. Modeling may be used whenever patients feel it would be useful.

Cognitive Models

It is apparent from the phenomenology and characteristics of OCD that patients with this disorder exhibit some disturbances in cognitive functioning. Accordingly, several cognitive models for OCD have been proposed, many of which emphasize similar features of the disorder (see Steketee et al. 1998 and summary below). Pitman's (1987) cybernetic model suggested that faulty beliefs and pathologic symptoms of OCD stem from signals experienced internally, such that a perceptual mismatch is registered in the perception of the input. This faulty perception leads to pervasive uncertainty and ritualistic efforts to correct it, along with difficulty withdrawing attention from intrusive thoughts. Pitman proposed neuroanatomic underpinnings for these processes.

From a more traditional cognitive perspective, Warren and Zgourides (1991) emphasized the role of irrational beliefs in a rational-emotive treatment (RET) model of OCD. They hypothesized that biologic vulnerability influenced by developmental and learning experiences determined which thoughts a person considers unacceptable and what meaning he or she attaches to the thoughts. Common irrational thoughts include assumptions about the need to make correct decisions, the need to be perfectly certain to avoid causing harm, and the unacceptableness of bizarre thoughts and impulses. According to the RET model, under stress, negative emotions tend to provoke such intrusive thoughts. Thereafter, attention narrows on these thoughts, with accompanying hypervigilance and efforts to avoid or escape them (see also Wegner 1989).

Salkovskis (1985) and Rachman (1993) formulated cognitive models

focused on the salience of common intrusive thoughts associated with negative automatic thoughts. Discomfort arises from mistaken assumptions about responsibility for endangering oneself or others, leading to self-blame and precautions to avoid guilt, shame, and depression. Neutralization (mental and behavioral rituals) serves to reduce discomfort, responsibility, and the possible consequences of having the thought. Freeston et al. (1996) broadened this formulation to include additional types of faulty appraisals, including overestimation of the consequences of thoughts and of anxiety, the presumption that thinking can lead directly to doing an act (thought–action fusion), and perfectionism and the need for control.

Additional hypothesized cognitive distortions include overestimation of threat or harm (Carr 1974; McFall and Wollersheim 1979), problems with epistemologic reasoning associated with safety (Kozak et al. 1987), a need for certainty (Beech and Liddell 1974), ideas that one must be perfectly competent and that failure to do so should be punished (Guidano and Liotti 1983; McFall and Wollersheim 1979), feelings of loss of control of thoughts (Clark and Purdon 1993) and consequent efforts at suppression (Wegner 1989), and underestimates of coping capacity (Carr 1974; Foa and Kozak 1986; Guidano and Liotti 1983). Experimental findings have supported some of the above assertions, particularly with respect to overspecification, the need for certainty (Makhlouf-Norris and Norris 1972; Makhlouf-Norris et al. 1970; Milner et al. 1971; Persons and Foa 1984; Reed 1985; Volans 1976), and excessive responsibility (e.g., Lopatka and Rachman 1995; Rheaume et al. 1995; Salkovskis 1989). Evidence is now accumulating to substantiate several aspects of these theoretical ideas, but it will undoubtedly be some time before the relationship among these concepts and their importance for effective treatment is clearly articulated.

Cognitive Treatment

To date, only a handful of studies, most of them uncontrolled, have attempted to determine whether treatments derived from cognitive models are fruitful for OCD. In an earlier study, cognitive methods proved minimally helpful in reducing OCD symptoms (Emmelkamp et al. 1980). In contrast to these disappointing findings, a study of RET compared with self-controlled ERP showed that both treatments improved OCD symptoms equally (Emmelkamp and Beens 1991; Emmelkamp et al. 1988).

However, the above-mentioned cognitive therapies did not appear to be designed specifically for cognitive distortions typical of patients with OCD. If certain cognitions (e.g., excessive responsibility, overestimation of

harm, need for control) are particularly germane to OCD, cognitive treatment focused on these patient-specific thoughts and beliefs may be even more effective (Beck and Emery 1985). Several case studies demonstrated good effects of a traditional Beckian cognitive therapy tailored specifically for participating OCD patients (e.g., Ladouceur et al. 1993; Salkovskis and Warwick 1986; Van Noppen et al. 1995). Treatment included socratic dialogue and the triple column technique, which consisted of listing thoughts/beliefs, and rating the strength of conviction in the belief, associated emotions, and possible alternative beliefs. Experimental testing of beliefs and other cognitive strategies were intended to dispute various OCD-associated distorted beliefs. This cognitive treatment was highly successful, reducing Y-BOCS scores by 11 points after treatment and 12 points at 6-month follow-up. This outcome matched the effects of ERP (Van Noppen et al. 1995). These findings suggest that cognitive therapy is a promising adjunctive or, perhaps, alternative treatment to ERP.

Many clinicians providing behavioral treatment informally incorporate cognitive techniques into the therapy. Psychoeducation and the labeling of OCD symptoms are standard in our treatment and likely to alter cognitive misinterpretations. We also encourage patients to separate affect ("I feel as though I have to wash") from distorted perceptions, assumptions, and beliefs ("I have to wash or I'll get AIDS") and to challenge faulty assumptions about harm, perceived responsibility, and unacceptableness of bizarre thoughts and impulses. A group context (see below) is particularly suitable for providing a normative consensus to test beliefs and rehearse alternative ways of thinking. The case example below illustrates ERP with an individual patient.

Case Example

Rick, a 40-year-old computer systems support analyst, sought individual behavioral treatment after 10 months of pharmacologic treatment with limited benefits. He was married, the father of an 18-month-old son, and of Italian-Catholic descent. Although he was raised in a devout family, he described himself as not religious and "liberal" in his political views.

Upon initial evaluation, Rick spoke about "disturbing" thoughts that interfered with his ability to enjoy his wife, Susan, and their son, Nate. Completion of the Y-BOCS Symptom Checklist revealed primary aggressive obsessions, a need to know, considerable avoidance, reassurance seeking, and mental rituals. Rick described "worrying that I might have the ability to impulsively hurt my son or wife.…Suppose I just do it for no reason at all." He was very bothered by the constant distraction of these "horrible" thoughts, which arose when he was in the company of his wife and son. Rick dreaded the days he had to drive Nate home from day care and be with him alone at home; when his wife was home he felt

reassured that his "impulses" might stay in check. Although Rick had no previous history of difficulty with loss of impulse control or aggressive outbursts, he was worried that "what if, one day, I might just lose control and do something awful?" When questioned about insight, Rick wavered, acknowledging that his fears and behaviors were unreasonable but uncertain whether he had reason to be concerned. Rick's initial Y-BOCS score was 25, reflecting moderate severity of symptoms, 3–8 hours a day of obsessions and compulsions, and little sense of control over the OCD.

Rick described mild childhood obsessive-compulsive symptoms that included an excessive need for reassurance, a fear of "germs," and some body dysmorphic symptoms (e.g., a preoccupation with his appearance, concern that he was "ugly," checking in mirrors). In his late teens and early 20s, Rick's fear of germs became more predominant, and on his own he used confrontation to help his fear "fade away." He sought psychiatric treatment at age 19 because he was having difficulty with social relationships at college and was feeling insecure and inadequate. Aggressive obsessions began to emerge. In his psychodynamic approach, he examined his relationships in his family of origin and intrapsychic conflicts. After 10 years of weekly psychotherapy and pharmacotherapy, Rick felt more "normal" socially and was able to have some meaningful relationships, graduate from college, secure a job, and live on his own. When he first presented for treatment, he knew he had OCD but spoke about the aggressive thoughts as though they were reflective of suppressed anger.

An individual behavioral treatment was outlined for Rick, who agreed to a protocol of two 90-minute information-gathering sessions, 12 weekly 2-hour treatment sessions, and six monthly check-in sessions. He decided to be maintained on a stable dose of a selective serotonin reuptake inhibitor (SSRI) throughout the therapy. During the first two information-gathering sessions, a more detailed history was taken; the intrapersonal behavior therapy was described, including a definition of ERP; and a more detailed description of Rick's OCD was elicited. Rick seemed motivated, engaged, and eager to get started. The therapist instructed him to read *When Once Is Not Enough* (Steketee and White 1990) during the first few weeks. He came to the first session with his exposure homework hierarchy folded into a tiny square. Rick stated that he was so ashamed of his thoughts and fearful that "if anyone knew" just what he thought, they might think he was capable of doing these terrible things and "put him away." He said he had never disclosed the exact content of his thoughts before and felt anxious to do so. Worried that someone would find the paper, he had put it in an envelope, placed the envelope into a jar, and hid the jar inside a bag of fertilizer, which he had then put into the trunk of his car and covered with a blanket. Thus, the very process of articulating the internal cues/triggers required Rick to expose himself to the obsessive thoughts and feared catastrophic consequences—in this case, that if he told someone about his obsessions, he would require hospitalization and possibly face divorce and loss of custody.

Rick's therapy was based on his exposure hierarchy, which was constructed around his fears of harming his wife and son. Table 9–1 lists ob-

Table 9–1. Subjective discomfort due to thoughts

Thought	Discomfort (0–100)	Treatment session
I will spray hair spray at Nate.	40	1
I will smash Sue in the head with a hammer.	40	1
I will give my Prozac to Nate.	50	2
I will smash Nate in the head with a hammer.	60	3
I will stab Nate.	70	4
I will hit Nate in the head with a bat.	75	5
I will lose control and go crazy killing.	85	6
I will put my hands around Nate's neck.	90	7
I will strangle Nate and snap his neck.	100	8

Table 9–2. Subjective discomfort due to situations

Situation	Discomfort (0–100)	Treatment session
Holding hair spray	10	1
Spraying hair spray	15	1
Holding hammer	15	1
Spraying hair spray near Nate	20	1
Holding hammer near Sue	25	1
Holding Prozac near Nate	45	2
Holding scissors near Sue	45	2
Seeing knives in kitchen	50	2
Standing near knives on counter	50	2
Holding scissors	50	2
Holding knives	50	2

sessive thoughts and situations and the subjective discomfort they provoked on a scale of 0–100. Similarly, a hierarchy of situations that Rick avoided or endured with anxiety was constructed; this is shown in Table 9–2.

Treatment, which consisted of ERP in vivo, imagined exposure in vivo, homework ERP assignments, and self-monitoring, proceeded based on these hierarchies. The first few sessions also contained psychoeducation on OCD, reading assignments (finish reading *When Once Is Not*

Enough), and the viewing of a videotaped discussion by Michele T. Pato, M.D., on the neurobiology of OCD.

Because of the nature of Rick's aggressive obsessions, most of the in vivo therapy involved the use of scripted imagery that he read aloud, audiotaped, and replayed. He was given instructions to write the scripts in the first person and to be as descriptive and detailed as possible, as though the obsessive idea or image were happening. Whenever possible, the therapist encouraged Rick to bring "props" to the sessions to heighten his discomfort. For example, to confront the fear of smashing his son in the head with a hammer, Rick brought in a hammer and pictures of his son. The exposure task was for Rick to look at the pictures while swinging the hammer toward the photos and saying "I will smash Nate in the head with a hammer." Initially, Rick said "I'm afraid I will hit my son in the head," but the therapist reminded him of the scripting instructions, adding that to make the technique effective he needed to confront the exact fear. As the behavioral treatment continued, Rick combined in vivo and imaginal exposure using a bat, scissors, and knives (first small then large). Rick found the in vivo practice, coupled with the exposure homework, to be highly effective in reducing his anxiety. The day Rick entered the session with a baseball bat hidden under his coat, he laughed and joked with the therapist about becoming a "bat killer."

The therapist used modeling, often participating in the exposure challenge when Rick expressed difficulty getting started. For instance, the therapist took out a picture of her daughter, jabbed a knife at the photo, and said "I will stab Jill!" Observing this, Rick asked with puzzlement, "Doesn't that bother you? You seem so calm about saying that…almost with no emotion." The therapist asked Rick how other people would feel about the same thought. He said that they "wouldn't think it in the first place." The therapist provided information that many people have intrusive aggressive thoughts but dismiss them as such. She pushed him to reflect further on this—to think about the process of OCD rather than the content. In other words, it was not the thought itself that created the problem, it was the worrying about the thought or the thinking about the thought that was the real problem in OCD. Such mainly cognitive interventions are intended to redefine the feared ideas or images as normative intrusions about which the patient has become oversensitive.

Rick was diligent about following through on his homework assignments, and within 4 weeks he reported only very mild distress evoked by purposeful or spontaneous exposure to the thoughts that had been in the 40–50 range initially. ERP proceeded in a step-wise fashion. Rick self-monitored his anxiety levels and stayed in exposure situations until his distress declined significantly. He listened to his scripted imagery tapes in the car on the way to pick his son up from day care, when he was alone with his son, and while unloading knives from the dishwasher; thus, he became able to practice independently outside of the sessions.

Rick reported that the indifferent response he received after disclosing the detailed content of his thoughts was a therapeutic breakthrough for him because he had never "divulged his worries" to anyone before. To

be able to discuss the content in such a matter-of-fact way reinforced the idea that the thoughts were in fact meaningless. This in-session experience, coupled with the between-session ERP practice, reduced the intensity and frequency of Rick's obsessive-compulsive symptoms so that by session 8, he was able to confront his "worst" fear of strangling Nate. After the second reading, followed by several repetitions of listening to the tape, Rick reported a decline in distress (50). Rick was gradually able to view the strangling fear as "just another OCD thought" without becoming embroiled in analyzing the content. Rick's assignment was to go home and practice putting his hands around Nate's neck while allowing the "terrible" thoughts to come to his mind without engaging in mental rituals or reassurance seeking to decrease his anxiety. Again, the therapist reminded him he would most likely feel very anxious at the start but to stay with the anxiety, rating it every 10 minutes on his self-monitoring form until it diminished considerably.

At session 9, Rick reporting feeling proud of himself that he listened to the tape and performed the exposure exercise repeatedly to the point of no longer feeling the previous dread and fear. He rated his discomfort at 40, less than half of the initial rating. After the 12 weekly sessions, Rick's symptoms had dramatically reduced in frequency and intensity and his functioning had improved. His posttreatment Y-BOCS score was 8, indicating mild obsessive-compulsive symptoms that intruded less than 1 hour per day with control over obsessions and compulsions.

Key elements in this case were the positive therapeutic relationship that developed between Rick and his therapist, the therapist's empathic yet firm stance, consistent use of in vivo and imaginal exposure, response prevention, reviewing of homework, and Rick's motivation to overcome the OCD despite previous failure in therapy.

Group Behavioral Treatment

Group behavioral treatments have proven effective for several other patient populations with anxiety disorders, but only a handful of studies, most of them uncontrolled, have investigated group treatments for OCD (Epsie and Michelson 1996; Hand and Tichatzky 1979; Taylor and Sholomskas 1993). This treatment holds considerable interest because of its potential for reducing costs without sacrificing benefits. Furthermore, the group context may offer added benefits for patients with OCD who experience stigma and social isolation or who need the motivational boost of a supportive treatment group. Yalom (1975) identified "curative factors" at work in group therapy, such as cohesiveness, imitative learning, imparting of information, and universality, that are clearly present in behavioral treatment groups for patients with OCD. Also, Budman (1981) recognized the importance of time-limited models of group therapy for pragmatic, economic reasons and to enhance motivation.

Four large uncontrolled trials have been reported. Enright (1991) used nine weekly 90-minute sessions with the addition of assertiveness training. Significant decreases in OCD symptoms and depressed and anxious mood and improvement in functioning were evident at posttest and at 6-month follow-up, although only 17% of those studied made clinically significant improvement according to strict standards. It is noteworthy that this study included less focus on exposure and blocking of rituals during sessions. In a second trial, Krone et al. (1991) treated 36 patients with OCD using short, 7-week group programs of education, instruction in cognitive and behavioral self-treatment, and therapist-directed ERP. Significant improvement was evident in the reductions of Y-BOCS scores from moderately severe before therapy to below clinical levels at 3-month follow-up. Interestingly, this improvement was independent of medication use. In another study, 10 sessions of group ERP produced moderate reductions (5–6 points) in the Y-BOCS scores of 90 outpatients with OCD, which were noted at least 6 months after treatment (Van Noppen et al. 1998).

Finally, Fals-Stewart et al. (1993) have conducted the only controlled trial for OCD comparing group imagined and/or in vivo ERP ($N=30$) with comparable individual ERP ($N=31$) and an individual relaxation control treatment ($N=32$). After 24 twice-weekly sessions, subjects in both ERP treatment conditions showed significant improvement in OCD symptoms, depression, and anxiety at posttest and follow-up, whereas the control group changed only on anxiety. Group treatment led to substantial reductions of 10 points in Y-BOCS scores at posttest and 8 points at follow-up, results quite similar to those of Van Noppen et al. (1998). Unfortunately, this study excluded patients with major depression and Axis II diagnoses, limiting the generalizability of these findings.

However, it is apparent from the above case series and controlled trial that behavioral treatment can be applied to group contexts with results that are generally equivalent to those of individual treatment, particularly when the number of sessions is comparable with that usually provided to individual patients in other controlled research (12–20 sessions). For clinical settings in which there is sufficient patient flow but a limited number of trained therapists, this is clearly a cost-effective and efficacious alternative to standard individual treatment.

Case Example: Group Behavioral Treatment

Eight patients with OCD were referred for group behavioral treatment. They were initially screened by an experienced clinician and then evaluated by the group therapist to ensure appropriateness for group treatment. Each patient participated in two 90-minute information-gathering

sessions before starting with the group. During these meetings, the therapist collected general information; history of OCD, other symptoms and mental health treatment; and a general history about family and social relationships. The detailed information about OCD symptoms was used to generate a hierarchy that each patient brought to the first group session. The goals of the group therapy were outlined, OCD and behavior therapy were defined, and family members were invited to accompany the patient to the first half of the second information-gathering session, although they were not involved in the treatment. The behavioral treatment group ran for 12 consecutive weeks with each session lasting 2 hours.

The first three sessions consisted of introductions and psychoeducation about phenomenology, etiology, and behavioral and cognitive techniques. Simultaneously, in-group ERP was demonstrated and practiced and group modeling took place. Patients were required to select homework assignments and record daily distress levels between group sessions. After completing the active treatment of 12 sessions, the group members continued to meet for six monthly sessions to consolidate their treatment gains and discuss relapse prevention. Some of the details of these group sessons are highlighted below.

GBT Session 1. The therapist discussed confidentiality, coverage between groups, a crisis plan, and the importance of consistent attendance and posed questions such as "What do you hope to get out of this group?" and "What do you expect to gain from this group?" A handout entitled "Obsessive-Compulsive Disorder: What is OCD?" was distributed, and each patient took turns reading aloud from it. Each patient was given the self-rated version of the Y-BOCS Symptom Checklist to review, with members volunteering to read. Allowing patients to draw from their experience of OCD in order to provide examples for each symptom type promoted disclosure. Jan, a single, 34-year-old computer programmer, spoke about her extensive repeating rituals to ward off "bad things from happening." Relieved to hear this, Dan, a married, 52-year-old salesman, told the group about his fear of the number 4 and how he "couldn't say that number" in the same sentence as one of his kid's names because they might get hurt and it would be his fault. "Oh, everything's always my fault!" chuckled Jan. The group laughed along with her at this common trait, underscoring a general theme of excessive responsibility. Others felt inspired by these stories, and it generated discussion about the effect of OCD on people's lives. The group's "curative factors," as described by Yalom (1975), were evident even in this first session. The group process appeared effective in decreasing feelings of isolation, stigma, and shame while universalizing problems, instilling feelings of hope, and using imitative behavioral methods to promote change.

Disclosure during the group session paved the way for the use of ERP and modeling. In addition, the heterogeneity of symptoms seemed to promote insight by facilitating greater participation in the in vivo exercises that led to group normative behavior and beliefs. For example, it would be difficult to get a group of eight patients with contamination fears to agree that people should be able to touch the flusher of a toilet

and resist washing their hands without feeling significantly anxious. Patients had learned to appreciate the various forms of symptoms that allowed them to depersonalize the obsessive content.

After disclosing their situation, patients were asked to select an item in the 35–45 discomfort range from their personal hierarchy as part of their ERP homework. Homework forms were distributed (as they would be in every subsequent session) and explained. The therapist instructed the group members to record their distress levels throughout the week while practicing their homework task. Everyone was reminded of the time-limited nature of the group and that there was a lot to cover in a relatively short period of time.

GBT Session 2. At the second session, patients reported on their homework, receiving praise for accomplishments and problem-solving feedback when they experienced difficulties achieving habituation. The group input was intended to expand behavioral alternatives and offer consensual validation on normative beliefs and behaviors. Mark said it was helpful to talk with other patients with OCD and to "hear that no one else gets upset when they hear what I do. When I'm here, I feel at home because everybody has their weird worries and strange behaviors. We can laugh at ourselves without feeling like freaks that no one else can relate to. We know we aren't alone!" During this psychoeducational phase, the therapist also introduced the concept that although patients "feel" or "think" they have to perform their rituals, almost everyone spoke in absolutes: "I have to check," "I have to straighten the magazines." She attempted to get them to restructure this cognitive distortion by having them restructure their speech from "I have to check" to "because of my OCD I think (or feel) I have to check."

After the therapist gave a detailed 15-minute overview of in vivo and imaginal exposure, examples of these techniques were practiced in the group. Chuck and others in the group were asked to take out their wallets, shuffle around the money and credit cards, report on their distress, put the wallet away, continue to monitor the distress, then repeat the task. All of the patients rehearsed their exposure tasks and rated their discomfort levels. The exercises were repeated until discomfort was reduced. This in vivo exposure was very lively, as is typical in group behavioral therapy.

During this time, some patients displayed tremendous discomfort and seemed to benefit from the support, feedback, and encouragement of the other patients to stay in the dreaded situation. Most patients reported that it was invaluable to observe others exposing themselves to stimuli and experiencing mounting anxiety and, after repeated and prolonged exposure, watching their discomfort recede. Thus, although therapist modeling has not been shown empirically to improve outcome, patients have reported that participant modeling was beneficial to them. For homework, the patients often continued their in-group challenges and added items from their hierarchies. The exposure homework practice and discomfort ratings were recorded on the homework forms.

GBT Session 3. Patients began with a check-in and go-around, report-

ing on homework tasks. A 15-minute videotape that discussed the neurobiology of OCD and medications was viewed, followed by a brief discussion of this material. The remainder of the 2-hour session was devoted to in vivo and imagined exposure. At this session, patients selected items with higher discomfort ratings (between 50 and 60) on their hierarchies. Again, in-group exposure exercises were modified to address individual symptoms. All of the patients selected homework assignments and received feedback from the group as to whether the tasks chosen were reasonable but challenging. This process was intended to increase individual patients' problem-solving options and to promote the use of various behavioral techniques. Imparting information and learning from other patients appeared to be beneficial because patients respected the advice that came from someone "in the same boat" whom had had success.

GBT Sessions 4–11. These sessions proceeded in a similar fashion as outlined in Session 3. After a check-in and go-around report from each patient on his or her homework successes and obstacles, the therapist quickly addressed any problems patients had encountered in carrying out their homework assignments. For patients who had not experienced any progress, it was often in this phase that dropout occurred. Although the sense of competition ("If Cheryl can do that, so can I") was a powerful motivator, patients who had selected inappropriate challenges or had not used exposure long enough to allow habituation felt discouraged as others progressed. Other non-ERP obstacles may also hamper treatment. To prevent dropout, which can discourage other group members, the therapist looked for signs that a patient was repeatedly unsuccessful in employing ERP and used in vivo group exercises to provide an opportunity for a corrective experience. Often, group cohesion had become so developed that patients took more risks to avoid disappointing other group members.

As each session progressed, patients selected items from their hierarchies that evoked increasing levels of distress. By session 8, the most distressing stimulus was introduced to allow time for habituation. The group experience became more interactive, and patients pressed one another to tolerate anxiety. Many patients have reported that they felt a sense of pride and self-worth when they could help fellow patients. This may be another active ingredient of group therapy.

GBT Session 12. The final session was conducted in the same way as those described above, except that the therapist left ample time to address concerns and questions about the end of active treatment. Jan expressed fear that she "wouldn't be able to do it" on her own without the support of the group. Peter reminded her that she had come so far because of her independent use of the behavioral techniques in her homework and that she had become a primary inspiration for others. The therapist allowed individual expression of parting but did not let the group stray too far off the track. The task of giving closure to the weekly treatment sessions needed attention in order to manage the high level of intimacy in the group. The main focus was on fostering self-instruction and self-efficacy.

Group members were asked to comment on the enormous changes they had observed in others while identifying the most helpful elements of the group treatment. Six monthly meeting dates were scheduled, and patients were encouraged to call for help trouble-shooting between sessions as needed.

Family Treatment Interventions

Another potential strategy for reducing treatment costs and enhancing maintenance of gains is the use of a multiple-family group format that we call multifamily behavioral treatment (MFBT). It is clear that patients' OCD symptoms can engender extensive family involvement (Calvocoressi et al. 1995) and have adverse effects on family functioning (e.g., Allsopp and Verduyn 1990; Marks et al. 1975). Calvocoressi et al. (1995) reported that 88% of family members participated in some way in OCD symptoms and that greater family participation in symptoms was significantly correlated with family dysfunction and negative attitudes toward the patient. Intervention to address these difficulties might be helpful in overall recovery. To date, however, most the research reported on family treatment for OCD has not directly addressed family involvement in symptoms or family stress and associated costs.

Family Response Patterns

In our clinical experience, family responses to obsessive-compulsive symptoms fall along a continuum of behavioral interactional patterns. This spectrum can be visualized as having two polar opposites of either totally giving in to, and even assisting in, the symptomatic behavior or unequivocally opposing the behavior. The two most extreme positions are depicted in Figure 9–1.

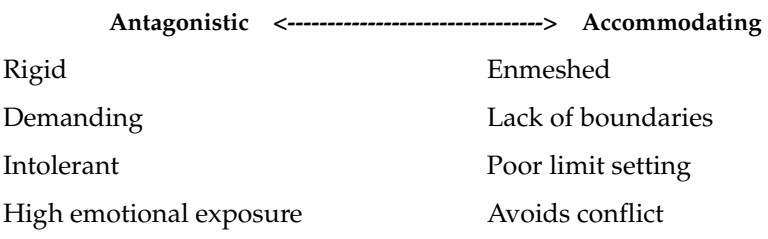


Figure 9–1. The spectrum of family response patterns in OCD.

A third type of response pattern that is commonly seen is a split family. In this case, the family members (usually parents) are divided in their reactions to the symptoms, with one family member at the antagonistic end and one at the enmeshed, accommodating end of the response continuum. Another common scenario occurs when family members oscillate in their responses, swinging from one end of the spectrum to the other as frustration and anger toward the patient and his or her symptoms escalate. Family members, usually out of frustration that "nothing seems to work," become inconsistent by trying to participate in the rituals and then trying to cut them off. It should be kept in mind that most families lie somewhere in the middle of the continuum. Regardless of the family response pattern, both patients and their families often feel confused, angry, and anxious.

Relatives are often uncertain whether the prolonged rituals and constant need for reassurance are really part of an illness or are willful rebelliousness and demands for attention and control. Such perceptions may influence the ways in which family members respond to or try to cope with the symptoms of OCD. In turn, a transactional coping process unfolds in which family responses may facilitate or extinguish obsessive-compulsive symptoms, thereby affecting the patients' functioning. Preoccupied with the needs of the patient and feeling blamed and burdened, family members may pull away from their usual social contacts or work commitments and become increasingly socially isolated themselves. Patients with OCD may become more impaired if it seems that less is expected of them, but hostile criticism and unrealistic expectations from relatives can also evoke undue anxiety and perpetuate impairment.

Expressed Emotion

Another area of interest in family research that aptly extends to understanding transactional coping processes in OCD families is the concept of expressed emotion. Expressed emotion appears to be particularly applicable to our understanding of and treatment approach with OCD patients and their families. Based on British studies of families coping with a member diagnosed with schizophrenia (see Brown et al. 1972; Falloon et al. 1984), *expressed emotion* refers to relatives' critical, hostile, or overinvolved attitudes toward the diagnosed patient. Numerous studies have consistently reported that high expressed emotion is significantly correlated with high rates of relapse. Studies have reported on the association of expressed emotion with relapse mainly for patients with schizophrenia, depression, and bipolar manic depression. Expressed emotion has been found to predict outcome independent of illness severity (see Hooley et al.

1986), supporting the contention that criticism and emotional overinvolvement are not merely responses to severe symptoms in patients. Expressed emotion has been less well studied in OCD. Hibbs et al. (1991) noted that high expressed emotion was more frequent among parents of children with OCD or conduct disorder than among control subjects. Leonard et al. (1993) reported a 2–7 year follow-up study of 54 children and adolescents with OCD in which high parental expressed emotion was the second strongest predictor of long-term global functioning, superceded only by response to clomipramine at 5 weeks. Although not a direct study of expressed emotion, a study with similar findings was reported by Steketee (1993a), who found that negative family interactions (e.g., anger, criticism) and relatives' beliefs that the patient with OCD was malingering predicted fewer gains at 9-month follow-up.

Family Interventions for Other Disorders

Numerous studies have demonstrated the importance of family education and treatment in the outcome of schizophrenia and affective disorders (Brown et al. 1972; Falloon et al. 1984; Miller et al. 1986); this may also hold true in OCD. Family psychoeducation and communication training approaches have demonstrated that patients from families whose expressed emotion levels were reduced from high to low after treatment were considerably less likely to relapse than were those from families who remained high on expressed emotion (Anderson et al. 1986; Falloon et al. 1984; Hogarty et al. 1986; Leff et al. 1982; McFarlane et al. 1995). In addition, McFarlane et al. (1995) found that patients with schizophrenia who received multifamily treatment had lower rates of relapse than did those in single-family treatment. There are few data on behaviorally oriented multifamily groups. However, Falloon et al. (1981) were among those to report on such a treatment. They noted a reduction in critical comments and overinvolvement among family members after 25 sessions of a multifamily group for patients with schizophrenia. Applications of family interventions to OCD are not well studied.

Our clinical experience suggests that the family support system often plays a critical role in the prognosis and outcome of treatment. This may be particularly true for those patients who fail to respond to standard individual behavioral treatment and pharmacologic interventions. With regard to family involvement in treatment, Hafner (1982) reported several cases in which poor marital relationships appeared to interfere with the benefits from behavioral treatment for OCD outpatients. He noted that such patients showed improvement when spouses participated in the be-

havioral treatment process (Cobb et al. 1980; Hafner 1992). Similar benefits were also evident in case studies of parental involvement in behavioral treatment of children (e.g., Dalton 1983), adolescents, and adults (Hafner et al. 1981; Hoover and Insel 1984). Mehta (1990) reported that involving family members in behavioral treatment for 30 patients in India led to significantly greater gains in OCD symptoms, mood state, and social and occupational functioning compared with unassisted treatment. At follow-up, family treatment patients showed continued improvement, whereas patients treated individually lost some gains, making the outcome gap even wider. Patients with family members who were not anxious and who were firm were more successful than patients who had anxious and inconsistent family members, especially ones who engaged in argument and ridicule.

Correspondingly, our own work with family group interventions has led us to believe that special strategies are needed to alter such antagonistic communication styles. Two uncontrolled trials of family treatment have included efforts to reduce relatives' involvement in OCD symptoms. An inpatient treatment program in Great Britain emphasized self-treatment and teaching relatives to assist in the therapy program for inpatients with various diagnoses, including OCD (Thornicroft et al. 1991). Individual behavior therapy was combined with a family component that focused on training relatives to monitor patient behavior and encourage self-exposure in a noncritical manner. Relatives practiced under the therapist's supervision on the ward. This treatment program led to a 45% decrease in symptoms at discharge and a 60% decrease at 6-month follow-up, with concomitant improvement in functioning. Such results indicated excellent success for this severe inpatient population, who scored in the extreme range on disability from OCD symptoms.

Like group behavioral treatment, MFBT may also be a cost-effective and efficacious alternative to individual treatment for OCD. A pilot study of 19 patients in our center examined the effects of 10–12 sessions of family treatment conducted in groups of 6–8 families that included a mixture of spouses, partners, parents, and others in daily contact with the patient (Van Noppen et al. 1996). Treatment included psychoeducation, family exchange of information about OCD symptoms and coping strategies, exposure with modeling and response prevention, and family communication skills training, including family behavioral contracting for homework assignments. Good effects were observed after treatment and 1 year later: Y-BOCS scores improved by an average of 9–10 points and 58% of MFBT patients were clinically significantly improved, somewhat more than occurred with group behavioral treatment (43%). Significant improvements

in disability scores were also evident. In addition, most scales assessing family functioning showed improvement posttest, although significant differences were not evident at follow-up on a smaller sample. The Family Accommodation Scale for OCD (FAS-OCD; Calvocoressi et al. 1995) was used to assess family involvement in rituals.

Support groups with psychoeducational foci for patients and family members may provide a useful avenue for family assistance in the treatment of OCD (Black and Blum 1992; Cooper 1993; Tynes et al. 1992). Psychoeducational group goals usually include improving self-esteem, sharing feelings and experiences, accepting patients' realistic limitations, and learning strategies for coping with OCD symptoms. Participants have reported good satisfaction with psychoeducational groups, but no outcome data are available regarding group effects on patient symptoms.

Our MFBT uses interventions that are specifically aimed at reducing obsessive-compulsive symptoms as well as changing transactional patterns of communication between family members that may facilitate these symptoms. The MFBT incorporates psychoeducation, communication skills training, increased problem solving, boundary clarification, social learning, and rehearsal of ERP with therapist and participant modeling.

Case Example: Multifamily Behavioral Treatment

Information gathering. Kim, a 28-year-old mother of a 2-year-old daughter, described symptoms of OCD that dated back to her childhood. She sought treatment after severe exacerbation of her symptoms during her first pregnancy. Kim was referred for MFBT after a partial response to an SSRI and a low dose of a neuroleptic and 6 months of unsuccessful psychotherapy elsewhere. Kim reported that her primary fears had to do with extreme worry that she would contract cancer from various "substances," even when they could not be seen. These included detergents, chemicals (e.g., asbestos, lawn service truck), gasoline, "oil spills" on the sand at the beach, batteries, exhaust, make-up, and cigarettes. In response to these fears, she was washing her hands more than 100 times a day and avoiding any situation or object that would trigger the worry about cancer. In addition, out of fear of "additives," she had restricted her diet to only one brand of natural ice cream and natural granola. Kim also spoke about feeling as if she "had to sit with clenched fists to be sure" that she wasn't making blasphemous gestures to God. She had given up on doing laundry, grocery shopping, and cooking because every task "took too long." Kim described piles of unwashed laundry in her basement, some more than 3 years old, that were starting mold because of her avoidance. When asked about her husband's response, Kim said that he would surrender to her requests in order to "keep the peace." She involved him in extensive reassurance-seeking rituals, usually more than 50 times a day, although she stated that she wanted to stop her "strange behaviors" be-

cause it was tearing her family apart. However, Kim "really believed" she could die from the "cancer germs." She had begun to involve her daughter, Lilly, by washing Lilly's hands so frequently that she had protested against it. Kim's husband, Joe, had also given up on trying to get Kim to cook. Sneaking food into the house created such an uproar that he resorted to taking Lilly to his mother's house for most suppers.

Joe had viewed Kim's worries as just part of her personality. Joe worked as a salesman and Kim was offered a good job as a secretary at a local company. Shortly after they bought their own home, Mary, Kim's sister with whom she was very close, was diagnosed with cancer. To make it easier to receive chemotherapy, Kim insisted that Mary move in with her and Joe. Kim was wonderful to Mary during this time, sharing everything she owned. Mary's cancer remitted and she moved back to live with their mother. Two years later, Kim became pregnant and began to express fears that she and the fetus would contract cancer from Mary or anything Mary had touched. Because Mary had been living in Kim's house, nearly everything seemed "contaminated." To avoid conflict, Joe went along with all of Kim's requests, no matter how extreme. For example, he complied with her rules of taking specific routes to the grocery store, so as not to drive by "asbestos-contaminated" areas; buying dairy items at the back of the case so they weren't exposed to "radiation"; not using certain dishes, spices, or foods that had been used by Mary; and not sitting on certain "clean" chairs.

Kim and Joe appeared at the second of two information-gathering sessions, eager to learn more about OCD and how to handle it. Joe spoke of feeling as though "Kim's demands were controlling everything." He had given up trying to convince her not to be afraid because nothing seemed to work. Joe reported that "lately, Kim was going too far by involving Lilly." He went on to report that Lilly was not allowed to go to his mother's house if anyone in the neighborhood had had their lawn treated with chemicals, which involved a lengthy interrogation process. Lilly's clothes were changed at least 5 times a day, $25.00 a week was being spent on paper towels, and family activities were usually abandoned prematurely because of Kim's demands to go home to wash and shower. Joe's strategy had been to give in, but he felt that Kim's behavior had gotten "way out of hand" and that he did not know what to do about it. The therapists spoke about the MFBT offering this kind of help to family members. Besides problem solving with other families dealing with OCD, Joe would learn a specific technique, behavioral contracting, that would help him begin to set some limits on his participation in Kim's compulsions. Also, the more that Kim and Joe could learn about OCD, the more they would be able to control it. Hierarchies were established for fears of contamination-cancer from Kim's sister and from chemicals. One such hierarchy is listed in Table 9–3.

MFBT Session 1. Kim and Joe were asked to read Chapters 1–4 in *When Once is Not Enough* before the group began. At the outset of the MFBT group, anticipatory anxiety ran high. Kim and Joe were among a total of seven couples/families. Some families arrived very early to be

Table 9–3. Hierarchy for fears of contamination-cancer from sister and her cigarettes

Situation	Discomfort (1–100)	Treatment session
Holding unopened cigarette pack	45	1
Stepping with shoe on cigarette butt	45	1
Touching make-up sister used	50	1
Standing near someone smoking, outside	65	3
Touching doorknobs at work	70	4
Holding clothes worn by sister	70	4
Standing near someone smoking, inside	80	5
Touching "dirty" clothes (basement)	85	5
Touching side of dryer	85	5
Using cup served by a smoker	90	6
Stepping barefoot on a cigarette	95	7
Holding a "used" cigarette	95	7
Rubbing cigarette on food and eating	100	8

certain they were not late, whereas others, arriving late, rushed through the door with apologies, reporting that the patient had trouble getting to places on time because of obsessions and compulsions. The initial anxiety about the group was alleviated by providing structure, especially at this first session. However, the therapists also allowed room for individual expression that would collectively determine the "climate" of the group with regard to blame, responsibility, overprotection, overinvolvement, distance, impotence, and denial. The therapists observed the level of interaction and content as well as seating choices that could reveal alliances, conflicts, and level of trust within the group. Each person was asked to introduce him- or herself and indicate what he or she hoped to get out of the group. This facilitated participation and began the foundation for trust and group cohesiveness. Questions asked included, "What should I do when my daughter is in the shower for 3 hours? Can that really be OCD?"; "How do other families deal with the rituals?"; "What is OCD?"; and "How can each of us cope with it effectively?"A quick review of the ground rules clarified group expectations about the time frame of the group, the meeting place, confidentiality, and notification of absence from the group. A handout entitled "What is OCD?" that provided a definition

of obsessions and compulsions and described theories of etiology, course of illness, common coexisting disorders, and treatment was distributed as well as the Y-BOCS Symptom Checklist. The information was reviewed and the checklist served as a springboard for the group to disclose the obsessive-compulsive symptoms and behaviors that they typically hid in shame. As usual, there was great relief that others had similar thoughts and experiences. Kim, for example, said "Wow, you do that too! I thought I was the only one who won't let anyone else sit in my chair!" As family members heard others describe symptoms and feelings identical to those they have struggled with for many years, they began to realize that OCD was a real disorder beyond the patient's control. The group also provided the first real opportunity for several family members to learn about the content of the patient's obsessions and the extent of the rituals.

Families enthusiastically compared experiences. Joe was relieved to hear other spouses express helplessness and how they would surrender "to keep the peace." Families talked about the bizarre symptoms in an atmosphere with little social stigma. Fears that maybe their loved one was going crazy seemed quieted by meeting others with OCD who were "normal people."

The leaders left time for patients to select their ERP homework challenges. Kim chose to begin with the items lowest on her hierarchies. The session formally ended after homework forms were distributed and the therapists explained that this first week would be a trial time to begin to practice ERP. If patients did not sense that their distress was decreasing, they were encouraged to modify the exposure challenge and stay with one item until the discomfort diminished. Family members were reminded that one of the goals of the MFBT was to learn to be involved in the OCD as little as possible except in life-threatening or dangerous situations. Family members were instructed to keep their involvement to a minimum but not to make any drastic changes in their responses to the demands of OCD until they learned to use behavioral contracting. All families and patients were asked to finish reading *When Once is Not Enough* before the next session.

MFBT Session 2. The second session began with a review of what had been covered and accomplished the previous week. The leaders then asked whether anyone had any thoughts, questions, or feelings that they wanted to talk about. This discussion, which was brief and to the point, provided continuity between sessions, allowed members to warm up, and conveyed a sense of respect and appreciation for members' concerns. Each patient reported on the homework he or she had completed during the week, and the therapists collected homework forms, verifying that patients completed them as assigned. Therapists provided positive reinforcement to patients who had completed the form and performed the exposure, thereby modeling positive feedback to the group. Kim reported that she was unsure whether she was doing the homework correctly but that she had had success with holding a cigarette pack. She said that her discomfort level decreased to about 20 in all of these situations. Joe said he felt Kim should do the homework alone and asked what he should do

if she wants him present "for security." Some group members made suggestions that if it helped Kim to get started with the exposure, it was probably okay as long as he did not encourage her rituals.

Most of this second session involved the description of behavioral therapy and ERP techniques. Group leaders asked members what they thought *behavioral therapy* meant and explained that behavioral therapy provides tools for changing unwanted behaviors without analyzing the childhood history and meaning of the behaviors in detail. Next, the sequence of obsessions and compulsions was reviewed, explaining how a trigger or cue evoked an obsession, which led to feelings of anxiety and the urge to ritualize. The techniques of direct and imagined ERP in vivo and imaginal exposure were described. As each patient selected his or her homework, the group leader translated the task into a form that could be rehearsed in the group, and the therapist and other group members participated in the exposure challenge. Kim was asked to touch the doorknobs in the room along with all the other group members. This was difficult for other patients who had contamination fears for other reasons. Kim commented that it helped to see so many people unaffected by the task and that this observation made her question her own behavior and beliefs. Joe spoke about all the hours they had wasted talking about the irrationality of Kim's beliefs and how these discussions would lead to a point of desperation at which he would shout at her and call her "crazy": "Kim would end up crying, but at least it would stop the questioning."

At the end of the second session, the therapists instructed patients to continue the exposure from that day's session and add any other homework items to be practiced at least 1 hour a day, preferably all at one time rather than split into segments. Patients were reminded not to leave the exposure situation until their anxiety had declined noticeably and to record their distress levels on their homework form. Joe asked what he should do if Kim asked him to buy her more paper towels or to bathe Lilly "for the third time?" The therapists acknowledged that all families were eager to have these dilemmas resolved and that they would be getting to this more specifically at the next session. Families were encouraged to use what they had learned so far to modify their responses and to limit their involvement in rituals while communicating an appreciation for how hard it is for the patients to "just stop."

MFBT Session 3. The group began in its usual way, with each patient reporting on his or her homework task results. Members engaged in troubleshooting for problems that they were experiencing with the ERP homework and the homework forms. Kim reported that she continued to make headway but felt that so many things bothered her that she was not sure she would ever "get over" her OCD. Joe added that he had noticed a big improvement in Kim's outlook and that she seemed more willing to take risks. For example, they had gone out to eat pizza for the first time in 8 months, and Kim had stepped on a cigarette butt, driven behind a bus, touched the doorknobs, and sat with her hands open without performing any rituals. The group was tremendously supportive of Kim, but in spite of this support she asked how, if OCD is a neurobiologic disorder, she

would be able to change it. Others nodded, and one insightful spouse responded, "it's just as our therapist said: changing behavior can change thoughts and feelings. Look, it's already happening for you."

At this session, the therapists presented a brief videotaped lecture on the neurobiology of OCD that provided information on medication and the interplay of behavioral therapy with biologic processes in the treatment of OCD. After a discussion of this tape, the therapists asked each patient to select exposure items with a discomfort level of approximately 50–60. After about an hour of in vivo or imaginal exposure, the group began to discuss the "Guidelines For Living with OCD" described by Van Noppen and colleagues in their pamphlet, "Learning to Live With OCD." These guidelines included the following:

- Learn to recognize the signals that indicate a person is having problems
- Modify expectations during stressful times
- Measure progress according to the person's level of functioning
- Don't make day-to-day comparisons
- Give recognition for "small" improvements
- Create a strong, supportive home environment
- Keep communication clear and simple
- Stick to a behavioral contract
- Set limits, yet be sensitive to the person's mood
- Keep your family routine "normal"
- Use humor
- Support the person's medication regimen
- Make separate time for other family members
- Be flexible

Group members took turns reading aloud and the therapists asked the families which of the five family responses best described them. These reponses include

1. Families that assist with rituals to keep the peace
2. Families that do not participate in rituals but allow them to occur
3. Families that refuse to acknowledge or allow the compulsions in their presence
4. Families that are split in their responses—some members always give in, whereas others refuse to do so
5. Families in which members swing from one extreme to the other

This discussion promoted insight into family response patterns and the impact of those responses on the patient. Joe spoke about the accommodating pattern as fitting for him, yet he started to see that he also oscillated at times out of frustration. He spoke about the time he got so angry because Kim wouldn't get out of the shower that he shut off the hot water. She continued to shower anyway, in the cold water, so he turned off all the water in the house. This resulted in a screaming battle that woke Lilly

and made her cry, so he turned the water back on. Other families related to Joe's story, adding that it was hard to be consistent or to really follow through on threats. Kim reported that she had given this pamphlet to her mother and siblings to read and that "for the first time they seemed to understand that my fears weren't personal feelings about them."

Kim and the other patients reassessed their behavioral homework task with the family guidelines in mind and added another challenge. Members told Joe that he should not blame himself for "helping" because he was doing the best that he could, even more so because he had not known what he was dealing with. Now, with education and some tools, there was hope.

MFBT Session 4. The first three sessions had provided patients and families with a clearer understanding of OCD. The next step was to learn how to cope more productively with the symptoms as a family using cognitive and behavioral techniques. This fourth session was designed to prepare the families for family contracting, which forms the essence of family collaboration in the treatment of OCD and would be the focus of upcoming sessions. As usual, the meeting began with a review of homework. Kim and Joe described being discouraged because they had gone away for the weekend and Kim had been afraid that their condo was sprayed with pesticide. She had stayed in the same clothes all weekend, would not let Joe bring their suitcases out of the car, would not allow Lilly to play on the floor, and felt that she was "back to base 1." Joe brought to the session some of the clothes that they had worn, despite Kim's pleas not to do so; he knew he had to be firmer and insisted despite their bickering. The group gave Joe positive feedback for doing this and confronted him about his tendency to give in too much. The therapists asked that these items be used in the session during the behavioral contracting.

The therapists introduced the concept of behavioral contracting by asking the group what they thought was meant by this term. The therapists then outlined the critical concepts in behavioral contracting: 1) realistic expectations on the part of patient and family are clearly defined; 2) the family learns how to be supportive in ways that are therapeutic to the patient; 3) the patient is given responsibility for therapy that enhances his or her sense of control, motivation, and confidence; and 4) limits of responsibility are clarified and family members are redirected to get involved in their own lives again.

The group discussed Kim's exposure homework and considered what Joe should do to be supportive but not facilitate the OCD. Kim and Joe decided they would target Kim's need for reassurance, which had decreased but was still out of hand. This led to a discussion of what was reasonable with regard to reassurance. One father asked, "But don't we all need reassurance?" One spouse responded that the kind of reassurance people with OCD ask for may seem reasonable at times, but the repetitive questioning and the urgency of the need for certainty were not "normal." Others agreed and added that in some cases the questions did not have absolute answers, and in other cases the patient already knew the answer to the question. All of the families identified the process of giving reassur-

ance as "futile," "exhausting," and "frustrating." Patients in the group expressed feelings of shame about their behavior.

One of the therapists led Kim and Joe through a detailed negotiation process to arrive at an agreement as to how Joe should respond to Kim's requests for reassurance. Kim gave Joe permission to label her questions as OCD and to remind her that she knows how he would answer the "OCD question." If she persisted, he was to suggest that she put the question on hold, even though it seemed urgent, and if it still bothered her they could talk about it later. If Kim continued to persist, Joe was to remind her again that this was a reassurance question and that he knew what she was going through but that it would not help to talk about it. Kim agreed that at this point Joe should suggest that she do something else to distract herself because she always felt better over time. If this did not work and the requests became very unreasonable, Joe was to leave the room, or the house if necessary, to remove himself from the situation. If Kim became very agitated, Joe would answer her once and only once.

All of the families left the session with a behavioral contract to practice and homework forms to record the progress. As had been done in previous sessions, each patient committed to performing individual exposure homework as well as the family contract. Family members were directed to get involved in their own lives again.

MFBT Sessions 5-11. As usual, each of these sessions began with discussion of exposure homework and behavioral contract. During these 2-hour sessions, the group practiced in vivo and imaginal ERP, family contracting, self-monitoring of distress levels, and homework planning. Family responses to OCD symptoms were discussed in greater detail, and greater disclosure about symptoms emerged. Group interaction became highly personalized as families described the interpersonal conflicts that arose in their attempts to manage the obsessive-compulsive symptoms.

Families were supported by the therapists and group members in their efforts to help. Many were unaware of how to negotiate a family approach with patient consent. One husband grasped the general concept of ERP, but tried a new response without first discussing it with his wife; this backfired because the patient felt powerless and out of control. During these sessions, group members who complained about not having enough guidance or who tried to rush the group ahead to the contracting were often those who avoided committing themselves to a task when given the opportunity. These patients consumed group time and were confronted about their behavior and given permission to pass or to work on an exposure challenge of their own without family involvement.

The decision to change was placed on the patient. Families were coached to accept that they could not make the patient participate in a treatment of their choosing unless they established and carried out consequences for certain behaviors. As for exposure homework, this had to be the patient's choice; however, when a chosen task was not sufficiently challenging, the therapists used the group process to encourage a more meaningful task. Group members were instrumental in helping one adolescent accept family limits as reasonable. The behavioral contract limited

parental responsibility for carrying out exposure homework, thus allowing the patient to engage in independent, responsible behavior.

In the later sessions, increasing emphasis was placed on independently initiating ERP challenges and behavioral contracting with less therapist involvement. The therapists stressed the importance of self-instruction and independent use of the techniques. In session 11, the therapists ensured that each family had reviewed its gains and the symptoms that needed more intensive work. As often occurs in group behavioral therapy, many patients expressed fear that they would not be able to maintain their improvement after the group ended. The therapists, with feedback from other group members, again highlighted the symptomatic improvement and wealth of knowledge and understanding gained through the MFBT, and they reminded the group that one of the purposes of the monthly follow-up sessions was to consolidate treatment gains. They emphasized that if patients anticipated stressors that might increase OCD symptoms (e.g., birth of a baby, job change), troubleshooting and preventative planning were needed.

MFBT Session 12. The weekly session began with homework review and the practice of ERP and family behavioral contracting. Throughout this session, families and patients asked questions such as "What will we do now?"; "Does this group have to end?"; and "Can't we extend it? We just got to know each other." The therapists addressed feelings of sadness and loss as part of ending the group. Kim and Joe spoke about how much they would miss the encouragement and coaching from the group. Kim, like other patients, was well aware of the importance of practicing the strategies consistently but feared she would not be as diligent without the accountability of the group. Joe told her that with the behavioral contracting and his better understanding, she did not have to worry because he would not let her "get away with as much." Through the MFBT, Joe had learned to communicate understanding and to set limits. Kim explained that she and Joe had made a contract that when they were in public and Kim got into "an OCD thing," Joe would gently squeeze her hand and wink at her as a signal that she was being unreasonable. This worked very well because there were no hostile, critical comments made toward the patient. Joe spoke for other family members in the group when he said that before the MFBT, "I thought I knew about OCD, but now I not only understand it intellectually, I understand it emotionally too."

Combined Behavioral and Pharmacologic Treatment

Studies examining pharmacologic treatments are reviewed in other chapters and are therefore not presented here. Instead, we focus on whether it is advantageous to patients to combine behavioral treatment with medications. To date, studies of this topic have employed the serotonergic drugs clomipramine and fluvoxamine, which have been demonstrated to have specific antiobsessive effects in addition to their antidepressant action.

Some studies of combined treatment have been published. Marks et al. (1980, 1988) conducted two trials contrasting individual ERP without medications to exposure with clomipramine. Behavioral therapy led to improvement in both depressive and OCD symptoms, as did the combination, with few differences detected between treatments after therapy or at follow-up. Combined treatment had a slight additive effect in the 1980 trial, particularly for depressed patients, and appeared to improve compliance with behavioral therapy. In the 1988 study, self-exposure plus clomipramine led to more rapid improvement, but differences did not persist.

Cottraux et al. (1989) found that adding fluvoxamine to ERP produced slight advantages at week 24, but these had disappeared by week 48. As in the 1980 Marks et al. trial, initial depression was associated with more gain for patients given medication. Preliminary findings from an ongoing multisite trial comparing gains in patients with OCD treated with ERP alone with those receiving ERP in combination with clomipramine suggest that adding medications may actually have adverse effects (Foa et al. 1993). However, the difficulty in obtaining subjects for this study suggests that results may not be generalizable to all patients with OCD, and findings are as yet preliminary. Meta-analyses from two research groups have produced slightly different results, with one group finding no additive effect of medications (Christensen et al. 1987) and a later group suggesting that serotonergic drugs confer some additional beneficial effects when combined with behavioral treatment (Van Balkom et al. 1994). In a more recent study by Van Noppen et al. (1998), 72 of 100 patients received group behavioral treatment as an adjunct to pharmacotherapy and had a greater drop in Y-BOCS scores (21.9 before the study compared with 16.2 afterward) than those who received group behavioral treatment alone ($n=18$; Y-BOCS scores 21.1 before study versus 18.5 afterward).

Predictors of Outcome

Treatment with ERP has led to improvement in approximately 75% of the patients with OCD who have received it, but it is clear that up to 25% of potential participants refuse to enter this treatment, and the same percentage fail to benefit sufficiently. A few studies have provided information about those who remain unaffected or who relapse.

Although high levels of pretreatment depression appeared problematic in early research (e.g., Foa et al. 1983; Marks et al. 1980), subsequent studies have failed to find an association of depression and ERP outcome (e.g., Basoglu et al. 1988; Mavissakalian et al. 1985; Steketee 1988). A 1995

comprehensive review of predictors of outcome found a slight preponderance of studies favoring depression as a predictor of posttest outcome but not long-term effects (Steketee and Shapiro 1995). One study indicated that high levels of depression after treatment were related to poorer long-term outcome (Steketee 1988). Comorbid major depression was not a clear predictor in another trial (Steketee et al. 1995a). In other comorbid mood states and disorders, anxious mood did not predict outcome at any point, but comorbid generalized anxiety disorder may interfere with benefits from ERP (Steketee et al. 1995b). Other comorbid conditions associated with poor outcome after behavior therapy include schizotypal personality disorder (Minichiello et al. 1987), passive-aggressive traits (Steketee 1990), and borderline personality disorder (Hermesh et al. 1987)

Summary

The conceptualization of obsessions as thoughts, images, impulses, or actions that increase anxiety and of compulsions as behaviors or cognitions that reduce anxiety has led to very successful treatment for OCD. Prolonged exposure to feared situations, accompanied by blocking of ritualistic responses, has proven to be a successful treatment for approximately 75% of those who elect to receive it. Research studies indicate that exposure should be lengthy rather than brief to allow anxiety to decline and that imaginal exposure to images that include the patient's feared disastrous consequence is a helpful adjunct to exposure in practice for those with such fears. In general, the more rigorous the program, the better the success achieved. Both exposure and ritual prevention are needed to effectively reduce OCD symptoms, and these can be conducted very successfully in an individual, group, or multifamily context. After behavioral treatment, patients should not be alarmed by the experience of mild obsessional symptoms, particularly in times of stress, but merely allow themselves to experience the obsessive thought until fear declines, without engaging in ritualistic efforts. Although the addition of cognitive therapy and serotonergic drug treatments has not been consistently found to significantly improve the benefits of behavioral treatment, these studies are not easy to interpret because of methodologic considerations. However, both of these treatments alone may be alternatives for patients who are unable or unwilling to engage in behavior therapy.

Some factors may make progress more difficult, including very severe symptoms, comorbid conditions, lack of insight into obsessions, and family responses to symptomatic behavior. Most family conflict centers on the patients' obsessive-compulsive symptoms and their impact on family

functioning. Nonetheless, the prognosis is positive for most patients who receive an adequate trial of behavioral treatment, whether it be in an individual, group, or multifamily modality. For patients who fail to respond to traditional individual or group treatment and pharmacologic interventions, multifamily treatment may be a successful alternative. In addition, those patients whose family members are very involved in or very critical of the obsessive-compulsive symptoms may benefit more from this type of treatment. Our clinical experience suggests that the family support system and family responses to OCD may play an important role in the prognosis and long-term outcome of treatment.

References

Allsopp M, Verduyn C: Adolescents with obsessive-compulsive disorder: a case note review of consecutive patients referred to a provincial regional adolescent psychiatry unit. Journal of Adolescence 13:157–169, 1990

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

Anderson CM, Reiss DJ, Hogarty GE: Schizophrenia and the family: a practitioner's guide to psychoeducation and management. New York, Guilford, 1986

Basoglu M, Lax T, Kasvikis Y, et al: Predictors of improvement in obsessive-compulsive disorder. J Anxiety Disord 2:299–317, 1988

Beck AT, Emery G: Anxiety Disorders and Phobias: A Cognitive Perspective. New York, Basic Books, 1985

Beech HR, Liddell A: Decision making, mood states and ritualistic behavior among obsessional patients in obsessional states. Edited by Beech HR. London, England, Methuen, 1974, pp 143–160

Black DW, Blum NS: Obsessive-compulsive disorder support groups: the Iowa model. Compr Psychiatry 33:65–71, 1992

Boersma K, Den Hengst S, Dekker J, et al: Exposure and response prevention: a comparison with obsessive-compulsive patients. Behav Res Ther 14:19–24, 1976

Boulougouris JC: Variables affecting the behaviour modification of obsessive-compulsive patients treated by flooding, in the Treatment of Phobic and Obsessive-Compulsive Disorders. Edited by Boulougouris JC, Rabavilas AD. Oxford, England, Pergamon, 1977, pp 73–84

Boulougouris JC, Bassiakos L: Prolonged flooding in cases with obsessive-compulsive neurosis. Behav Res Ther 11:227–231, 1973

Brown GW, Birley JLT, Wing JK: Influence of family life on the course of schizophrenic disorders: a replication. Br J Psychiatry 121:241–258, 1972

Budman S: Forms of Brief Therapy. New York, Guilford Press, 1981

Calvocoressi L, Lewis B, Harris M, et al: Family accommodation in obsessive compulsive disorder. Am J Psychiatry 152:441–443, 1995

Carr AI: Compulsive neurosis: a review of the literature. Psychol Bull 8:311–318, 1974

Christensen H, Hadzi-Pavlovic D, Andrews G, et al: Behavioral therapy and tricyclic medication in the treatment of obsessive-compulsive disorder: a quantitative review. J Consult Clin. Psychol 55:701–711, 1987

Clark DA, Purdon C: New perspectives for a cognitive theory of obsessions. Australian Psychologist 28:161–167, 1993

Cobb J, McDonald R, Marks IM, et al: Marital versus exposure therapy: psychological treatments of co-existing marital and phobic obsessive problems. Behavioural Analysis and Modification 4:3–16, 1980

Cooper M: A group for families of obsessive-compulsive persons. Families in Society May:301–307, 1993

Cottraux J, Mollard E, Bouvard M, et al: A controlled study of fluvoxamine and exposure in obsessive compulsive disorder. Int Clin Psychopharmacol 5:1–14, 1989

Dalton P: Family treatment of an obsessive-compulsive child: a case report. Fam Process 22:99–108, 1983

Dollard J, Miller NE: Personality and psychotherapy: an analysis in terms of learning, thinking and culture. New York, McGraw-Hill, 1950

Emmelkamp PMG, Beens I: Cognitive therapy with obsessive-compulsive disorder: a comparative evaluation. Behav Res Ther 29:293–300, 1991

Emmelkamp PMG, van Kraanen J: Therapist-controlled exposure in vivo: a comparison with obsessive-compulsive patients. Behav Res Ther 15:491–495, 1977

Emmelkamp PMG, van der Helm M, van Zanten BL, et al: Contributions of self-instructional training to the effectiveness of exposure in vivo: a comparison with obsessive-compulsive patients. Behav Res Ther 18:61–66, 1980

Emmelkamp PMG, Visser S, Hoekstra RJ: Cognitive therapy vs exposure in vivo in the treatment of obsessive-compulsives. Cogn Ther Res 12:103–114, 1988

Enright SJ: Group treatment for obsessive-compulsive disorder: an evaluation. Behavioural Psychotherapy 19:183–192, 1991

Epsie CA, Michelson L (eds): The group treatment of obsessive-compulsive ritualizers: behavioral management of identified patterns of relapse. Behavioural Psychotherapy 14:21–33, 1996

Falloon IRH, Liberman RP, Lillie IFJ, et al: Family therapy of schizophrenics with high risk of relapse. Fam Process 20:211–221, 1981

Falloon IRH, Boyd J, McGill CW: Family Care of Schizophrenia: A Problem-Solving Approach to the Treatment of Mental Illness. New York, Guilford, 1984

Fals-Stewart W, Marks AP, Schafer J: A comparison of behavioral group therapy and individual behavior therapy in treating obsessive-compulsive disorder. J Nerv Ment Dis 181:189–193, 1993

Foa EB, Goldstein A: Continuous exposure and complete response prevention of obsessive-compulsive disorder. Behav Ther 9:821–829, 1978

Foa EB, Kozak MJ: Emotional processing of fear: exposure to corrective information. Psychol Bull 99:20–35, 1986

Foa EB, Tillmanns A: The treatment of obsessive-compulsive neurosis, in Handbook of Behavioral Interventions: A Clinical Guide. Edited by Goldstein A, Foa EB. New York, Wiley, 1980, pp 416–500

Foa EB, Steketee GS, Milby JB: Differential effects of exposure and response prevention in obsessive compulsive washers. J Consult Clin Psychol 48:71–79, 1980a

Foa EB, Steketee G, Turner RM, et al: Effects of imaginal exposure to feared disasters in obsessive-compulsive checkers. Behav Res Ther 18:449–455, 1980b

Foa EB, Grayson JB, Steketee GS, et al: Success and failure in the behavioral treatment of obsessive-compulsives. J Consult Clin Psychol 51:287–297, 1983

Foa EB, Steketee G, Grayson J, et al: Deliberate exposure and blocking of obsessive-compulsive rituals: immediate and long-term effects. Behav Ther 15:450–472, 1984

Foa EB, Kozak MJ, Steketee G, et al: Treatment of depressive and obsessive compulsive symptoms in OCD by imipramine and behavior therapy. Br J Clin Psychol 31:279–292, 1992

Foa EB, Kozak M, Liebowitz M, et al: Treatment of obsessive-compulsive disorder by behavior therapy, clomipramine, and their combination: preliminary results of a multicenter double-blind controlled trial. Paper presented at the meeting of the Association for Advancement of Behavior Therapy, Atlanta, GA, November 1993

Freeston MH, Rheaume J, Ladouceur R: Correcting faulty appraisals of obsessional thoughts. Behav Res Ther 34:433–446, 1996

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman WK, Price LH, Rasmussen SA, et al: The Yale-Brown Obsessive Compulsive Scale, II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Griest JH: New developments in behavior therapy for obsessive-compulsive disorder. Int Clin Psychopharmacol 11:53–73, 1996

Greist JH, Marks IM, Baier L, et al: Computer-assisted behavior therapy for OCD. Paper presented at the American Psychiatric Association, New York, May 1996

Guidano VL, Liotti G: Cognitive Processes and Emotional Disorders. New York, Guilford, 1983

Hafner RJ: Marital interaction in persisting obsessive-compulsive disorders. Aust N Z J Psychiatry 16:171–178, 1982

Hafner RJ: Anxiety disorders and family therapy. Aust N Z J Fam Ther 13:100–104, 1992

Hafner RJ, Gilchrist P, Bowling J, et al: The treatment of obsessional neurosis in a family setting Aust N Z J Psychiatry 15:145–151, 1981

Hand I, Tichatzky M: Behavioral group therapy for obsessions and compulsions: first results of a pilot study, in Trends in Behavior Therapy. Edited by Sjoden PO, Bates D, Dockens WS. New York, Academic Press, 1979, pp 269–297

Hermesh H, Shahar A, Munitz H: Obsessive-compulsive disorder and borderline personality disorder (letter to the editor). Am J Psychiatry 144:120-12, 1987

Hibbs ED, Hamburger SD, Lenane M, et al: Determinants of expressed emotion in families of disturbed and normal children. J Child Psychol Psychiatry 32:757–770, 1991

Hodgson RJ, Rachman S: The effects of contamination and washing in obsessional patients. Behav Res Ther 10:11–117, 1972

Hogarty GE, Anderson CM, Reiss DJ, et al: Family psychoeducation, social skills training and maintenance chemotherapy in the aftercare treatment of schizophrenia. Arch Gen Psychiatry 43:633–642, 1986

Hoogduin CAL, Duivenvoorden HJ: A decision model in the treatment of obsessive-compulsive neuroses. Br J Psychiatry 152:516–521, 1988

Hoogduin K, DeHaan E, Schaap C, et al: Exposure and response prevention in patients with obsessions. Acta Psychiatr Belg 87:640–633, 1987

Hooley JM, Orley J, Teasdale JD: Levels of expressed emotion and relapse in depressed patients. Br J Psychiatry 148:642–647, 1986

Hoover CF, Insel TR: Families of origin in obsessive-compulsive disorder. J Nerv Ment Dis 172:207–215, 1984

Hornsveld RHJ, Kraaimaat FW, van Dam-Baggen RMJ: Anxiety/discomfort and handwashing in obsessive compulsive and psychiatric control patients. Behav Res Ther 17:223–228, 1979

Kozak MJ, Foa EB, McCarthy PR: Assessment of obsessive compulsive disorder, in Handbook of Anxiety Disorders. Edited by Last C, Hersen M. New York, Pergamon, 1987

Krone KP, Himle JA, Nesse RM: A standardized behavioral group treatment program for obsessive compulsive disorder: preliminary outcomes. Behav Res Ther 29:627–632, 1991

Ladouceur R, Freeston MH, Gagnon F, et al: Idiographic considerations in the cognitive-behavioral treatment of obsessional thoughts: J Behav Ther Exp Psychiatry 24:301–310, 1993

Leff J, Kuipers L, Berkowitz R, et al: A controlled trial of social intervention in the families of schizophrenic patients. Br J Psychiatry 141:121–134, 1982

Leonard H, Swedo S, Lenane M, et al: 2–7 year follow-up study of 54 obsessive compulsive children and adolescents. Arch Gen Psychiatry 50:429–439, 1993

Lopatka C, Rachman SJ: Perceived responsibility and compulsive checking: an experimental analysis. Behav Res Ther 33:673–684, 1995

Makhlouf-Norris F, Norris H: The obsessive compulsive syndrome as a neurotic device for the reduction of self-uncertainty. Br J Psychiatry 121:277–288, 1972

Makhlouf-Norris F, Jones HG, Norris H: Articulation of the conceptual structure in obsessive neurosis. Br J Soc Clin Psychol 9:264–274, 1970

Marks IM, Hodgson R, Rachman S: Treatment of chronic obsessive-compulsive neurosis in vivo exposure, a 2 year follow-up and issues in treatment. Br J Psychiatry 127:349–364, 1975

Marks IM, Stern RS, Mawson D, et al: Clomipramine and exposure for obsessive compulsive rituals. Br J Psychiatry 136:1–25, 1980

Marks IM, Lelliott P, Basoglu M, et al: Clomipramine, self-exposure and therapist-aided exposure for obsessive compulsive rituals. Br J Psychiatry 152:522–534, 1988

Mavissakalian M, Turner SM, Michelson L, et al: Tricyclic antidepressants in obsessive compulsive disorder: antiobsessional or antidepressant agents? II. Am J Psychiatry 142:572–576, 1985

McFall ME, Wollersheim JP: Obsessive compulsive neurosis: a behavioral formulation and approach to treatment. Cogn Ther Res 3:333–348, 1979

McFarlane WR, Lukins E, Link B, et al: Multiple-family groups and psychoeducation in the treatment of schizophrenia. Arch Gen Psychiatry 52:679–687, 1995

Mehta M: A comparative study of family-based and patient-based behavioral management in obsessive compulsive disorder. Br J Psychiatry 157:133–135, 1990

Meyer V: Modification of expectations in cases with obsessional rituals. Behav Res Ther 4:273–280, 1966

Meyer V, Levy R: Modification of behavior in obsessive-compulsive disorders, in Issues and Trends in Behavior Therapy. Edited by Adams HE, Unikel P. Springfield, IL, Charles C. Thomas, 1973, pp 77–137

Meyer V, Levy R, Schnurer A: A behavioral treatment of obsessive compulsive disorders, in Obsessional States. Edited by Beech HR. London, England, Methuen, 1974, pp 233–258

Miller IW, Kabacoff RI, Keitner GI, et al: Family functioning in the families of psychiatric patients. Compr Psychiatry 27:302–312, 1986

Mills HL, Agras WS, Barlow DH, et al: Compulsive rituals treated by response prevention. Arch Gen Psychiatry 28:524–552, 1973

Milner AD, Beech HR, Walker VJ: Decision processes and obsessional behaviour. Br J Soc Clin Psychol 10:88–89, 1971

Minichiello W, Baer L, Jenike MA: Schizoptypal personality disorder: a poor prognostic indicator for behavior therapy in the treatment of obsessive compulsive disorder. J Anxiety Disord 1:273–276, 1987

Mowrer OH: Learning Theory and Behavior. New York, Wiley, 1960

Persons JB, Foa EB: Processing of fearful and neutral information by obsessive compulsives. Behav Res Ther 22:259–265, 1984

Pitman RK: A cybernetic model of obsessive-compulsive psychopathology. Compr Psychiatry 28:334–343, 1987

Rabavilas AD, Boulougouris JC: Physiological accompaniments of ruminations, flooding, and thought-stopping in obsessive patients. Behav Res Ther 12:239–243, 1974

Rabavilas AD, Boulougouris JC, Stefanis S: Duration of flooding sessions in the treatment of obsessive compulsive patients. Behav Res Ther 14:349–355, 1976

Rabavilas AD, Boulougouris JC, Perissaki C: Therapist qualities related to outcome with exposure in vivo in neurotic patients. J Behav Ther Exp Psychiatry 10:293–299, 1979

Rachman S: Obsessional ruminations. Behav Res Ther 14:229–235, 1976

Rachman SJ: Obsessions, responsibility, and guilt. Behav Res Ther 31:149–154, 1993

Rachman S, Hodgson R: Obsessions and Compulsions. Englewood Cliffs, NJ, Prentice-Hall, 1980

Rachman S, Marks IM, Hodgson R: The treatment of obsessive compulsive neurotics by modeling and flooding in vivo. Behav Res Ther 11:463–471, 1973

Reed GF: Obsessional Experience and Compulsive Behavior: A Cognitive Structural Approach. New York, Academic Press, 1985

Rheaume J, Ladouceur R, Freeston MH, et al: Inflated responsibility and its role in OCD, I: validation of a theoretical definition of responsibility. Behav Res Ther 33:159–169, 1995

Roper G, Rachman S, Hodgson R: An experiment on obsessional checking. Behav Res Ther 11:271–277, 1973

Roper G, Rachman S, Marks IM: Passive and participant modeling in exposure treatment of obsessive compulsive neurotics. Behav Res Ther 13:271–279, 1975

Salkovskis PM: Obsessional compulsive problems: a cognitive-behavioural analysis. Behav Res Ther 23:571–583, 1985

Salkovskis PM: Cognitive-behavioral factors and the persistence of intrusive thoughts in obsessional problems. Behav Res Ther 27:677–682, 1989

Salkovskis PM, Warwick HMC: Morbid preoccupations, health anxiety and reassurance: a cognitive-behavioral approach to hypochondriasis. Behav Res Ther 24:597–602, 1986

Salkovskis PM, Westbrook D: Behaviour therapy and obsessional ruminations: can failure be turned into success? Behav Res Ther 27:149–169, 1989

Steketee G: Intra- and interpersonal characteristics predictive of long-term outcome following behavioral treatment of obsessive compulsive disorder, in Treatments of Panic and Phobias. Edited by Wittchen H, Hand I. New York, Springer-Verlag, 1988

Steketee G: Personality traits and disorders in obsessive compulsive patients. J Anxiety Disord 4:351–364, 1990

Steketee G: Social support as a predictor of follow-up outcome following treatment for OCD. J Behav Psychother 21:81–95, 1993a

Steketee G: Treatment of Obsessive-Compulsive Disorder. New York, Guilford, 1993b

Steketee G, Shapiro L: Predicting behavioral treatment outcome for agoraphobia and obsessive compulsive disorder. Clin Psychol Rev 15:317–346, 1995

Steketee G, White K: When Once is Not Enough. Oakdale, CA, New Harbinger Press, 1990

Steketee G, Chambless DL, Tran GQ, et al: Behavioral avoidance test for obsessive compulsive disorder. Behav Assess 34:73–83, 1995a

Steketee G, Chambless D, Tran GQ: Comorbidity and outcome for behaviorally treated clients with OCD and agoraphobia. Paper presented at the World Congress of Behavioral and Cognitive Therapy, Copenhagen, Denmark, July 1995b

Steketee G, Frost RO, Bogart K: Yale Brown Obsessive Compulsive Scale: interview versus self-report. Behav Assess 34:675–684, 1996

Steketee G, Rheaume J, Frost RO: Cognitions in obsessive compulsive disorder, in Obsessive Compulsive Disorder: Theory and Treatment, 3rd Edition. Edited by Jenike MA, Baer L, Minichiello WE. Chicago, IL, Yearbook Medical, 1998, pp 368–399

Taylor CJ, Sholomskas DE: Group exposure and response prevention for OCD. Paper presented at the annual meeting of the Anxiety Disorders Association of America, Santa Monica, CA, March 1993

Thornicroft G, Colson L, Marks I: An in-patient behavioural psychotherapy unit description and audit. Br J Psychiatry 158:362–367, 1991

Turner SM, Hersen M, Bellack AS, et al: Behavioral and pharmacological treatment of obsessive-compulsive disorders. J Nerv Ment Dis 168:651–657, 1980

Tynes LL, Salins C, Skiba W, et al: A psychoeducational and support group for obsessive compulsive disorder patients and their significant others. Compr Psychiatry 33:197–201, 1992

Van Balkom AJLM, van Noppen B, Vermeulen AWA, et al: A meta-analysis on the treatment of obsessive compulsive disorder: a comparison of antidepressants, behavior and cognitive therapy. Clin Psychol Rev 14:359–382, 1994

Van Noppen BL, Pato MT, Rasmussen S: Learning to Live With OCD (pamphlet). OC Foundation, P.O. Box 70, Milford, CT 06460.

Van Noppen B, de Haan E, Van Balkom AJLM, et al: Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. Behav Res Ther 33:379–390, 1995

Van Noppen B, Steketee G, McCorkle BH, et al: Group and family behavioral treatment for obsessive compulsive disorder. Paper presented at the Association for Advancement of Behaviour Therapy, New York, May 1996

Van Noppen B, Pato M, Marshland R, et al: A time-limited behavioral group for treatment of obsessive-compulsive disorder. J Psychother Pract Res 7:272–280, 1998

Volans PJ: Styles of decision making and probability appraised in selected obsessional and phobic patients. Br J Soc Clin Psychol 15:305–317, 1976

Warren R, Zgourides G: Anxiety Disorders: A Rationale–Motive Perspective. New York, Pergamon, 1991

Wegner DM: White Bears and Other Unwanted Thoughts. New York, Penguin, 1989

Woody SR, Steketee G, Chambless DL: The usefulness of the obsessive compulsive scale of the Symptom Checklist 90-Revised. Behav Res Ther 33:607–611, 1995
Yalom I: Theory and Practice of Group Psychotherapy. New York Basic Books, 1975

CHAPTER 10

Treatment of Strictly Religious Patients

David Greenberg, M.D.
Eliezer Witztum, M.D.

> I advise all to take heed of placing religion too much in fears and tears and scruple.
>
> *Baxter 1692/1963*

History and Epidemiology of Religious Symptoms in Obsessive-Compulsive Disorder

Treatment of obsessive-compulsive disorder (OCD) in strictly religious patients requires therapists to be sensitive to a plethora of issues not always encountered when treating other patients with the disorder. Therapists should be aware of the inseparable historical influence of religious culture on psychiatric symptoms and the areas of religious practice that lend themselves to obsessive-compulsive behavior. With this understanding, therapists need to discriminate between normal and pathologic religiosity. In addition, religiosity can introduce unique challenges to the therapeutic relationship itself for which therapists must be prepared. Finally, therapists should possess a set of guidelines and a repertoire of treatment approaches specialized to managing OCD in strictly religious patients. We address these topics and present a case history that illustrates treatment of OCD manifested in the matrix of religious practice.

Obsessions were a feature of religious life before they achieved psychiatric status. The original meaning of obsession was "actuation by the devil or an evil spirit from without." An early example was "a compulsion to

blaspheme or swear aloud in church…referred to as the 'devil in the tongue,'" (Enoch and Trethowan 1979). John Moore, Bishop of Norwich, wrote in his treatise *Of Religious Melancholy* of good moral worshippers who are assailed by "naughty and sometimes blasphemous thoughts" that "start in their minds, while they are exercised in the worship of God" despite "all their efforts to stifle and suppress them" (Moore 1692/1963, p. 252).

Detailed accounts of obsessions with religious content are provided by two of the most significant figures in sixteenth-century Christendom. Ignatius of Loyola (1548/1978), father of the Jesuit order, described obsessive thoughts and their association with repetitive religious rituals: "After I have trodden upon a cross formed by two straws, or after I have thought, said or done some other thing, there comes to me from without a thought that I have sinned; I feel some uneasiness on the subject inasmuch as I doubt and do not doubt" (p. 54). He noted that devout people need to be sure that they have pleased God and that they have not sinned. If unable to convince themselves of this, they may perform acts of penance. If these, too, fail to allay their anxiety, then they will be tormented by doubts and preoccupied by rituals.

Martin Luther was a devout monk before revolting against Catholicism and founding Protestant Christianity. Luther would spend hours confessing his sins, repeating minute details to be sure that nothing had been deleted. When leaving, he would fear he had omitted something and would go back and start again. "Luther would repeat a confession and, to be sure of including everything, would review his entire life until the confessor grew weary and exclaimed: 'Man, God is not angry with you, you are angry with God; don't you know that God commands you to hope.'" (Bainton 1950, p. 41).

Religion has been listed as one of the four main topics of obsessions along with dirt, harm, and sex (Lewis 1936). Research in patients with OCD has presented a range of findings. In India, religious concerns were a relatively rare presentation in Chandigarh, where 82 patients reported a total of 119 topics, of which 9 were religious (Akhtar et al. 1975); a large study in Bangalore found religious symptoms in only 4.74% of 410 patients with OCD (Khanna and Channabasavanna 1988). In Western populations, a study of 45 patients with OCD in the United Kingdom did not record religion among the 100 themes patients associated with their rituals (Stern and Cobb 1978), whereas in three studies in the United States, religious themes among both past and present symptoms were found in 6 of 21 patients in New Haven, Connecticut (Riddle et al. 1990), 9 of 70 patients had religious obsessions as a major presenting symptom in Bethesda,

Maryland (Swedo et al. 1989), and about 10% of 560 clinic patients in a large OCD clinic in Rhode Island reported religious obsessions (Rasmussen and Eisen 1992). A Danish study of 61 cases in Arhus found religious obsessions in only 5 cases (Thomsen 1991).

These findings may be contrasted with three recent studies carried out in Islamic and orthodox Jewish populations that found religion to be the most common theme in OCD. Of 90 patients with OCD in Cairo, Egypt, 60% had religious obsessions. The most common compulsions of a religious nature were ordering, cleaning, and washing. The role of repeated ablutions before prayers and the recitation of prayers and phrases in fixed sequence is described in everyday Islamic life, and some patients had religious symptoms even if they were not "practicing their religious duties" (Okasha et al. 1994). In a sample of 32 patients with OCD in Al-Khobar in Saudi Arabia, 40 of the 60 themes of obsessions recorded concerned religion: 50% of patients had obsessions related to prayer or body washing, 41% had obsessions related to body contamination, and 34% had obsessive thoughts about faith. Fifty percent of the sample had repeating compulsions of a religious nature, and 37% had washing compulsions arising out of religious concerns (Mahgoub and Abdel-Hafeiz 1991). The role of religious affiliation in determining the topics in OCD is demonstrated by a study comparing the content of obsessions in 34 patients with OCD in the Jewish population in Jerusalem, Israel. Religious concerns and rituals dominate the lives of ultraorthodox Jews, and their secular education is minimal. Of 19 ultraorthodox Jewish patients with OCD, 13 had symptoms of religious content as opposed to 1 of 15 non–ultraorthodox Jewish patients with OCD. Interestingly, most of the ultraorthodox patients who had nonreligious obsessions, such as illness, dirt, violence, and sex, were born in nonreligious homes and had been exposed to different cultural influences than those who were ultraorthodox (Greenberg and Witztum 1994b).

It may be suggested, in summary, that obsessions of OCD appear to mirror the prevalent habits and values of a culture. Religious symptoms are common in OCD in cultures in which religious practice and ritual are important. It appears that if a topic is dealt with scrupulously in everyday life, then it is a likely focus for the symptoms of OCD that will emerge in that culture. The exception among the studies presented was the consistent rarity of religious issues in OCD in India despite the importance of religious life in that country. This was understood to be a result of strong social taboos; neither religion nor sex was the subject of conversation, and these topics were therefore absent from psychopathology (Akhtar et al. 1975).

Presentation of Obsessive-Compulsive Disorder Within Religious Practice

In religions with extensive codes, rituals pervade many areas of daily life. Nevertheless, OCD symptoms of a religious nature are not found in all areas of ritual, nor necessarily in the areas of ritual most hallowed by the religion. In our experience with religious Jewish patients, for example, Sabbath observance is a very important feature of religious life associated with many detailed laws but does not appear frequently among the religious obsessions of OCD in our clinic. However, cleaning the perianal region before prayer gets one line in the footnote of a latterday code of Jewish law, but this ritual presents often in patients with OCD in our practice (Greenberg and Witztum 1994a).

The presentation of OCD in a religious context is less typically religious than it is classically obsessive-compulsive. The psychiatrist acquainted with OCD cannot fail to recognize in religious OCD patients familiar obsessions (e.g., dirt and contamination, aggression, sex, and meticulousness) and compulsive behaviors (e.g., washing, checking, repeating, and slowness) that present in any other sample of patients with OCD (Rachman and Hodgson 1980). However, therapists treating strictly religious patients with OCD may benefit from recognizing religious practice areas that seem especially prone to obsessive-compulsive symptoms. A survey of the literature on religious presentations in OCD reveals two main areas: 1) cleanliness and purity and 2) liturgy.

Cleanliness and Purity

Symptoms of OCD related to religious cleanliness and purity have been noted across many religions. Dietary, menstrual, and preprayer ablutions and checking have been reported in Jewish and Islamic patients. Some examples arise out of our clinical experience with Jewish patients. Meat can only come from certain animals (known as kosher), which must be slaughtered and prepared in a particular way, and milk and meat foods must be kept separate (the presentation of these symptoms in OCD is described in detail in the case report). All bread must be removed from every Jewish home before the festival of Passover; for weeks before this festival, religious housewives meticulously clean their homes. Patients with OCD may clean repeatedly and for lengthy periods and may then return and start again. Children are checked for crumbs, marks, or hints of "bread," and the cleaning starts over again (Greenberg et al. 1987). An awareness of the possibility of excessive concern can be found in the earliest Rabbinic guide to Jewish law, the Mishna, which wrote on this point 1800 years ago:

> One is not to be concerned that, having completed the pre-Passover cleaning in one room of the house, a rat from another (as yet uncleaned) room may drag a crumb into the cleaned room. Why not?—because if such a thought could be entertained, then why not the additional possibility that the crumb may be brought from one house to another, or from one town to another—and there would be no end to the matter! (Mishna Succa, 1:2)

For women, menstrual purity is another potential focus for obsessive-compulsive symptoms. They may check themselves repeatedly during the days before ritual immersion; clean and check themselves excessively immediately before the immersion; and repeat the immersion over and over, to the exasperation of the ritual bath attendant, because they are concerned that they may not have soaked themselves completely (Greenberg and Witztum 1994a). Maimonides, the twelfth-century physician, philosopher, and codifier of Jewish law, wrote in Mishne Tora: "No woman can divest herself of her ritual impurity or cease being forbidden from having relations unless and until she immerses herself in a ritual bath. Nor may anything interpose between herself and the water…if she does not, she is liable to excision" (Laws of Forbidden Relations, 11:16). The importance of this topic is stressed by the mystical text, the Zohar: "There is no stronger ritual impurity in the world than that of the menstrually unclean woman" (on Exod. 1:1). Men are expected to be clean before prayer; a common presenting symptom is repeated wiping and washing of the perianal region before prayers, sometimes taking so long that the patient arrives too late in the day to pray.

In Islamic law, similar issues are stressed. In Al Woodo, specific parts of the body are washed three times before daily prayers, which are performed five times each day. Particular emphasis is placed on cleanliness of the anal region, and Okasha (1970) described patients with OCD spending hours cleaning themselves before prayer. Menstrual impurity is very significant; women are forbidden to fast or pray at such times, and their underwear is washed separately. Clothes must be changed if they have been in contact with urine or feces, and for this reason, underwear must be changed before prayer. Okasha (1970) described a patient who fell asleep in the bath during her extensive washes during menstruation. It is interesting to note that Islamic women with OCD are concerned about the contaminating effects of menstrual blood during menstruation, whereas Jewish women with OCD are concerned about the presence of blood after the end of menstruation while they are counting "seven clean days" (Greenberg and Witztum 1994a); these concerns are each consistent with the concerns of their codes of law.

Berkeley-Hill (1921) described the Hindus of India as suffering from a

"pollution complex," exemplified by the existence of the class of "untouchables," and stressed the anal-erotic factors in their philosophy, religion, and character. A prominent part of Hindu festivals is bathing in a certain place at a certain time. The human body is considered to be basically dirty, and repeated washing of the body is encouraged (Akhtar et al. 1975). Nevertheless, the same authors only found 9 patients with religious symptoms in 82 patients with OCD in India. The topics of OCD for these patients were religious practices and festivals or matters of religious belief. However, 38 of the patients were concerned with dirt and contamination, such as semen, menstrual blood, and excreta, and one of the authors, Professor Wig (personal communication, 1984), suggested that many of these cases had a religious basis. Thus, the reported figure may be an underestimate.

A study of 42 patients with OCD in India (Dutta Ray 1964) found ideas of impurity and uncleanliness in 11 patients, although the author did not mention how many of these ideas were of a religious basis or the form they took. The author did note, however, that three strongly religious patients had dramatic improvement in their symptoms after a religious pilgrimage.

Liturgy

The second major area within religious life that is commonly the focus of obsessive-compulsive symptoms is liturgy. The preeminent role of prayer in Western religions is described by William James (1902/1982) in *The Varieties of Religious Experience*: "Prayer is religion in act; that is, prayer is real religion…wherever this prayer rises and stirs the soul, even in the absence of forms or of doctrines, we have living religion." In keeping with this primary role of prayer, we have found that the religious topics encountered among Protestant Christians with OCD have been limited to thoughts of blasphemy or of illness and harm coming to other people that arise during prayer.

Confession is one of the two sacraments that must be repeated frequently by Roman Catholics, and religious OCD symptoms tend to include repeated and lengthy confessions, as noted in three of the five patients studied by Fallon et al. (1990). Vergote (1988) described this phenomenon as the "religious neurosis of culpability." He states that "obsession can take a religious form. In these cases it is guilt that obsesses the individual. Its doubts and ruminations are of an immediately moral order; his fears relate to the defiances hurled against God…filthy words that interrupt his prayers; his means of verification or his ritualism takes the form of religious rites" (p. 51). Vergote, a Catholic philosopher and psychoanalyst, noted that "discourse on salvation has no effect on the illness"

and concluded that "this form of obsessive religiosity does not derive from a strictly religious conflict but rather that religion here serves as a means of displacing and expressing the conflict in an indirect way" (p. 51). Echoing Freud's observations, Vergote adds, "Religion could not divert the conflict if it did not share with the unconscious conflict certain analogies of context and structure" (p. 51). Vergote cites the example of a man who was tormented by his fear of committing mortal sins. At certain times, he went to confession every day, sometimes twice a day. Fortunately, his priest saw clearly into the matter and encouraged him to seek out a psychotherapist. For this man, every incident had become an occasion for torturous doubts of conscience, the themes of which were predominantly sexual; for example, if he met an attractive married woman and looked at and desired her, he considered this to be a sin (Vergote 1988).

Weisner and Riffel (1960) studied 23 patients with OCD in the form of "scrupulosity" among Roman Catholic referrals to a child guidance center. They described the same concerns and behaviors as experienced by Martin Luther at confession, although the high level of functioning at referral and the low level of pathology at follow-up suggested that these were obsessive-compulsive traits in adolescence rather than OCD.

Prayer developed in Judaism in place of daily sacrifice, and certain prayers are given special significance and require particular devotion. Patients with OCD may take the entire day to say their thrice-daily prayers if they have intrusive thoughts of a lewd, aggressive, or blasphemous nature, or they may repeat important sections because they feel they have inadequate devotion (Greenberg 1984; Greenberg et al. 1987).

Whereas confession in Catholicism is a regular ritual involving a complete declaration of misdemeanors, in Judaism it is a minor prayer with a fixed impersonal text: I have sinned, I have transgressed, and so on. We have noted that this becomes emphasized only among Jewish patients with agitated depression and not among those with OCD, reconfirming our impression that the topics that are repetitive and are dealt with scrupulously in normal religious practice become the focus of OCD in different cultures.

Clinical Issues in Diagnosis and Management

Equipped with an understanding of the cultural origins of the obsessions and compulsions, therapists need to be prepared to respond to challenging situations that differentiate treating OCD in strictly religious patients from treating OCD in other patients. If the symptoms are part of the regular religious practice of the individual, the therapist needs to distinguish be-

tween normal and pathologic religiosity. Both the therapist and the patient may be suspicious of each other and have difficulty in establishing a therapeutic relationship. Specifically, the patient may find it unacceptable to allow a therapist, who is usually either not of his religion or not as orthodox, to make pronouncements on his religious practice; these judgments are usually considered to be the province of the clergy.

Discriminating Between Normal and Pathologic Religiosity

A prerequisite to working with minorities, as stressed by all researchers, is an acquaintance with the values and details of that culture (German 1987; Rogler 1989; Sue 1988). Not only does this facilitate the therapeutic relationship, but it also enables the therapist to understand the language of the culture and, in the case of a religious group, to appreciate the meaning of its beliefs and practices. It also enables the therapist to distinguish between obsessive-compulsive symptoms and normal religious practice.

In our clinical observations, we have found that compulsive behavior can be distinguished from religious ritual in the following ways: 1) Compulsive behavior exceeds and sometimes disregards the requirements of religious law—for example, repeating the most important line of prayer, even though Jewish law states it must not be repeated. 2) Compulsive behavior usually concentrates on one specific area and does not reflect an overall concern for religious practice. 3) The choice of topic is typical of OCD—for example, cleanliness and checking—although trivial within religious practice. 4) While the patient focuses his attention on this one area, other features of religious life are often neglected. Many of our ultraorthodox Jewish patients had no time for religious study, which is viewed in that culture as the most valued of behaviors. One patient spent so long cleaning himself before prayers that by the time he was ready, prayer time was over, whereas another patient spent so much time repeating that he often had to omit large sections of the prayers. 5) The patient with OCD is racked with doubts that he may have omitted a ritual and repeats for this reason alone. Religious codes, however, only require a ritual to be carried out if it was definitely omitted the first time.

Therapists' Attitudes Toward Religious Patients

In general, people from one culture encountering another culture find its members to be shallow and distant and its family life and rituals to be dry and without meaning. These responses seriously hamper the development of the intimacy required in a therapeutic relationship and may account for the tendency of therapists with patients from other cultures to assess these

patients as unsuitable for psychotherapy (Good and Good 1985) but suitable for electroconvulsive therapy and high doses of medication (Littlewood and Cross 1980). In the case of religious patients, therapists have an even greater divide to overcome. In the early twentieth century, reflecting trends in Western culture, leading psychiatrists were known for their personal rejection of religious values and for constructing psychologic theories that construed religion as primitive and pathologic. This was reflected in such titles as "The Future of an Illusion" (Freud 1927/1961) and *Dogma and Compulsions* (Reik 1927). In Freud's (1907/1959) provocative paper on obsessive actions and religious practices, he wrote that religion might be regarded as a "universal obsessional neurosis" (p. 127). Ellis (1980) stated: "The devoutly religious person tends to be inflexible, closed, intolerant, and unchanging. Religiosity is in many respects equivalent to irrational thinking and emotional disturbance. The elegant therapeutic solution to emotional problems is to be quite unreligious." Psychiatry, therefore, has demonstrated a dismissive attitude toward religion in general, while religious ritual, in particular, has merited being likened to a psychiatric disorder, namely OCD.

The dissonance between the religious attitudes of psychiatrists and psychologists and those of the communities they treat has been noted in the United States (Marx and Spray 1969) and more recently in Israel (Rubinstein 1994). Bergin (1983) observed that the training of mental health professionals "is bereft of content that would engender an appreciation of religious variables," and that although race, gender, and ethnic origin have now gained respectability, religion "is still an orphan in academia."

Cohen and Smith (1976), raising the problematic issue of a condition induced, in their opinion, by religious belief, described a Christian Scientist patient with OCD who feared illness. Although the therapist "neither encouraged her to continue therapy or discouraged her from adhering to the tenets of the Christian Science philosophy" (p. 144), the authors noted that clinical improvement and disavowal of Christian Science were simultaneous. The paper precipitated a lively debate on the ethical issues of treatment of the religious patient. London (1976) stated that he considers the practice of psychotherapy that undermines the patient's belief system to be ethically justified if the therapist "*believes* that the religious convictions of the patient help sustain the disorder" (p. 146). The word *believes* (our italics) reflects that the therapist is responding to his own (professionally-based) value judgments. In Halleck's (1976) comments about the same patient, he candidly stated that there is no value-free therapy or therapist; if the therapist thinks that therapy may challenge the patient's belief system, then at least "the consumer should be adequately forewarned of the

possible consequences of treatment" (p. 147). Halleck noted that if patients can afford to select their own therapists, they tend to choose professionals who share their religious beliefs or are of the same religious faith "as though they want to protect their belief systems while changing their behavior" (p. 147).

In conclusion, although the psychiatric establishment has officially recognized the need to respect the religious beliefs of patients (American Psychiatric Association 1990), an awareness of the impact of the dissonance between the religious affiliation of therapist and patient on the course of therapy is increasing (Giglio 1993).

Religious Patients' Attitudes Toward Therapists

Within a religious group, the study and practice of psychology may be considered suspect and heretical, both in challenging the existence of God and in ridiculing dogma and codes of behavior. Religious patients and their families are aware that therapists are usually irreligious and may fear that the therapist will influence the patient against his or her religion or that the content of therapy may be immoral and will relate difficulties to unconscious sexual conflicts. Furthermore, many believe that turning to a doctor is an act of weak faith because God heals all ills. These attitudes may not be held only by individual religious people but may be the public attitudes of religious leaders, who may describe counsel from psychologists as "the counsel of sinners…they only cause destruction" (Greenberg and Witztum 1994a). Such concerns are particularly likely to arise in the management of religious symptoms. All of our patients with religious OCD have initially consulted their rabbis, and it is understandable and appropriate that a religious person with difficulties in performing religious rituals should turn to his or her spiritual mentor. A collection of letters belonging to Kanievski, an ultraorthodox rabbi and spiritual counselor, was published posthumously. The papers included advice on OCD symptoms such as "confusion from blasphemous thoughts," "concern over having made vows," "nervous tension over prayer and cleanliness," "concerns over bodily cleanliness," and "taking too long over the Shema prayer" (Kanievski 1990). Kanievski advises to give clear instructions, not to get into detailed discussions with the sufferer, to prescribe leniency and even define limits of excessive practices, and to encourage Tora study instead of spending time ritualizing. No mention is made of professional help, although recent discussions with rabbis have revealed that many are aware of the need to refer for medication.

An additional powerful force preventing religious patients from seek-

ing help is stigma. For ultraorthodox Jews, public psychiatric services are invidious because the stigma of mental illness is powerful in a close community in which marriages are arranged by matchmakers. Mental illness in one family member will adversely affect the matrimonial prospects of all the other children.

Guidelines for the Management of Obsessive-Compulsive Disorder in Strictly Religious Patients

Several Catholic pastoral counselors have described the presentation of religious rituals as psychiatric symptoms and have advised clergy not to cooperate with the patient's system of practice, but instead to refer him or her for psychiatric help (Autton 1963; Barbaste 1952; Ringel and Van Lun 1955). Wise (1983) observed that "giving assurances of a religious 'cure' must be avoided" (p. 239). Before discussing some of the issues involved in the specific forms of therapy, we suggest some general guidelines for overcoming the many barriers to establishing a therapeutic relationship: 1) It is helpful for the therapist to know basic tenets and practices of the patient's religion. As Gorkin (1987) warned, however, this understanding must not become such a fascination that the patient and his or her problems disappear from view. 2) The therapist should be aware of his or her own feelings about religion and the religious (Spero 1989). 3) In many cases, the patient is accompanied to the clinic. Therapists should allow the accompanying person to join the interview from the onset. If the patient is unsure of the therapist, then the therapist must be willing to be a minority presence in the room. 4) If the patient raises religious objections to attending and receiving treatment from irreligious people, the therapist should avoid a religious debate. If the patient wavers or refuses, he or she should be encouraged to discuss the matter with his or her clergyperson. We invariably offer to meet with the patient and the clergyperson, thus clearly implying that we see no dissonance between religious affiliation and psychiatry (Greenberg 1984; Lovinger 1984; Rapoport 1989).

Advantages and Pitfalls of Therapies for Obsessive-Compulsive Disorder

Pharmacotherapy

In general, we have found that patients are not opposed to medication. It is important to clarify what will change with therapy or medication and

that, for example, therapy will not cause the patient to stop performing regular religious ritual. We often write the name of the recommended medication in a letter and encourage the patient to take it to his or her clergyperson for approval, adding that we would be willing to provide more information and discuss it further if requested. The details and considerations for using medication to treat OCD are presented in individual chapters elsewhere in this book. The effectiveness of pharmacotherapy in such cases has been demonstrated in an open study of 10 patients, 5 Catholic and 5 Jewish, who had OCD with religious symptoms (Fallon et al. 1990). Patients received either clomipramine (200 mg or more) or fluoxetine (80mg or more), and of the 7 who completed the 8-week study, 5 were rated as much improved. Two others improved after 12 weeks, and another patient was much improved on a combination of clomipramine, fluoxetine, and diazepam.

Behavioral Psychotherapy

O'Flaherty (1973), a Catholic priest, described a broad treatment package based on the principle of *agere contra* (do the opposite), originally formulated by Ignatius of Loyola (1548/1978) for the improvement of the soul. The treatment has prominent behavioral and cognitive elements. The therapist is firmly discouraged from getting into detailed discussions over whether the patient has sinned or not, and proceeds on the assumption that no sin has occurred. O'Flaherty divides treatment into four phases:

1. *Booking the incidents*. Patients keep a diary of every event that precipitates a need to carry out rituals.
2. *Systematically studying the incidents*. This is a form of behavioral analysis in which therapists and patients note the people, places, and events that give rise to the incidents.
3. *Rejecting by distraction*. Patients are taught to focus their minds on a neutral subject instead of thinking about whether they have sinned.
4. *Breaking the habit*. If patients find themselves preoccupied with thoughts or carrying out rituals, they should lay their hands on their hearts and grieve that they have fallen.

Although O'Flaherty's package contains features of behavioral treatments of proven efficacy (see Marks 1987 and Chapter 9, this volume), no outcome data is presented by the author.

Giles (1982) described an orthodox Jewish patient whose obsessive fears included possible contact with nonkosher food. A combination of ex-

posure—holding a nonkosher sausage wrapped in plastic—and cognitive therapy resulted in a diminution of distress during sessions, although overall improvement and maintenance of gains were not described.

The advantage of behavioral psychotherapy is that it is symptom oriented. Patients who fear that treatment implies an assault on their religious beliefs will not feel threatened by a focused intervention. It is clear, nevertheless, that religious practices will be center stage during treatment and that the therapist can inadvertently jeopardize therapy by giving instructions that are not consistent with religious practice, such as if the therapist asks the patient to approach his or her clergyperson for a "dispensation" that gives the therapist carte blanche to proceed as he or she sees fit. The therapist in this case demonstrates limited patience at having his or her autonomy restricted and also demonstrates ignorance of the significant role religion plays in the life of the strictly religious patient. Most religions have no all-inclusive dispensations, although in specific situations clergy may permit specific solutions.

A second example of religiously inconsistent instructions occurs if the therapist asks the patient to eat nonkosher meat, to leave bread in the house on Passover, or to dip in the ritual bath while still menstruating to achieve "exposure." All strictly religious Jewish patients and their rabbis will decline for religious reasons. Consider how one treats a patient with OCD whose fear is that he or she will cause illness in his or her family, a fire at work, or kill pedestrians while driving along the road. Clearly, the therapist does not instruct the patient to go out and cause these events and expect that the patient will comply. Patients with OCD cannot cope with the possibility that they may have caused these events; therapy aims to enable them to live with this risk. Behavioral psychotherapy in the strictly religious, for example, aims to reduce the time spent cleaning before Passover to a sensible degree, while the patient accepts that he or she may or may not have done a thorough job.

At this stage of treatment, we usually draw up a list of problems and targets (Marks 1986), which describes the patient's current concerns and ultimate goals in treatment in behavioral terms. Examples of *problems* include difficulty at times of prayer because of a need to repeat all important sections or excessive cleaning before prayers. Examples of *targets* include praying without repetitions even if inadequate devotion is suspected or limiting time spent cleaning before prayers.

After preparing the problems and targets, we draw up a list of "Is it permitted?" statements. Is the patient permitted to continue praying if he or she thinks he or she has not been concentrating? Is this true of all prayers? What is the minimum cleaning necessary before prayer? Can it be

omitted completely? We ask patients to nominate the clergyperson of their choice, and we arrange to visit the clergyperson with the patient. At this meeting, the patient introduces the problem, and we then present the problems, targets, and particularly the list of "Is it permitted?" statements. If the clergyperson indicates that something is not permitted, we ask him or her to define a permissible situation that the patient cannot tolerate at present. The clergyperson's replies are noted and define the limits of exposure treatment.

We have noted that in some cases, after leaving the meeting with the clergyperson, patients will refuse to follow the decisions of the meeting. The reasons for this are usually wrapped in religious reasoning, such as "the clergyperson made particular allowances because of my problem," "he or she was willing to allow anything because of the treatment," or "I want to see a different clergyperson." Indecision is a classical feature of OCD, and the patient's response is to be understood as emerging from that indecision. The therapist should be willing to focus briefly with the patient on this self-imposed stumbling block. Behavioral psychotherapy requires a clear commitment by the patient, and therapists whose patients disqualify their own clergy should place the responsibility for the next step in the patients' hands and should not offer to go "clergy shopping." They should, ideally, return to their chosen clergyperson to clarify their difficulties. Therapy can proceed once the patient has found answers to the "Is it permitted?" questions from a single source.

Summary

The strictly religious patient with OCD presents a series of challenges to the therapist. In any therapeutic encounter between people of differing cultures, therapists should be acquainted with aspects of the patients' cultures and be aware of their own attitudes toward those cultures. This situation is more complicated in contact with religious patients because psychiatry has a tradition of reductionist and dismissive attitudes toward religious affiliation. Furthermore, many religious groups have negative attitudes toward psychiatry and its therapists.

Patients who have OCD and are strictly religious often have symptoms of a religious nature. The assessing therapist must distinguish between normal and pathologic religiosity. In this task and in the task of proposing therapy, therapists are advised to avoid all religious disputation and to work as closely as possible with the clergy of authority selected by the patients.

Case Example

John, a 40-year-old married father of four children, was an ultraorthodox Jew. He was excessively concerned over the religious dietary laws, particularly that milk and meat may become mixed together, and thereby food would become nonkosher and food utensils unusable. As a result, he spent mealtimes anxiously watching his children, lest they touch ketchup and other bottles with greasy hands. He insisted the children use napkins every few minutes and would get up himself to wipe them throughout the meal. If he thought a bottle or utensil may have been touched by a milk food, he would either label it "milk" or hide it until he could decide what to do, and in this way the kitchen cupboards gathered collections of unusable items over the years. He would wipe his own hands more than 30 times during a meal and would wash his mouth, teeth, face, hands, and particularly his fingernails after any meal for fear that they may have gathered food. The more crowded the mealtime, the more tense he became, and the family had not invited guests for several years. He avoided helping in the kitchen and had not washed the dishes for 10 years because he feared that the water washing the milk dishes would splash onto meat dishes and foods.

The onset of these concerns was 13 years earlier, when he had first become more religiously observant. He had always been a pedantic person with scrupulous morals. When he was 17, he became concerned that he had been unjustly awarded a scholarship, and the preoccupation only left him after he returned the money 2 years later. He was slow and indecisive in many areas; kept long, detailed lists of things to be done; and stored all of these lists in case they were needed. He married at age 27, and both he and his wife became more observant, although his wife subsequently became more ambivalent about religious practice. They had been in individual and marital therapy with little change, and his wife seemed content to be practicing and ambivalent.

At the interview, John was neatly dressed and carried a notebook to which he referred throughout. He was articulate and circumstantial. He was upset by his problems, which he perceived as excessive. There were no psychotic features.

The targets of John's treatment were to eat meals without wiping his own or his family's hands; to invite guests regularly, especially guests with young children; to wash with splashing water; to "rehabilitate" all stored utensils; and to leave meals without having a wash. A list of "Is it permitted?" statements included the following: "Is the patient permitted to put milk on his hands and then touch all utensils before a meat meal?"; "Is the patient permitted to put milk directly onto a meat plate or vice versa?"; "Is it necessary to wipe hands and utensils during a meal?"; "Can the same bottle of ketchup be used for milk and meat meals despite being touched by greasy hands?"; and "Does one need to be concerned at washing-up time that water may splash from one area to another?"

John's rabbi knew him well from the countless questions and requests for reassurance that John had posed to him several times a week

over the years. He believed that John had a psychologic problem and was more than willing to help, adding with a sigh that "There are many more like him." Seeking rabbinic advice is rarely a matter of a textbook response. Within the framework of the law, the decision is tailored to the individual situation. It was clear that John's rabbi tended toward lenient decisions as much as possible to facilitate the therapeutic process.

John's treatment included 10 sessions—15 hours—of therapy. Because the focus of his problems was limited to his own home ("Other people's dietary observance is their problem, not mine!"), the first sessions took place during lunchtime in his home. After modeling by the therapist, John was asked to put butter on his hands before a milk meal, set the table, actively pass bottles, food, and cutlery during the meal, and clear the table at the end of the meal. The wiping of hands was banned, as were the napkins. Initially, John's anxiety was high, but it reduced gradually during a 90-minute session. During homework sessions over the next 2 weeks, he became less anxious about handing out food and reduced his hand wiping to twice a meal.

At the next session, the therapist modeled handwashing without also washing the face, teeth, and fingernails and included contaminating his hands with butter immediately after washing. During remaining sessions, residual foci were treated: John had avoided using ointments and creams if it was not clear from the list of ingredients that they were kosher; in treatment, he used them and then went about the house touching door handles, chairs, and food containers. He became very anxious when asked to wash the dishes using splashing water; homework included washing the dishes daily, for which his wife was a very encouraging cotherapist.

At follow-up 1 year after treatment, John no longer wiped hands at the table or stored contaminated bottles. He was relaxed at mealtime and enjoyed the company of guests. He regularly helped wash the dishes. John considered himself slightly more vigilant about dietary laws than most people.

References

Akhtar S, Wig NN, Varma VK, et al: A phenomenological analysis of symptoms in obsessive-compulsive neurosis. Br J Psychiatry 227:342–348, 1975

American Psychiatric Association: Official actions: guidelines regarding possible conflict between psychiatrists' religious commitments and psychiatric practice. Am J Psychiatry 147:542, 1990

Autton N: The Pastoral Care of the Mentally Ill. London, England, SPCK, 1963

Bainton RH: Here I Stand: A Life of Martin Luther. New York, New American Library, 1950

Barbaste A: Le traitement du scrupule et les donnees actuelles de la psychiatrie. Revue d'Ascetique et de Mystique 28:96–120, 1952

Baxter R: Autobiography (1692), in Three Hundred Years of Psychiatry 1535–1860. Edited by Hunter D, Macalpine I. Cambridge, England, Cambridge University Press, 1963

Bergin AE: Religiosity and mental health: a critical reevaluation and meta-analysis. Professional Psychology 14:170–184, 1983

Berkeley-Hill O: The anal-erotic factor in the religion, philosophy and character of the Hindus. Int J Psychoanal 2:306–329, 1921

Cohen RJ, Smith FJ: Socially reinforced obsessing: etiology of a disorder in a Christian Scientist. J Consult Clin Psychol 44:142–144, 1976

Dutta Ray S: Obsessional states observed in New Delhi. Br J Psychiatry 110:181–182, 1964

Ellis A: Psychotherapy and atheistic values: a response to AE Bergin's "Psychotherapy and religious values." J Consult Clin Psychol 48:635–639, 1980

Enoch MD, Trethowan WH: Uncommon Psychiatric Syndromes, 2nd Edition. Chicago, IL, Year Book Medical, 1979

Fallon BA, Liebowitz MR, Hollander E, et al: The pharmacotherapy of moral or religious scrupulosity. J Clin Psychiatry 51:517–521, 1990

Freud S: Obsessive actions and religious practices (1907), in Complete Psychological Works of Sigmund Freud, Vol 9. Translated and edited by Strachey J. London, England, Hogarth 1959, pp 115–127

Freud S: The future of an illusion (1927), in Complete Psychological Works of Sigmund Freud, Vol 21. Translated and edited by Strachey J. London, England, Hogarth, 1961, pp 1–56

German GA: Mental health in Africa, I: the extent of mental health problems in Africa today. Br J Psychiatry 151:435–439, 1987

Giglio J: The impact of patients' and therapists' religious values on psychotherapy. Hospital and Community Psychiatry 44:768–771, 1993

Giles TR: Cognitive restructuring and exposure with a compulsive washer: a test of reciprocal inhibition. J Behav Ther Exp Psychiatry 13:221–224, 1982

Good B, Good MD: The cultural context of diagnosis and therapy: a view from medical anthropology, in Mental Health Research in Minority Communities: Development of Culturally Sensitive Training Programs. Edited by Miranda MR, Kitano HHL. Rockville, MD, National Institute of Mental Health, 1985

Gorkin M: The Use of Countertransference. Northvale, NJ, Jason Aronson, 1987

Greenberg D: Are religious compulsions religious or compulsive? A phenomenological study. Am J Psychother 38:524–532, 1984

Greenberg D, Witztum E: The influence of cultural factors on obsessive-compulsive disorder: religious symptoms in a religious society. Isr J Psychiatry 31:211–220, 1994a

Greenberg D, Witztum E: Ultra-orthodox Jewish attitudes towards mental health care. Isr J Psychiatry 31:143–144, 1994b

Greenberg D, Witztum E, Pisante J: Scrupulosity: religious attitudes and clinical presentations. Br J Med Psychol 60:29–37, 1987

Halleck S: Discussion of "socially reinforced obsessing." J Consult Clin Psychol 44:146–147, 1976

Ignatius of Loyola: Spiritual Exercises of Ignatius of Loyola (1548). Boston, MA, Daughters of Saint Paul, 1978

James W: The Varieties of Religious Experience (1902). London, England, Penguin, 1982

Kanievski Y: Krayna Da'Agarta, Vol 1. Bnei Brak, Kanievski, 1990

Khanna S, Channabasavanna SM: Phenomenology of obsessions in obsessive-compulsive neurosis. Psychopathology 21:12–18, 1988

Lewis A: Problems of obsessional illness. Proc R Soc Med 29:325–336, 1936

Littlewood R, Cross S: Ethnic minorities and psychiatric services. Sociology of Health and Illness 2:194–201, 1980

London P: Psychotherapy for religious neuroses? Comments on Cohen and Smith. J Consult Clin Psychol 44:145–146, 1976

Lovinger RJ: Working with Religious Issues in Therapy. Northvale, NJ, Jason Aronson, 1984

Mahgoub OM, Abdel-Hafeiz HB: Pattern of obsessive-compulsive disorder in Eastern Saudi Arabia. Br J Psychiatry 158:840–842, 1991

Marks IM: Behavioural Psychotherapy: Maudsley Pocket Book of Clinical Management. Chicago, IL, Year Book Medical, 1986

Marks IM: Fears, Phobias, and Rituals. New York, Oxford University, 1987

Marx JH, Spray SL: Religious bibliographies and professional characteristics of psychotherapists. Journal of Health and Social Behavior 10:275–288, 1969

Moore J: Of religious melancholy (1692), in Three Hundred Years of Psychiatry 1535–1860. Edited by Hunter D, Macalpine I. Cambridge, England, Cambridge University Press, 1963, pp 252–253

O'Flaherty VM: Therapy for scrupulosity, in Direct Psychotherapy: Twenty-Eight American Originals. Edited by Jurjevich RM. Miami, FL, University of Miami Press, 1973, pp 221–243

Okasha A: Presentation and outcome of obsessional disorders in Egypt. Ain Shams Medical Journal 21:367–373, 1970

Okasha A, Saad A, Khalil AH, et al: Phenomenology of obsessive compulsive disorder: a transcultural study. Compr Psychiatry 35:191–197, 1994

Rachman SJ, Hodgson RJ: Obsessions and Compulsions. Englewood Cliffs, NJ, Prentice-Hall, 1980

Rapoport J: A thousand commitments to God, in The Boy Who Couldn't Stop Washing. New York, Dutton, 1989, pp 159–173

Rasmussen SA, Eisen JL: The epidemiology and clinical features of obsessive compulsive disorder. Psychiatr Clin North Am 15:743–758, 1992

Reik T: Dogma and Compulsions. Westport, CT, Greenwood, 1927

Riddle MA, Scahill L, King R, et al: Obsessive compulsive disorder in children and adolescents: phenomenology and family history. J Am Acad Child Adolesc Psychiatry 29:766–772, 1990

Ringel E, Van Lun W: Psychotherapie et Direction de Conscience. Tours, France, Mame, 1955

Rogler LH: The meaning of culturally sensitive research in mental health. Am J Psychiatry 146:296–303, 1989

Rubinstein G: Political attitudes and religiosity levels of Israeli psychotherapy practitioners and students. Am J Psychother 48:441–454, 1994

Stern RS, Cobb JP: Phenomenology of obsessive-compulsive neurosis. Br J Psychiatry 132:233–239, 1978

Spero MH: Current trends in psychotherapy, clinical social work, and religious values: a review and bibliography. Journal of Social Work and Policy in Israel 2:81–110, 1989

Sue S: Psychotherapeutic services for ethnic minorities. American Psychologist 43:301–308, 1988

Swedo SE, Rapoport JL, Leonard H, et al: Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry 46:335–341, 1989

Thomsen PH: Obsessive-compulsive symptoms in children and adolescents: a phenomenological analysis of 61 Danish cases. Psychopathology 24:12–18, 1991

Vergote A: Guilt and Desire: Religious Attitudes and Their Pathological Derivatives. New Haven, CT, Yale University, 1988

Weisner WM, Riffel PA: Scrupulosity: religion and obsessive-compulsive behavior in children. Am J Psychiatry 117:314–318, 1960

Wise CA: Pastoral Psychotherapy. Northvale, NJ, Jason Aronson, 1983

This page intentionally left blank

CHAPTER 11

Serotonergic Drugs and the Treatment of Disorders Related to Obsessive-Compulsive Disorder

Eric Hollander, M.D.
Andrea Allen, Ph.D.

Although controversy among clinicians and researchers remains, there is increasing support for the value of conceptualizing a group of disorders as obsessive-compulsive spectrum disorders. These disorders are drawn from several classifications, including somatoform (e.g., body dysmorphic disorder), impulse control (e.g., trichotillomania), dissociative (e.g., depersonalization disorder), childhood or adolescent onset (e.g., Tourette's syndrome), and eating disorders (e.g., anorexia nervosa, bulimia nervosa). For each of these disorders, obsessive thoughts and/or compulsive behaviors are core symptoms. Evidence that these disorders are related comes from clinical presentation, symptoms, comorbidity, family history, and treatment response, with most obsessive-compulsive spectrum disorders being more likely to respond to serotonin reuptake inhibitors and cognitive-behavioral therapy than to other treatments.

Importantly, there are also ways in which each of these disorders is unique. Some of the differences between them may be accounted for by their degree of impulsivity versus compulsivity; thus, their variation along the impulsive–compulsive continuum has been a focus of theoretical discussion (Hollander 1993; McElroy et al. 1994). The impulsive–compulsive continuum may also be conceptualized as a risk-seeking/pleasure-maximizing to risk-avoidant/discomfort-decreasing continuum with implications for understanding pathophysiology and treatment

(Hollander 1993; Hollander and Wong 1995). Evidence to date indicates that increased frontal lobe activity and serotonergic sensitivity characterize the compulsive end of the spectrum; decreased frontal lobe activity and low presynaptic serotonin levels characterize the impulsive end (Hollander and Wong 1995).

Body Dysmorphic Disorder

Diagnostic Considerations

Body dysmorphic disorder is currently classified as a somatoform disorder (DSM-IV-TR; American Psychiatric Association 2000). The essential feature of this disorder is preoccupation with an imagined defect in appearance in a normal-appearing person or markedly excessive concern about a slight physical anomaly. Distress about facial flaws is the most common symptom, but any part of the body can be the focus of concern and the perceived defect may be either specific, such as a large nose, or more general, such as being ugly (Hollander 1993). However, to meet diagnostic criteria, the symptoms cannot be better accounted for by another mental disorder, such as a preoccupation with being fat in anorexia nervosa or distress about physical sexual characteristics in gender identity disorder.

In addition, the preoccupation must cause clinically significant distress or impairment in functioning. This criterion distinguishes the disorder from the lesser degrees of dissatisfaction with appearance that are common in this culture (Fitts et al. 1989). Body dysmorphic disorder often has a devastating impact on functioning, including withdrawal from school, work, and social relationships because of preoccupation with the imagined defect; hours each day can be consumed by worry, rituals, and efforts at camouflage. As many as one-third of patients may become housebound (Andreasen and Bardach 1977; Phillips 1991; Phillips et al. 1993). In one study sample, more than 50% of the patients reported psychiatric hospitalizations and 30% had attempted suicide (Phillips et al. 1994).

Body dysmorphic disorder does have similarities to obsessive-compulsive disorder (OCD) and its spectrum disorders. It seems to lie at the compulsive, risk-averse end of the obsessive-compulsive spectrum. Both body dysmorphic disorder and OCD have an early onset and a generally chronic course and occur approximately equally in adult men and women (Phillips 1996). There is relatively high comorbidity between body dysmorphic disorder and OCD. In the DSM-IV OCD Field Trial, 12% of the patients with OCD had a lifetime comorbid diagnosis of body dysmorphic

disorder (Simeon et al. 1995a). In addition, 37%–56% of patients with body dysmorphic disorder have histories of OCD (Hollander et al. 1993b; Phillips et al. 1993). Both patients with OCD and those with body dysmorphic disorder may engage in checking behaviors; however, whereas patients with OCD will check doors and windows to make sure they are locked, those with body dysmorphic disorder will check their appearance in mirrors. The preoccupation with appearance is generally considered an obsession, but the diagnosis of OCD is not given if a patient's obsessions focus only on appearance. This differentiation, establishing body dysmorphic disorder as distinct from OCD, is supported by the presence of other characteristic differences between patients with the two disorders. Notably, the insight of patients with body dysmorphic disorder seems to be significantly more impaired than that of patients with OCD (Simeon et al. 1995a). Phillips et al. (1994) noted that of the first 100 patients with body dysmorphic disorder studied, none had excellent insight and 52 were delusional. This lack of insight can lead to delay in seeking psychiatric treatment. Because they consider their perceived defects to be real, people with body dysmorphic disorder present to specialists such as plastic surgeons or dermatologists. When patients do consult with mental health professionals, it is most often for depression or anxiety. Careful questioning may be required to uncover the dysmorphic concerns of these patients because of the patients' extreme secrecy and self-consciousness.

As with OCD, body dysmorphic disorder may be conceptualized as varying along a continuum of insight or certainty (Insel and Akiskal 1986). The distinction between insight and delusional certainty was at the center of theoretical debate as this disorder was being formally defined: Does this difference in insight reflect two different disorders (American Psychiatric Association 1987; Thomas 1985), or two variants of the same disorder (Brotman and Jenike 1984)? The controversy remains; however, evidence lends increasing support for there being only one disorder with widely varying levels of insight (Hollander 1993; McElroy et al. 1993; Phillips et al. 1994, 1995; Simeon et al. 1995a). This developing understanding of the disorder was recognized in DSM-IV (American Psychiatric Association 1994), in which the diagnosis of body dysmorphic disorder is applied to all patients who are preoccupied with an imagined or exaggerated defect in appearance and the additional diagnosis of delusional disorder, somatic type, is allowed for those patients who hold their belief with delusional intensity. Phenomenologically, there may be a continuum, but additional biologic mechanisms may occur when patients reach the delusional end and when concerns become fixed beliefs. This characteristic may explain the partial efficacy of pimozide (Munro and Chmara 1982), a dopamine-recep-

tor blocker, in changing certainty to uncertainty. However, more recent research has demonstrated that two potent serotonin reuptake inhibitors, fluvoxamine (Phillips and McElroy 1995; Phillips et al. 1998) and clomipramine (Hollander et al. 1999), are equally effective among delusional and nondelusional patients with body dysmorphic disorder.

Body dysmorphic disorder has also been found to have high comorbidity with social phobia and major depression (Phillips et al. 1994). Brawman-Mintzer et al. (1995) found concurrent body dysmorphic disorder in 11% of patients with social phobia and 8% of those with OCD, although they did not find it among patients with major depression or other anxiety disorders. For social phobia and major depression, it is difficult to determine causality: body dysmorphic disorder may lead to fear of rejection and depression. There are some behaviors, common in patients with body dysmorphic disorder, that also appear in other disorders. For example, face picking is common in body dysmorphic disorder (Phillips and Taub 1995) and also occurs in trichotillomania.

Treatment

A great deal of progress has been made in the past decade in the pharmacologic treatment of body dysmorphic disorder. Preliminary open treatment studies suggested a response to serotonin reuptake inhibitors such as clomipramine, fluoxetine, and fluvoxamine (Hollander et al. 1989b). Other pharmacologic agents such as neuroleptics, trazodone, lithium, benzodiazapines, tricyclic antidepressants (TCAs) other than clomipramine, and anticonvulsants were found to be ineffective or much less beneficial (Hollander et al. 1993b; Phillips et al. 1993). A retrospective study of 50 patients with body dysmorphic disorder showed that those treated with clomipramine, fluoxetine, or fluvoxamine were found to have been very much or much improved, whereas those receiving other TCAs showed only slight improvement (Hollander et al. 1993b). In another retrospective report of patients with body dysmorphic disorder ($N=30$), Phillips et al. (1993) reported successful treatments with fluoxetine and clomipramine and with clomipramine augmented by fluoxetine or buspirone. There was no or minimal response to other classes of drugs including TCAs, benzodiazepines, neuroleptics, and anticonvulsants. In a study of patients with body dysmorphic disorder with skin picking behavior, Phillips and Taub (1995) reported significant improvement in 49% of patients receiving serotonin reuptake inhibitors, whereas only 10% improved with other psychotropic medications. Dermatologic treatments have proved largely ineffective.

Hollander et al. (1999) conducted a double-blind, 16-week crossover study of 29 patients with body dysmorphic disorder that compared clomipramine, a serotonin reuptake inhibitor, and desipramine, a norepinephrine reuptake inhibitor. Clomipramine was superior to desipramine in the acute treatment of both specific symptoms and overall severity of body dysmorphic disorder. Clomipramine was also superior to desipramine in improving functional disability. The mean dose of clomipramine was 138 mg/day (SD=87). In a careful, open-label trial of fluvoxamine in 30 patients, Phillips et al. (1998) found that 63% of patients responded to treatment. The mean dose of fluvoxamine was 238 mg/day (SD=85.8).

Thus, based on current information, a serotonin reuptake inhibitor would be the first-line treatment for body dysmorphic disorder, given at the dose and for the length of trial used for OCD. In refractory, delusional cases, augmentation with low doses of a neuroleptic such as pimozide or risperidone might be undertaken (Songer and Roman 1996).

Case Example

Ms. A. is an attractive, intelligent, 25-year-old white female. Shortly after getting married and graduating from law school, she presented with the belief that vascular markings on her nose made her unattractive. She was fearful that these vascular markings would cover her face, causing her husband to leave her. She used make-up to cover the imagined defect, avoided mirrors, and made multiple visits to dermatologists and plastic surgeons. There were no vegetative symptoms of major depression, but she was demoralized. After treatment with imipramine (150 mg/day) her outlook improved, and she became less preoccupied with thoughts of her vascular markings. However, after looking in the mirror on one occasion while not wearing makeup to cover the defect, she deteriorated, and her overvalued belief developed into delusional certainty about the vascular markings. An addition of pimozide (2 mg/day) was effective for 2 months in altering this belief from a delusional certainty to a level of uncertainty. Nevertheless, overvalued concern about her face persisted, and new obsessional fears about possible damage to future babies as a result of medication developed. An increase in imipramine to 300 mg/day failed to result in additional improvement. The patient then agreed to a trial of fluoxetine. The pimozide and imipramine were discontinued. Six weeks after receiving fluoxetine, 80 mg/day, she reported a dramatic improvement in her overvalued concern about facial defects. She was able to resume socializing, made plans to resume her career, and overcame her avoidance of potential dermal traumatic agents such as sun and wind. This improvement continued at a 2-year follow-up. Notably, there was a clear family history of OCD. The patient's sister had classic obsessions and compulsions regarding contamination and feared exposure of radiation to her family. The patient's father, a successful businessman, had subclinical symptoms of OCD, such as the need for symmetry and

overconcern about the health of his children, but these symptoms were ego-syntonic and did not interfere with functioning.

Trichotillomania

Diagnostic Considerations

Trichotillomania, classified in DSM-IV-TR as an impulse control disorder, involves the recurrent pulling out of one's hair, resulting in noticeable hair loss. Typically, scalp hair is pulled, but eyelash and eyebrow pulling are also common. In fact, any body hair may be the target; patients often pull hair from more than one site (Christenson et al. 1991a; Cohen et al. 1995). For the diagnosis to be made, the disturbance must cause clinically significant distress or impairment in functioning and the hair pulling cannot be better accounted for by another mental disorder (e.g., in response to a delusion or hallucination) or be caused by a general medical condition (e.g., a dermatologic condition).

Current diagnostic criteria require an increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior and a sense of pleasure, gratification, or relief when pulling out the hair. Some chronic hair pullers do not meet this criterion despite experiencing significant distress and impairment in functioning. A great deal of research has been done with mixed samples, that is, some subjects who meet the DSM criteria and some who do not; this heterogeneity may underlie some of the unexpected and conflicting research results.

Based on phenomenology, comorbidity, familiarity, and treatment response, trichotillomania has notable similarities to OCD and has been included as an obsessive-compulsive spectrum disorder (Hollander 1991; Leonard 1989; Swedo et al. 1989b). The core feature, hair pulling, is often described as a habit or compulsion that is disturbing (ego-dystonic) and resisted. There are also some notable differences between OCD and trichotillomania. Although it seems that most adult patients with trichotillomania are women with childhood onset (Cohen et al. 1995), there are equal numbers of adult men and women with OCD. In contrast, during childhood, there may be nearly equal numbers of boys and girls with trichotillomania (Muller 1990), but there seems to be an excess of boys with childhood-onset OCD.

In OCD, repetitive behaviors are seemingly purposeful and designed to prevent or produce some future adverse event or situation; this is not the case with trichotillomania. Although patients with OCD are disturbed by their rituals, some patients with trichotillomania describe a pleasurable

aspect to the hair pulling, in terms of both tension reduction and cleansing or purging; this is, in some ways, similar to an orgasm. In a study of pain, there was no difference in detection or tolerance of pain between patients with trichotillomania and a control group (Christenson et al. 1994).

Research on trichotillomania as an obsessive-compulsive spectrum disorder has generated valuable findings and raised additional questions. Various predicted similarities between OCD and trichotillomania have not materialized. For example, neurobiologic studies have not shown as strong a similarity between OCD and trichotillomania as had been expected, but these studies are difficult to interpret because of gender differences in the samples (Christenson and Crow 1996; Stein et al. 1994, 1995b). Rettew et al. (1991) did find some support for neuropsychologic similarities between trichotillomania and OCD; notably, these samples were matched for gender and age.

Trichotillomania can be viewed as inappropriately released excessive grooming behavior (Swedo 1993; Swedo and Leonard 1992). Rapoport, Swedo, and colleagues have proposed a fascinating model of neuroethologic grooming behavior; similar behavior patterns in animals respond to serotonin reuptake inhibitors, thus suggesting that animals may serve as a model for trichotillomania. There are numerous reports of the effectiveness of clomipramine in treating acral lick in dogs (Goldberger and Rapoport 1991; Rapoport 1990; Rapoport et al. 1992) and feather picking in birds (Bordnick et al. 1994; Grindlinger and Ramsay 1991). There is also a case report of acral lick in a cat responding to fluoxetine (Hartmann 1995).

In general, trichotillomania seems to be best conceptualized as belonging at the impulsive end of the obsessive-compulsive spectrum. However, although patients with trichotillomania show more impulsive and fewer compulsive characteristics than do patients with OCD and body dysmorphic disorder, they appear to have both compulsive and impulsive features (Stein et al. 1995a).

Several areas of exploration would be helpful in delineating similarities and differences between trichotillomania, OCD, and other obsessive-compulsive spectrum disorders. These would allow greater understanding of the pathophysiology of the disorder and would have implications for treatment. Important areas to explore include serotonergic subtypes and gender differences (Stein et al. 1994, 1995b) and the heterogeneity of trichotillomania itself.

Treatment

Serotonin reuptake inhibitors are considered first-line treatments for trichotillomania; however, research results are less consistent, less robust,

and less well maintained than those found for OCD and body dysmorphic disorder. In both an open trial and a double-blind comparison of clomipramine and desipramine in eight patients with trichotillomania, clomipramine was superior to desipramine (Swedo et al. 1989a, 1989b). However, there have been conflicting reports concerning maintenance of this therapeutic effect. Pollard et al. (1991) reported complete relapse in three of four patients after 3 months of treatment with clomipramine. However, Swedo et al. (1993) reported maintenance of at least some of the initial therapeutic effect in 16 women with ongoing clomipramine treatment over an average of 4 years.

Two crossover trials failed to demonstrate any advantage for fluoxetine over placebo (Christenson et al. 1991c; Streichenwein and Thornby 1995). Christenson et al. (1991c) may not have provided a sufficient trial of fluoxetine because their trial lasted only 6 weeks and patients were on the maximum dose (80 mg) for no longer than 2 weeks; however, Streichenwein and Thornby (1995) provided a more compelling trial that also found no effect. Their subjects had a 12-week trial of fluoxetine in which patients received 80 mg for 6 weeks. Another study compared fluoxetine and clomipramine and found a therapeutic effect for both (Pigott et al. 1992).

Open-label studies of fluvoxamine showed improvement in acute treatment (Christenson and Crow 1996; Stanley et al. 1997), but one study found that this effect was not maintained 6 months into continuing treatment (Christenson and Crow 1996). A 12-week, open-label trial of venlafaxine was successful in reducing symptoms of trichotillomania, with 8 of 12 patients considered to be responders (Ninan et al. 1998). An open-label trial of citalopram in 13 patients showed significant improvement across measures, with 5 (38.5%) patients considered to be responders (Stein et al. 1997b). Case reports note the effectiveness of sertraline (Bradford and Gratzer 1995; Rahman and Gregory 1995) and paroxetine (Reid 1994). In addition, fenfluramine, a serotonin releaser and reuptake inhibitor usually prescribed as an anorectic, has also been reported effective in relieving symptoms of trichotillomania in individual cases, either as an augmentation of fluoxetine (Hollander 1991) or alone (Mahr 1993). An open-label study of patients receiving clomipramine, fluoxetine, or fluvoxamine showed improvement with 10 weeks of treatment, but symptoms rebounded almost to pretreatment levels by week 12 (Iancu et al. 1996).

There have been reports of other successful pharmacologic treatments of trichotillomania. Lithium was effective in decreasing hair pulling in 8 of 10 patients in one study (Christenson et al. 1991b), and naltrexone, an opiate antagonist, was shown to be helpful in alleviating trichotillomania in a placebo-controlled trial (Christenson et al. 1994). Individual cases have

also responded to trazodone (Sunkureddi and Markovitz 1993) and to clomipramine and topical steroids (Black and Blum 1992; Gupta and Freimer 1993). There have been individual case reports of successful treatment of trichotillomania with antidepressants (Christianson and Crow 1996), and pimozide has been used successfully to augment serotonin reuptake inhibitors (Stein and Hollander 1992).

Thus, serotonin reuptake inhibitors such as clomipramine and fluoxetine appear to be helpful in some patients with trichotillomania, both in terms of reducing anxiety and subjective tension and in reducing or eliminating compulsive hair pulling. However, these effects may not be maintained with continued treatment. Overall, research suggests that trichotillomania shows a more minimal response for all treatment modalities compared with OCD and body dysmorphic disorder. This includes a weaker response to serotonin reuptake inhibitors.

A possible cautionary note is that patients with a high degree of impulsivity may occasionally become even more impulsive on high doses of serotonin reuptake inhibitors. This side effect could be problematic if it interferes with the patient's judgment or ability to control these impulses. Discontinuation, adjustment of dose, addition of lithium or valproate to control impulsive behaviors, or addition of neuroleptics such as pimozide or risperdone for "tic-like" hair pulling may be helpful.

Case Example

Ms. B. is a 31-year-old reporter with a 27-year history of trichotillomania. Onset began at age 4, when she began to pull out eyelashes. She recalls that this occurred in response to hearing a doctor describe dandruff and her mother mention that false eyelashes looked "cheap." By age 18, she began to pull out and rub off her eyebrows. She used make-up to conceal her eyebrow hair loss. In addition, she wore glasses instead of contact lenses to hide her eyebrows. She wore false eyelashes to improve her appearance and to help prevent her from pulling her eyelashes. She also avoided swimming to prevent exposure of her problem. She reported feeling self-conscious and humiliated about her hair loss. The hair pulling increased before menstrual periods and was exacerbated by caffeine and alcohol. She also described a sense of pleasure associated with the hair pulling, or a release of tension and a sense of purging, similar to that of an orgasm or of "popping" a pimple. Her family history was significant, including a maternal grandmother who compulsively picked at her face, a mother who uncontrollably cried and had tics, and a brother who compulsively rubbed his lip with his hands.

Ms. B. had seen a therapist briefly while in the fifth grade and for the past 5 years had been seen in individual psychotherapy, but this problem was not discussed. She participated in a National Institute of Mental

Health study, where she responded to a 6- to 8-week trial of clomipramine that was then discontinued. On clomipramine, she had experienced dry mouth, constipation, and fatigue. In addition, she had had a hypomanic episode that resulted in a job change and a move to another city to pursue a boyfriend. Following discontinuation of clomipramine, she relapsed and again experienced compulsive hair pulling and compulsive eating.

Fluoxetine treatment was instituted at 20 mg/day and rapidly increased to 100 mg/day over 2 weeks. On fluoxetine, 100 mg/day, she felt an infusion of nervous energy, leg tapping, hand clenching, generalized stiffness, restless sleep, a feeling of being "revved up," and an urge to make animal noises to relieve tension. Fluoxetine was lowered to 60 mg/day, and the muscle stiffness, hand clenching, and "revved up" feeling resolved. Within 12 weeks she had a substantial reduction in hair pulling to a degree similar to that which had occurred while receiving clomipramine. The addition of fenfluramine at 20 mg/day resulted in almost complete resolution of hair pulling and no additional side effects.

Depersonalization Disorder

Diagnostic Considerations

Depersonalization disorder is classified as a dissociative disorder in DSM-IV-TR. The essential feature is the occurrence of "persistent or recurrent experiences of feeling detached from one's mental processes or body, as though one is an outside observer" (DSM-IV-TR, p. 532). During the experience, "reality testing remains intact" (DSM-IV-TR, p. 532). The symptoms of depersonalization involve alteration in the perception or experience of the self in which the usual sense of one's own reality is temporarily lost or changed. Various types of sensory anesthesia, lack of affective response, and a sensation of not being in complete control of one's actions, including speech, are often present. All of these feelings are egodystonic. The onset of an episode of depersonalization is usually rapid, and its disappearance is usually gradual.

The experience of depersonalization may be relatively common; episodes of depersonalization have been reported in up to 70% of young adults (Kluft 1988) and 80% of psychiatric inpatients (Brauer et al. 1970). It is also known to occur with the use of drugs such as marijuana and during meditation but without the distress and anxiety commonly reported in depersonalization disorder (Castillo 1990; Mathew et al. 1993; Simeon 1993). However, the diagnosis is made only when the symptoms are severe enough to cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

In addition, feelings of depersonalization are often reported in association with other syndromes, such as depression, schizophrenia, temporal

lobe epilepsy and complex partial seizures, anxiety disorders and phobic-anxiety, depersonalization syndrome, and migraines. According to DSM-IV-TR, the diagnosis is not made when the symptoms of depersonalization occur exclusively during the course of another disorder, such as panic disorder (e.g., during a panic attack), acute stress disorder, or other dissociative disorder. In addition, the symptoms must not be caused by the direct effects of a substance or a general medical condition. The maintenance of intact reality testing differentiates this disorder from schizophrenia.

Obsessionalism has long been linked to depersonalization. Early analytic writers noted obsessional characteristics in depersonalized patients (Torch 1978). Depersonalization has been viewed as a repetitive tendency toward self-observation. For example, an episode of unreality feelings in an obsessive personality could lead to the repetitive experience of the feeling as an obsessional focus. Alternatively, an obsessional thought about the "self" could lead to feelings of depersonalization. The incidence of premorbid obsessional traits was 88% and 75%, respectively, in two series studying depersonalized patients (Roth 1959; Torch 1978).

Three of the eight patients with depersonalization disorder studied by Hollander et al. (1990) had obsessions and/or compulsions. Studies using DSM criteria to examine comorbidity between OCD and depersonalization disorder have not been reported; however, there is accumulating evidence that depersonalization disorder fits in the obsessive-compulsive spectrum. Both OCD and depersonalization disorder seem to have a similar age at onset (i.e., typically during adolescence) and a chronic course (Simeon et al. 1995b). Patients with each of these disorders experience repetitive ego-dystonic thoughts. In OCD, the focus of these disturbing thoughts usually involves uncertainty and an exaggerated perception of future harm. In depersonalization disorder, the disturbing thoughts center around discomfort and sensory perceptual distortions involving the self or body and its relation to the world. Results of an in-depth neurobiologic and neuropsychologic case study appear to be similar to those found with OCD (Hollander et al. 1992), including increased frontal alpha activity, overactivation of the left frontal hemisphere, impairment in left caudate perfusion, and mild visual memory deficits.

As with OCD, serotonergic dysfunction has been implicated in depersonalization disorder. In addition to the comorbidity between depersonalization disorder and OCD and their similarity in symptoms and course, Simeon et al. (1995b) noted four lines of evidence supporting the hypothesis of serotonergic dysregulation. First, depersonalization co-occurs with migraines, which are also believed to be influenced by serotonin (Comfort 1982). Second, depersonalization is exacerbated or induced by marijuana

(Mathew et al. 1993; Szymanski 1981). Third, neurochemical studies have shown that in placebo-controlled double-blind challenges, depersonalization can be inducted by a serotonin agonist (methyl-chlorophenylpiperazine [m-CPP]) (Simeon et al. 1995c). Finally, as discussed later in the chapter, depersonalization disorder is responsive to serotonin reuptake inhibitors. Note that symptoms of depersonalization have been reported after both the acute administration and the abrupt discontinuation of serotonin reuptake inhibitors (Black and Wojcieszek 1991; Hollander et al. 1993a).

Treatment

No formal controlled trials of pharmacologic treatment for depersonalization disorder have been reported. Early case reports documented improvement of depersonalization symptoms with antidepressants (Walsh 1975), stimulants (Davison 1964), benzodiazepines, and antiepileptics (Greenberg et al. 1984). More recent studies support the use of serotonin reuptake inhibitors as the first-line treatment for symptoms of depersonalization (Hollander et al. 1990). Davison (1964) described the use of intravenous methamphetamine, 10–20 mg, in four patients with episodic depersonalization. Complete abolition of the symptoms was produced in less than l minute, and the remission lasted for days, weeks, or months. Greenberg et al. (1984) described the use of carbamazepine (400 mg three times daily) in one patient, with resolution of symptoms within 24 hours. More recently, Hollander et al. (1990) reported a preferential response of depersonalization symptoms or depersonalization disorder to agents that manifest potent serotonin reuptake inhibition. Chronic depersonalization symptoms resolved in six of the eight patients treated with fluoxetine (5–80 mg/day) or fluvoxamine (300 mg/day). However, not all patients with depersonalization disorder responded to all serotonin reuptake inhibitors. These patients experienced at least partial resolution of obsessional symptoms as well. Additional cases have been reported that found favorable responses to fluoxetine (Abbas et al. 1995; Fichtner et al. 1992; Ratliff and Kerski 1995). In some patients, the ability of fluoxetine to ameliorate symptoms of depersonalization has been enhanced by augmentation with buspirone (Abbas et al. 1995).

Further work is needed to determine whether the antidepersonalization effect is really an antiobsessional effect or an effect caused by some other mechanism. The chronicity of this disorder, coupled with a poor response to prior somatic and psychologic treatments, makes the positive therapeutic response of depersonalization to serotonin reuptake inhibitors noteworthy.

Gilles de la Tourette's Syndrome

Diagnostic Considerations

Tourette's disorder (more commonly known as Tourette's syndrome), is classified in DSM-IV-TR as a tic disorder with onset before age 18 that consists of multiple motor and one or more vocal tics present at some time during the illness, although not necessarily concurrently. Tics—sudden recurrent and nonrhythmic stereotyped movements or vocalizations—either occur frequently during the day almost every day or occur intermittently for a year or more, during which there is never a period of time without tics lasting more than 3 consecutive months. The disorder must cause marked distress or significant impairment in functioning to meet diagnostic criteria.

Gilles de la Tourette (1885) first reported an association between recurrent motor and phonic tics and obsessive-compulsive symptoms. Recent studies have examined psychiatric symptoms in patients with Tourette's syndrome, compared clinical characteristics of patients with Tourette's syndrome or OCD, and examined relatives of patients with Tourette's syndrome for the presence of Tourette's syndrome, chronic motor tics, and OCD.

There are high rates of comorbidity between Tourette's syndrome and OCD. Numerous studies have reported obsessive-compulsive symptoms in more than half of the patients with Tourette's syndrome studied and reported rates have ranged as high as 74% (Stefl 1984), 68% (Nee et al. 1980), and 67% (Montgomery et al. 1982). In addition to finding a 63% incidence of obsessive-compulsive symptoms in patients with Tourette's syndrome, Pitman et al. (1987) found a 6% incidence of Tourette's syndrome and a greater than 35% incidence of tic disorders in patients with OCD. However, all of these studies had methodologic limitations. Shapiro et al. (1988) used stricter criteria for a diagnosis of OCD, and at present their study is the only one that does not report an increased rate of OCD in subjects with Tourette's syndrome. Studies also show close family links between OCD and Tourette's syndrome (Pauls et al. 1986). The rate of OCD was elevated in relatives of Tourette's syndrome probands, both with and without OCD symptoms, compared with adoptive relatives. This finding suggests that Tourette's syndrome and OCD are etiologically related, at least within the families of patients with Tourette's syndrome, and that OCD may represent a different manifestation of the same underlying factor responsible for Tourette's syndrome.

There is evidence, primarily treatment response to neuroleptics, that the dopaminergic system is involved in Tourette's syndrome (Shapiro et

al. 1988, 1989). In addition, comorbidity and familial association with OCD (Pauls et al. 1986) suggest serotonergic involvement, and treatment response to clonidine as well as comorbidity with attention deficit/hyperactivity disorder (Matthews 1988) suggest noradrenergic dysfunction. Although the cause of Tourette's syndrome is unknown, there is substantial evidence for the involvement of the basal ganglia and frontal cortex. Magnetic resonance imaging studies have uncovered a loss of left–right symmetry of the putamen in patients with Tourette's syndrome, both children (Singer et al. 1993) and adults (Peterson et al. 1993). The basal ganglia and frontal cortex are also implicated in the development of OCD.

Considerable disagreement remains in the field over conceptual issues, such as how to distinguish between a tic and a compulsion, that complicate the interpretation of research findings. Tics are often divided into simple or complex tics. Simple tics, which involve only one muscle group and include movements such as blinks or facial twitches, may be easy to classify, but complex tics create more difficulties. Sandor (1995) described many complex tics as semipurposeful movements that involve multiple muscle groups; these include touching or punching as well complex vocal tics such as swearing or other involuntary words or phrases. The criterion of purpose (i.e., preventing some dreaded consequence) has been used in research to distinguish compulsions from tics (McDougle et al. 1994b). Pitman et al. (1987) noted that "it was sometimes impossible to tell where [the tic] ended and the [compulsion] began, supporting the notion of a symptomatic continuum from simple tic through complex tic and compulsion" (p. 1170). The results suggest "symptomatic overlap tending to blur the two disorders as well as symptomatic poles tending to distinguish them…the ease of differential diagnosis of a given patient would depend on his or her proximity to one of the poles" (p. 1171).

Treatment

The standard treatment for Tourette's syndrome is the use of neuroleptics such as haloperidol and pimozide, which are dopamine receptor antagonists (Shapiro et al. 1989). Generally, lower doses are effective for Tourette's syndrome than are required for treatment of psychosis, and it is important to begin with a very low dose such as 1 mg/day of pimozide or 0.25 mg/day of haloperidol. Doses are gradually raised to an average of 8–13 mg/day for pimozide and 2–10 mg/day for haloperidol. Possible side effects include dystonic reactions, akinesia, extrapyramidal parkinsonian effects, cognitive impairment, and depression. Shapiro et al. (1988) estimated that 25% of Tourette's syndrome patients have at least a 70% reduction of symptoms with a low dose of haloperidol without adverse effects.

Another 50% of patients develop adverse effects when treated with therapeutic doses, but these side effects can be managed over time. Another 25% became "treatment failures" on neuroleptics because adverse effects nullified therapeutic benefits. The development of depression with neuroleptics may be treated by lowering the dose or by adding low-dose methylphenidate or antidepressant medication.

Risperidone, a dopamine and serotonin receptor antagonist, has recently been shown to be effective for Tourette's syndrome. Unfortunately, some case reports suggest it may also increase obsessive-compulsive symptoms in some patients (Remington 1993; Remington and Adams 1994). Generally, this medication is well tolerated by patients with OCD, and it may even be a helpful augmenting agent (McDougle et al. 1995; Ravizza et al. 1996) (see Chapter 12 in this volume).

Although effective for motor and vocal tics, neuroleptics are not effective for associated obsessions or compulsions. Thus, serotonin reuptake inhibitors may be added to neuroleptics for these patients. An open study of fluoxetine treatment in two patients with Tourette's syndrome with concomitant obsessions and compulsions showed improvement in obsessive-compulsive symptoms when low doses of fluoxetine were given (20–40 mg/day) (Riddle et al. 1988). In another case, fluvoxamine and pimozide reduced both obsessive-compulsive symptoms and tics (Delgado et al. 1990). The combination of risperidone (3 mg twice daily) and fluoxetine (40 mg/day) was effective in the case of a man with Tourette's syndrome and comorbid OCD (Giakas 1995). In this case, clomipramine had been ineffective both alone and in combination with numerous other agents including haloperidol and pimozide. When antiobsessionals are used in combination with neuroleptics to treat Tourette's syndrome, we recommend using slightly lower doses of the antiobsessional medications than are typically used for OCD.

Patients with Tourette's syndrome who experience episodic rages (estimated to be as many as 30%) may be helped by serotonin reuptake inhibitors. An 8-week open-label trial of paroxetine resulted in a reduction or elimination of rage episodes in 76% (29/45) of such patients (Brun and Budman 1998).

Serotonin reuptake inhibitors seem to be less effective for treating obsessive-compulsive symptoms in patients with a concurrent tic disorder. McDougle et al. (1993) found that 52% of patients with OCD without tics responded to fluvoxamine, but only 21% of patients with both OCD and tics showed a decrease in obsessive-compulsive symptoms. In a study of patients with fluvoxamine-refractory OCD, augmentation with low doses of haloperidol or pimozide led to improvement in seven of the eight

nonresponders who had concurrent OCD and tics (McDougal et al. 1990). These findings were confirmed in a double-blind, placebo-controlled study using haloperidol and fluvoxamine (McDougle et al. 1994b). For a number of obsessive-compulsive spectrum disorders, some refractory cases seem to benefit from augmentation by neuroleptics. The role of atypical neuroleptics is not yet clear; however, risperidone might have a special role in this cohort (McDougle et al. 1995; Stein et al. 1997a), which suggests that in addition to serotonergic dysfunction, there may also be an underlying dopaminergic dysfunction for some spectrum disorders, including some cases of OCD itself (McDougle et al. 1994a).

Case reports suggest that, in the absence of a neuroleptic, serotonin reuptake inhibitors such as fluvoxamine and fluoxetine may either increase tics (Delgado et al. 1990; Giakas 1995) or result in the emergence of tics in patients with OCD who have no prior history of tic disorder (Fennig et al. 1994).

In patients with Tourette's syndrome, there were early reports that clonidine, a presynaptic noradrenergic agonist, was effective in treating both tics and obsessive-compulsive symptoms (Cohen et al. 1980; Leckman et al. 1982). However, other studies, including double-blind trials, have shown less positive results (Leckman et al. 1991; Shapiro et al. 1988). The addition of clonidine may be helpful for patients who experience considerable anxiety during initiation of serotonin reuptake inhibitor treatment.

If Tourette's syndrome is accompanied by attention-deficit disorder with or without hyperactivity, methylphenidate may be added in initial doses of 2.5 mg/day with a gradual increase to an effective dose. Patients with Tourette's syndrome, OCD, and attention deficit disorder occasionally may be effectively managed with low doses of pimozide, methylphenidate, and fluoxetine (or equivalent medications) for treatment of specific disabling symptoms. Although it is widely believed that methylphenidate treatment will exacerbate tics, this is generally not the case. In addition, clonidine may reduce hyperactivity (Steingard et al. 1993) and thus could be of use in treating patients with comorbid Tourette's syndrome and attention deficit/hyperactivity disorder.

Eating Disorders

Diagnostic Considerations

In DSM-IV-TR, eating disorders form an independent diagnostic category that includes two specific diagnoses: anorexia nervosa and bulimia ner-

vosa. One additional eating disorder, binge-eating disorder, is included in DSM-IV-TR as a diagnosis for further study. All three eating disorders are characterized by "severe disturbances in eating behavior," but there are distinctions between them that reflect a changing understanding of key symptoms. Anorexia nervosa is distinguished by a failure to maintain body weight at or above a "minimally normal" level by either restricting eating or by binge eating and purging. Bulimia nervosa is characterized by binge eating with a sense of lack of control over eating during binge-eating episodes; in addition, patients must use compensatory behaviors such as fasting, purging, or exercising to avoid weight gain. Anorexia nervosa and bulimia nervosa are known to be very serious psychiatric disorders with dangerous medical complications. According to DSM-IV-TR, anorexia has a long-term mortality of more than 10% because of the medical complications of starvation and as a result of suicide. The long-term outcomes of bulimia and binge eating are unknown, although both can be life threatening—the former because of electrolyte imbalance and dehydration, which can cause cardiac arrhythmias with increased risk of sudden death, and the latter because of obesity.

Patients with anorexia nervosa and bulimia nervosa are known to have well-characterized obsessions about food, body image, and food preparation. In addition, they have clear-cut rituals regarding diet, exercise, food preparation, and eating. In our clinical experience, many patients may initially present with obsessional concerns about body image and food intake and go on to develop other, more classic obsessions about, for example, contamination, that would then meet criteria for OCD. There is also such a high degree of symptomatic overlap between body dysmorphic disorder and anorexia nervosa that DSM-IV-TR lists anorexia as a specific exclusion criterion if the distortion centers exclusively on weight. In a review of early studies of comorbid disorders among patients with anorexia nervosa, Rothenberg (1988) found rates of obsessive-compulsive symptoms ranging from 11% to 88%. Recent studies have documented varying high rates of obsessive-compulsive behaviors unrelated to food and weight among patients with eating disorders. A study of patients with anorexia found a 7% rate of OCD (Halmi et al. 1991), whereas a study of patients with bulimia found 10% had OCD (Schwalberg et al. 1992). Fahy (1991) found no OCD among his patients with eating disorders. Thiel et al. (1995) used a different methodology to measure OCD (i.e., the Yale-Brown Obsessive-Compulsive Scale [Y-BOCS; Goodman et al. 1989a, 1989b]), and found that 37% of 93 patients with either anorexia nervosa or bulimia met diagnostic criteria for OCD. These patients also had more severe eating disorder symptoms. Kaye et al. (1993) reported a study of 19 patients with

anorexia in which all were found to have OCD-like symptoms even after all core symptoms typical of anorexia nervosa were excluded; there was no overlap between the Y-BOCS scores of the patients and control subjects.

A serotonergic role in appetite regulation and eating disorders has long been postulated. Feeding and dieting can affect the supply of the serotonin precursor tryptophan to the brain and thereby affect serotonin synthesis. In animals, tryptophan and fenfluramine, a serotonin releaser and reuptake inhibitor, suppress appetite and feeding. Recent studies suggest that inhibitory 5-HT_{1A} agonists increase eating, whereas 5-HT_{1B} and 5-HT_{1C} agonists acting on the paraventricular nucleus of the hypothalamus decrease eating in rats (Curzon 1989). In humans, cerebrospinal fluid studies of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) and blunted prolactin response to the orally administered 5-HT agonist m-CPP suggest diminished central serotonergic function associated with the binge-eating pattern of bulimia (Brewerton et al. 1989; Jimerson et al. 1989). After weight gain, the neuroendocrine responsivity of patients partially normalizes (Brewerton et al. 1989). Furthermore, in preliminary studies with oral m-CPP, we found exacerbation of obsessions and compulsive urges regarding food and body image in approximately 60% of patients with eating disorders after orally administered m-CPP, with normalization of this effect after weight gain. There appear to be similar behavioral and neuroendocrine responses to oral m-CPP in patients with OCD at baseline (Hollander et al. 1988; Zohar et al. 1987), such that both patients with OCD and those with eating disorders show some behavioral sensitivity and neuroendocrine blunting. Chronic treatment with serotonin reuptake inhibitors normalized behavioral and neuroendocrine responses in OCD (Hollander et al. 1989a; Zohar et al. 1988), with changes in a direction similar to that found in patients with eating disorders after weight gain.

Treatment

There is evidence that anorexia nervosa and bulimia nervosa respond differently to pharmacotherapy, with bulimia responding to all types of antidepressants, albeit with an often modest response, whereas anorexia responds preferentially to serotonin reuptake inhibitors (Advokat and Kutlesic 1995). Interestingly, serotonergic drugs have long been administered for appetite control. Fenfluramine, a serotonin releaser and reuptake inhibitor, has been administered to more than 50 million patients around the world for appetite suppression (Derome-Tremblay and Nathan 1989).

In placebo-controlled studies, symptoms of bulimia nervosa have

been ameliorated by a monoamine oxidase inhibitor (phenelzine), TCAs (imipramine, desipramine), bupropion (although contraindicated because of an increased risk of seizures in bulimic patients), trazodone, and a selective serotonin reuptake inhibitor (fluoxetine) as well as the anorectic fenfluramine. In case reports, symptoms of bulimia nervosa were helped by a monoamine oxidase inhibitor (tranylcypromine), a TCA (amitryptaline), nomifensine, and selective serotonin reuptake inhibitors (fluvoxamine and paroxetine) (Advokat and Kutlesic 1995; Hudson et al. 1996). Effective doses are generally in the same range as those recommended for depression, although fluoxetine may require slightly higher doses. The presence of depression does not predict whether a patient's bulimia will respond to antidepressant medication.

Although more research needs to be done, binge-eating disorder seems to respond to treatments suited for bulimia nervosa (Hudson et al. 1996). One placebo-controlled trial of desipramine for binge-eating disorder (or the earlier bulimia, nonpurging type) showed significantly greater effectiveness versus placebo. Another study of desipramine and one of imipramine showed minimal differences, but these studies had serious methodologic flaws. Studies of fluvoxamine (Fichter et al. 1996, 1997), including a large placebo-controlled study (Hudson et al. 1998), have shown significant reduction in binge eating and other symptoms of bulimia nervosa.

Research on treatment of anorexia nervosa is less encouraging and less definitive. Because of the potential lethality of the disorder, studies generally look at combined treatments such as behavioral and nutritional therapies along with medication. Although there is high comorbid depression in anorexia, treatment with antidepressants shows little impact on the disorder and the medical fragility of these patients makes pharmacologic treatment complex. Although fluoxetine has a more favorable side effect profile, there is reluctance toward use in patients with anorexia because of its appetite-suppressive effect in some populations. In the first open-label trial of fluoxetine in the treatment of anorexia nervosa, Gwirtsman et al. (1990) studied six patients with anorexia whose symptoms were chronic and refractory and who had coexisting depression. Their major aim was to assess the effectiveness in treating the patients' depression without an adverse impact on their appetite or weight. The patients received fluoxetine (20–60 mg/day) in addition to other treatments, including hospitalizations and psychologic treatments. The patients' depressive symptoms eased and most experienced weight gain, although the effects cannot be clearly attributed to fluoxetine.

Kaye et al. (1991) studied fluoxetine for anorexia nervosa based on the similarities of the disorder to OCD. They studied 31 patients in an open tri-

al; most of the patients began their study participation as inpatients and were followed-up afterward as outpatients. Patients received a variety of treatments. Fluoxetine doses ranged from 10–80 mg/day. Most of the patients showed some positive response to the treatment; 10 of the patients had a good response whereas another 17 had a partial response. More recent studies have shown improvement during a course of combined treatments including pharmacotherapy and highlight the difficulties of drawing conclusions based on such designs. Two studies by Brambilla et al. (1995a, 1995b) showed improvement in most patients with anorexia after a 4-month course of combined cognitive-behavioral, psychopharmacologic, and nutritional therapy. Neither study showed differences between the medication groups (in each case fluoxetine versus a nonserotonergic antidepressant); it is possible that this is because of small sample sizes, but there were no consistent directional differences. One study of anorexia nervosa, restricted type, found no difference between nortriptyline, chosen because of its noradrenergic stimulating activity (thought to increase hunger and carbohydrate preference), and fluoxetine (Brambilla 1995a). A second study of anorexia nervosa, restricted type, found no difference between amineptine, chosen because of its dopaminergic stimulating effect (thought to inhibit hunger), and fluoxetine (Brambilla 1995b). These reports underline the importance, at this time, of combining pharmacologic treatment of anorexia nervosa with other treatment modalities.

Summary

This chapter addresses diagnostic considerations and treatment approaches for disorders related to OCD. Although there is currently debate about which disorders are most closely related to OCD, the most current evidence linking these disorders to OCD is presented. Body dysmorphic disorder, trichotillomania, depersonalization disorder, Tourette's syndrome, and eating disorders are discussed, and case management summaries for two disorders are described. A review of past and current treatment approaches to OCD-related disorders is presented, and common pitfalls are discussed. These findings remain tentative, however, given the limited amount of research to date.

References

Abbas S, Chandra PS, Srivastava M: The use of fluoxetine and buspirone for treatment-refractory depersonalization disorder. J Clin Psychiatry 56:484, 1995

Advokat C, Kutlesic V: Pharmacotherapy of the eating disorders: a commentary. Neurosci Biobehav Res 19:59–66, 1995

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Washington, DC, American Psychiatric Association, 1994

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision. Washington, DC, American Psychiatric Association, 2000

Andreasen NC, Bardach J: Dysmorphophobia: symptom or disease? Am J Psychiatry 134:6, 1977

Black DW, Blum N: Trichotillomania treated with clomipramine and a topical steroid (letter). Am J Psychiatry 149:842–843, 1992

Black DW, Wojcieszek J: Depersonalization syndrome induced by fluoxetine (letter). Psychosomatics 32:468–469, 1991

Bordnick PS, Thyer BA, Ritchie BW: Feather picking disorder and trichotillomania: an avian model of human pychopathology. J Behav Ther Exp Psychiatry 25:189–196, 1994

Bradford JMW, Gratzer TG: A treatment for impulse control disorders and paraphilia: a case report. Can J Psychiatry 40:4–5, 1995

Brambilla F, Draisci A, Peirone A, et al: Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders, 1: anorexia nervosa—restricted type. Neuropsychobiology 32:59–63, 1995a

Brambilla F, Draisci A, Peirone A, Brunetta M: Combined cognitive-behavioral, psychopharmacological and nutritional therapy in eating disorders, 2: anorexia nervosa—binge-eating/purging type. Neuropsychobiology 32:64–7, 1995b

Brauer R, Harrow M, Tucker GJ: Depersonalization phenomena in psychiatric inpatients. Br J Psychiatry 117:509–515, 1970

Brawman-Mintzer O, Lydiard RB, Phillips KA, et al: Body dysmorphic disorder in patients with anxiety disorders and major depression: a comorbidity study. Am J Psychiatry 152:1665–1667, 1995

Brewerton T, Murphy D, Jimerson DC: A comparison of neuroendocrine responses to L-TRP and m-CPP in bulimics and controls. Biol Psychiatry 25 (suppl):18A–21A, 1989

Brotman AW, Jenike MA: Monosymptomatic hypochondriasis treated with tricyclic antidepressants. Am J Psychiatry 141:1608–1609, 1984

Brun RD, Budman CL: Paroxetine treatment of episodic rages associated with Tourette's disorder. J Clin Psychiatry 59:581–584, 1998

Castillo RJ: Depersonalization and meditation. Psychiatry 53:158–168, 1990

Christenson GA, Crow SJ: The characterization and treatment of trichotillomania. J Clin Psychiatry 57(suppl):42–49, 1996

Christenson GA, Mackenzie TB, Mitchell JE: Characteristics of 60 adult chronic hair pullers. Am J Psychiatry 148:365–370, 1991a

Christenson GA, Popkin MK, Mackenzie TB, et al: Lithium treatment of chronic hair pulling. J Clin Psychiatry 52:116–120, 1991b

Christenson GA, Mackenzie TB, Mitchell JE, et al: A placebo-controlled, double-blind crossover study of fluoxetine in trichotillomania. Am J Psychiatry 148:1566–1571, 1991c

Christenson GA, Raymond NC, Faris PL, et al: Pain thresholds are not elevated in trichotillomania. Biol Psychiatry 36:347–349, 1994

Cohen DJ, Detlor J, Young J, et al: Clonidine ameliorates Gilles de la Tourette syndrome. Arch Gen Psychiatry 37:1350–1357, 1980

Cohen LJ, Stein DJ, Simeon D, et al: Clinical profile, comorbidity, and treatment history in 123 hair pullers: a survey study. J Clin Psychiatry 56:319–326, 1995

Comfort A: Out-of-body experiences and migraine (letter). Am J Psychiatry 139:1379–1380, 1982

Curzon G: Serotonin and appetite. Paper presented at the Symposium on the Neuropharmacology of Serotonin, New York Academy of Sciences, New York, July 1989

Davison K: Episodic depersonalization: observations on seven patients. Br J Psychiatry 110:505–513, 1964

de la Tourette G: Etude sur une affection nerveuse caraterisée par de l'incoordination motrice accompagnée d'echolalie et de coprolie. Arch Neurol 9:19–42, 158–200, 1885

Delgado PL, Goodman WK, Price LH, et al: Fluvoxamine/pimozide treatment of concurrent Tourette's and obsessive-compulsive disorder. Br J Psychiatry 157:762–765, 1990

Derome-Tremblay M, Nathan C: Fenfluramine studies (letter). Science 243:991, 1989

Fahy TA: Obsessive-compulsive symptoms in eating disorders. Behav Res Ther 29:113–116, 1991

Fennig S, Naisberg Fennig S, Pato M, et al: Emergence of symptoms of Tourette's syndrome during fluvoxamine treatment of obsessive-compulsive disorder. Br J Psychiatry 164:839–841, 1994

Fichter MM, Kruger R, Rief W et al: Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. J Clin Psychopharmacol 16:9–18, 1996

Fichter MM, Leibl C, Kruger R, Rief W: Effects of fluvoxamine on depression, anxiety, and other areas of general psychopathology in bulimia nervosa. Pharmacopsychiatry 3085–92, 1997

Fichtner CG, Horevitz RP, Braun BG: Fluoxetine in depersonalization disorder. Am J Psychiatry 149:1750–1751, 1992

Fitts SN, Gibson P, Redding CA, et al: Body dimorphic disorder: implications for its validity as a DSM-III-R clinical syndrome. Psychol Rep, 64:655–658, 1989

Giakas WJ: Risperidone treatment for a Tourette's disorder patient with comorbid obsessive-compulsive disorder (letter). Am J Psychiatry 152:1097–1098, 1995

Goldberger E, Rapoport J: Canine acral lick dermatitis: response to the anti-obsessional drug clomipramine. J Am Anim Hosp Assoc 22:179–181, 1991

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Greenberg DB, Hochberg FH, Murray GB: The theme of death in complex partial seizures. Am J Psychiatry 141:1587–1589, 1984

Grindlinger HM, Ramsay E: Compulsive feather picking in birds (letter). Arch Gen Psychiatry 48:857, 1991

Gupta S, Freimer M: Trichotillomania, clomipramine, topical steroids. Am J Psychiatry 150:3, 1993

Gwirtsman DS, Guze BH, Yager J, et al: Fluoxetine treatment of anorexia nervosa: an open clinical trial. J Clin Psychiatry 51:378–382, 1990

Halmi KA, Eckert E, Marchi P, et al: Comorbidity of psychiatric diagnoses in anorexia nervosa. Arch Gen Psychiatry 48:712–718, 1991

Hartmann L: Cats as possible obsessive-compulsive disorder and medication models (letter). Am J Psychiatry 152:1236, 1995

Hollander E: Serotonergic drugs and the treatment of disorders related to obsessive-compulsive disorder, in Current Treatments of Obsessive-Compulsive Disorder. Edited by Pato MT, Zohar J. Washington, DC, American Psychiatric Press, 1991, pp 173–191

Hollander E: Obsessive-compulsive spectrum disorders: an overview. Psychiatr Ann 23:355–358, 1993

Hollander E, Fay M, Cohen B, et al: Serotonergic and noradrenergic function in obsessive-compulsive disorder: behavioral findings. Am J Psychiatry 145:1015–1017, 1988

Hollander E, DeCaria C, Fay M, et al: Repeat m-CPP challenge during fluoxetine treatment in obsessive compulsive disorder: behavioral and neuroendocrine responses (abstract). Biol Psychiatry 25(suppl):8A, 1989a

Hollander E, Liebowitz MR, Winchel R, et al: Treatment of body dysmorphic disorder with serotonin reuptake blockers. Am J Psychiatry 146:768–770, 1989b

Hollander E, Liebowitz MR, DeCaria C, et al: Treatment of depersonalization with serotonin reuptake inhibitors. J Clin Psychopharmacol 10:200–203, 1990

Hollander E, Carrasco JL, Mullen LS, et al: Left hemisphere activation in depersonalization disorder: a case report. Biol Psychiatry, 31:1157–1162, 1992

Hollander E, Hwang M, Mullen LS, et al: Clinical and research issues in depersonalization syndrome (letter). Psychosomatics 34:193–194, 1993a

Hollander E, Cohen LJ, Simeon D: Obsessive-compulsive spectrum disorders: body dysmorphic disorder. Psychiatr Ann 23:359–364, 1993b

Hollander E, Wong CM: Introduction: obsessive-compulsive spectrum disorders. J Clin Psychiatry 56(suppl):3–6, 1995

Hollander E, Allen A, Kwon J, et al: Clomipramine vs. desipramine crossover trial in body dysmorphic disorder: selective efficacy of a serotonin reuptake inhibitor in imagined ugliness. Arch Gen Psychiatry, 56:1033–1039, 1999

Hudson JI, Carter WP, Pope HG, Jr: Antidepressant treatment of binge-eating disorder: research findings and clinical guidelines. J Clin Psychiatry 57(suppl):73–79, 1996

Hudson JI, McElroy SL, Raymond NC et al: Fluvoxamine in the treatment of binge-eating disorder: a multicenter placebo-controlled, double-blind trial. Am J Psychiatry 155:1756–1762, 1998

Iancu I, Weizman A, Kindler S, et al: Serotonergic drugs in trichotillomania: treatment results in 12 patients. J Nerv Ment Dis 184:641–644, 1996

Insel TR, Akiskal HS: Obsessive-compulsive disorder with psychotic features: a phenomenological analysis. Am J Psychiatry 143:1527–1533, 1986

Jimerson DC, Lesem MD, Kaye WH, et al: Serotonin and symptom severity in eating disorders. Biol Psychiatry 25(suppl):141A–143A, 1989

Kaye WH, Weltzin T, Hsu LKG: An open trial of fluoxetine in patients with anorexia nervosa. J Clin Psychiatry 52:464–471, 1991

Kaye WH, Weltzin T, Hsu LKG: Anorexia nervosa, in Obsessive-Compulsive Related Disorders. Edited by Hollander E. Washington, DC, American Psychiatric Press, 1993, pp 49–70

Kluft RP: The dissociative disorders, in The American Psychiatric Press Textbook of Psychiatry. Edited by Talbot JA, Hales RE, Yudofsky SC. Washington, DC. American Psychiatric Press, 1988, pp 557–585

Leckman JF, Cohen DJ, Detlov J, et al: Clonidine in the treatment of Tourette syndrome and their neuroendocrine implications, in Advances in Neurology, Vol 35: Gilles de la Tourette Syndrome. Edited by Friedhoff AJ, Chase TN. New York, Raven Press, 1982, pp 391–401

Leckman JF, Hardin MT, Riddle MA, et al: Clonidine treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 48:324–328, 1991

Leonard HL: Drug treatment of obsessive-compulsive disorder, in Obsessive-Compulsive Disorder in Children and Adolescents. Edited by Rapoport JL. Washington, DC, American Psychiatric Press, 1989, pp 217–236

Mahr G: Fenfluramine and trichotillomania (letter). Psychosomatics 34:284, 1993

Mathew RJ, Wilson WH, Humphreys D, et al: Depersonalization after marijuana smoking. Biol Psychiatry 33:431–441, 1993

Matthews WS: Attention deficit and learning disabilities in children with Tourette's syndrome. Psychiatr Ann 8:414–416, 1988

McDougle CJ, Goodman WK, Price LH: Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry 147:652–654, 1990

McDougle CJ, Goodman WK, Leckman JF, et al: The efficacy of fluoxetine in obsessive-compulsive disorder: effects of chronic tic disorder. J Clin Psychopharmacol 13:354–358, 1993

McDougle CJ, Goodman WK, Price LH: Dopamine agonists in tic-related and psychotic spectrum OCD. J Clin Psychiatry 55(suppl):24–31, 1994a

McDougle CJ, Goodman WK, Leckman JF, et al: Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: a double-blind, placebo-controlled study in patients with and with out tics. Arch Gen Psychiatry 51:302–308, 1994b

McDougle CJ, Fleischmann RL, Epperson CN, et al: Risperdone addition in fluvoxamine-refractory OCD: three cases. J Clin Psychiatry 56:526–528, 1995

McElroy SL, Phillips KA, Keck PE, Jr, et al: Body dysmorphic disorder: does it have a psychotic subtype? J Clin Psychiatry 54:389–395, 1993

McElroy SL, Phillips KA, Keck PE, Jr, et al: Obsessive compulsive spectrum disorder. J Clin Psychiatry 55(suppl):33–51, 1994

Montgomery MA, Clayton PJ, Friedhoff AJ: Psychiatric illness in Tourette syndrome patients and first degree relatives, in Gilles de la Tourette Syndrome. Edited by Friedhoff AJ, Chase TN. New York, Raven Press, 1982, pp 335–339

Muller SA: Trichotillomania: a histopathological study in sixty-six patients. J Am Acad Dermatol 23:56–62, 1990

Munro A, Chmara J: Monosymptomatic hypochondriacal psychosis: a diagnostic checklist based on 50 cases of the disorder. Can J Psychiatry 27:374–376, 1982

Nee LE, Caine ED, Polinsky RJ, et al: Gilles de la Tourette's syndrome: clinical and family study of 50 cases. Ann Neurol 7:41–49, 1980

Ninan PT, Knight B, Kirk L, et al: A controlled trial of venlafaxine in trichotillomania: interim phase 1 results. Psychopharmacol Bull 34:221–224, 1998

Pauls DL, Towbin KE, Leckman JF, et al: Gilles de la Tourette syndrome and obsessive-compulsive disorder. Arch Gen Psychiatry 43:1180–1182, 1986

Peterson B, Riddle MA, Cohen DJ, et al: Reduced basal ganglia volumes in Tourette's syndrome using tree magnetic resonance images. Neurology 43:941–949, 1993

Phillips KA: Body dysmorphic disorder: the distress of imagined ugliness. Am J Psychiatry 148:1138–1149, 1991

Phillips KA: Body dysmorphic disorder: diagnosis and treatment of imagined ugliness. J Clin Psychiatry 57(suppl):61–64, 1996

Phillips KA, McElroy SL: An open label study of fluvoxamine in body dysmorphic disorder. Poster presented at the annual meeting of the American Psychiatric Association, Miami, FL, May 1995

Phillips KA, Taub SL: Skin picking as a symptom of body dysmorphic disorder. Psychopharmacol Bull 31:279–288, 1995

Phillips KA, McElroy SL, Keck PE, Jr, et al: Body dysmorphic disorder: 30 cases of imagined ugliness. Am J Psychiatry 150:302–308, 1993

Phillips KA, McElroy SL, Keck PE, Jr, et al: A comparison of delusional and nondelusional body dysmorphic disorder in 100 cases. Psychopharmacol Bull 30:179–186, 1994

Phillips KA, Kim JM, Hudson JI: Body image disturbance in body dysmorphic disorder and eating disorders: obsessions or delusions? Psychiatr Clin North Am 18:317–34, 1995

Phillips KA, Dwight MM, McElroy SL: Efficacy and safety of fluvoxamine in body dysmorphic disorder. J Clin Psychiatry 59:165–171, 1998

Pigott TA, L'Heueux F, Grady TA, et al: Controlled comparison of clomipramine and fluoxetine in trichotillomania. Presented at the annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1992

Pitman RK, Green RC, Jenike MA, et al: Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. Am J Psychiatry 144:1166–1171, 1987

Pollard CA, Ibe IO, Krojanker DN, et al: Clomipramine treatment of trichotillomania: a follow-up report on four cases. J Clin Psychiatry 52:128–130, 1991

Rahman MA, Gregory R: Trichotillomania associated with HIV infection and response to sertraline (letter). Psychosomatics 36:417–418, 1995

Rapoport JL: Treatment of behavioral disorders in animals (letter). Am J Psychiatry 147:1249, 1990

Rapoport JL, Ryland DH, Kriete M: Drug treatment of canine acral lick: an animal model of obsessive-compulsive disorder. Arch Gen Psychiatry 49:517–521, 1992

Ratliff NB, Kerski D: Depersonalization treated with fluoxetine (letter). Am J Psychiatry 152:1689–1690, 1995

Ravizza L, Barzega G, Bellino S, et al: Therapeutic effect and safety of adjunctive risperidone in refractory OCD. Psychopharmacol Bull 32:677–682, 1996

Reid TL: Treatment of resistant trichotillomania with paroxetine (letter). Am J Psychiatry 151:290, 1994

Remington CG: Clinical considerations in the use of risperidone. Can J Psychiatry 38(suppl):96–100, 1993

Remington CG, Adams M: Risperidone and obsessive compulsive symptoms. J Clin Psychopharmacol 14:358–359, 1994

Rettew DC, Cheslow DL, Rapoport JL, et al: Neuropsychological test performance in trichotillomania: a further link with obsessive-compulsive disorder. J Anxiety Disord 5:225–235, 1991

Riddle MA, Leckman JF, Hardin MT, et al: Fluoxetine treatment of obsessions and compulsions in patients with Tourette's syndrome (letter). Am J Psychiatry 145:1173–1174, 1988

Roth M: The phobic anxiety depersonalization syndrome. Journal of Neuropsychiatry 1:293–306, 1959

Rothenberg A: Differential diagnosis of anorexia nervosa and depressive illness: a review of 11 studies. Compr Psychiatry 29:427–432, 1988

Sandor P: Clinical management of Tourette's syndrome and associated disorders. Can J Psychiatry 40:577–583, 1995

Schwalberg MD, Barlow DH, Alger SA, et al: Comparison of bulimics, obese binge eaters, social phobics and individuals with panic disorder on comorbidity across DSM-III-R anxiety disorder. J Abnorm Psychol 10:675–681, 1992

Shapiro AK, Shapiro ES, Young JG, et al: Gilles de la Tourette Syndrome, 2nd Edition. New York, Raven Press, 1988

Shapiro E, Shapiro AK, Fulop G: Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 46:722–730, 1989

Simeon D, Hollander E: Depersonalization disorder. Psychiatr Ann 23:382–388, 1993

Simeon D, Hollander E, Stein DJ, et al: Body dysmorphic disorder in the DSM-IV field trial for obsessive-compulsive disorder. Am J Psychiatry 152:1207–1209, 1995a

Simeon D, Stein DJ, Hollander E: Depersonalization and self-injurious behavior. J Clin Psychiatry 56(suppl):36–39, 1995b

Simeon D, Hollander E, Stein DL, et al: Induction of depersonalization by the serotonin agonist meta-chlorophenylpiperazine. Psychiatry Res 58:161–164, 1995c

Singer HS, Reiss AL, Brown JE et al: Volumetric MRI changes in basal ganglia of children with Tourette's syndrome. Neurology 43:950–956, 1993

Songer DA, Roman B: Treatment of somatic delusional disorder with atypical antipsychotic agents (letter). Am J Psychiatry 153:578–579, 1996

Stanley MA, Breckenridge JK, Swann AC et al: Fluvoxamine treatment of trichotillomania. J Clin Psychopharmacol 17:278–283, 1997

Stefl ME: Mental health needs associated with Tourette's syndrome. Am J Public Health 74:1310–1313, 1984

Stein DJ, Hollander E: Low-dose pimozide augmentation of serotonin reuptake blockers in the treatment of trichotillomania. J Clin Psychiatry 53:123–126, 1992

Stein DJ, Hollander E, Simeon D, et al: Neurological soft signs in female trichotillomania patients, obsessive-compulsive disorder patients, and healthy control subjects. J Neuropsych Clin Neurosci 6:184–187, 1994

Stein DJ, Mullen L, Islam MN, et al: Compulsive and impulsive symptomatology in trichotillomania. Psychopathology 28:208–213, 1995a

Stein DJ, Hollander E, Cohen L, et al: Serotonergic responsivity in trichotillomania: neuroendocrine effects of m-chlorophenylpiperazine. Biol Psychiatry 37:414–416, 1995b

Stein DJ, Bouwer C, Hawkridge S, et al: Resperidone augmentation of serotonin reuptake inhibitors in obscssive-compulsive and related disorders. J Clin Psychiatry 58:119–122, 1997a

Stein DJ, Bouwer C, Maud CM: Use of the selective serotonin reuptake inhibitor citalopram in treatment of trichotillomaina. Eur Arch Psychiatry Clin Neurosci 247:234–236, 1997b

Steingard R, Biederman J, Spencer T, et al: Comparison of clonidine response in the treatment of attention-deficit hyperactivity disorder with and without comorbid tic disorders. J Am Acad Child Adolesc Psychiatry 32:350–353, 1993

Streichenwein SM, Thornby JI: A long-term, double-blind, placebo-controlled crossover trial of the efficacy of fluoxetine for trichotillomania. Am J Psychiatry 152:1192–1196, 1995

Sunkureddi K, Markovitz P: Trazodone treatment of obsessive-compulsive disorder and trichotillomania (letter). Am J Psychiatry 150:523–524, 1993

Swedo SE: Trichotillomania. Psychiatr Ann 23:402–407, 1993

Swedo SE, Leonard HL: Trichotillomania: an obsessive compulsive spectrum disorder. Psychiatr Clin North Am 15:777–790, 1992

Swedo SE, Leonard HL, Rapoport JL, et al: A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling) N Engl J Med 321:497–501, 1989a

Swedo SE, Rapoport JL, Leonard H, et al: Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry 46:335–341, 1989b

Swedo SE, Lenane MC, Leonard HL: Long-term treatment of trichotillomania (hair pulling) (letter). N Engl J Med 329:141–142, 1993

Szymanski HV: Prolonged depersonalization after marijuana abuse. Am J Psychiatry 138:231–233, 1981

Thiel A, Broocks A, Ohlmeier M, et al: Obsessive-compulsive disorder among patients with anorexia nervosa and bulimia nervosa. Am J Psychiatry 152:72–75, 1995

Thomas CS: Dysmorphophobia and monosymptomatic hypochondriasis (letter). Am J Psychiatry 142:1121, 1985

Torch E: Review of the relationship between obsession and depersonalization. Acta Psychiatr Scand 58:191–198, 1978

Walsh R: Depersonalization: definition and treatment (letter) Am J Psychiatry 132:873, 1975

Zohar J, Mueller EA, Insel TR, et al: Serotonergic responsivity in obsessive-compulsive disorder: comparison of patients and healthy controls. Arch Gen Psychiatry 44:946–951, 1987

Zohar J, Insel TR, Zohar-Kadouch RC, et al: Serotonergic responsivity in obsessive-compulsive disorder: effects of chronic clomipramine treatment. Arch Gen Psychiatry 45:167–172, 1988

CHAPTER 12

Management of Treatment-Resistant Obsessive-Compulsive Disorder

Dan J. Stein, M.B.
Soraya Seedat, M.B.
Nathan Andrew Shapira, M.D., Ph.D.
Wayne K. Goodman, M.D.

The introduction of serotonin reuptake inhibitors (SRIs) and behavioral therapy for the treatment of obsessive-compulsive disorder (OCD) has been crucially important for clinicians and researchers as well as patients. Clinicians are now in the fortunate position of being able to offer several safe and effective first-line alternatives for OCD. Researchers have been challenged to answer such fascinating questions as the role of serotonin in mediating obsessive-compulsive symptoms. Patients have experienced remarkable reductions in symptoms with treatment, and some have formed consumer advocacy groups to encourage others with OCD to have their symptoms appropriately diagnosed.

Nevertheless, despite the excitement of these substantial advances, the SRIs and behavioral therapy are not always useful in the management of OCD. SRIs may be poorly tolerated by some patients or may simply be ineffective. Similarly, behavior therapy has proven intolerable or unhelpful for a significant subgroup of patients. This treatment resistance poses an ongoing challenge for clinicians and researchers in the field. In this chapter, we provide a practical step-wise approach to the clinical management of the patient with treatment-resistant OCD (Figure 12–1).

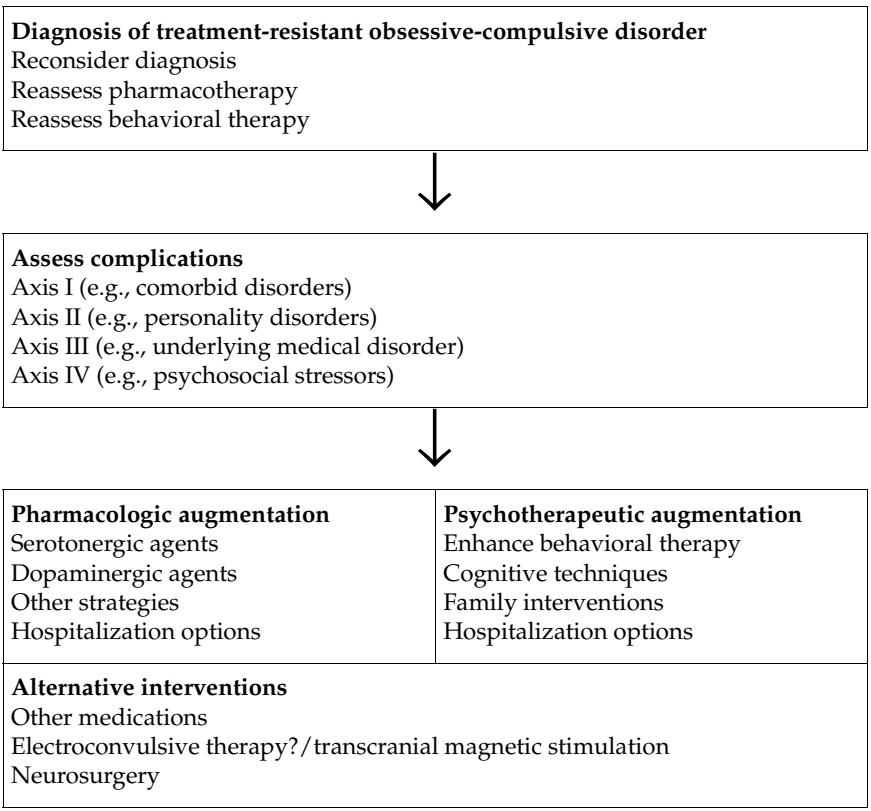


Figure 12–1. Approach to the patient with treatment-resistant obsessive-compulsive disorder.

Diagnosis of Obsessive-Compulsive Disorder

The characterization of a patient as having treatment-resistant OCD must be based on a careful evaluation of several aspects of the clinical presentation and psychiatric history. These aspects include confirmation of the diagnosis of OCD, assessment of pharmacotherapeutic history, and evaluation of past behavioral therapy.

Obviously, patients cannot be diagnosed with treatment-resistant OCD unless they actually have OCD. Although the diagnosis of OCD is often straightforward, it is possible to misdiagnose several other conditions that are characterized by repetitive thoughts or actions as OCD, including mood disorders with obsessional ruminations, anxiety disorders with intrusive worries (e.g., generalized anxiety disorder) or memories (e.g., post-

traumatic stress disorder), personality disorders with perfectionism, psychotic disorders with rituals, and pervasive developmental disorders with stereotypic behaviors.

Case Example

A 24-year-old woman presented with a history of repetitive showering over a period of several weeks and was referred to an OCD clinic. On detailed psychiatric history, it became clear that the showering had begun in the aftermath of a sexual assault by a blind date. The patient had recurrent memories of the assault, no longer socialized with men, and demonstrated several symptoms of hyperarousal including a startle response. When overwhelmed with intrusive thoughts of the assault, she would take a shower. She was diagnosed as suffering from posttraumatic stress disorder and referred to a different specialty clinic.

Differentiating from Spectrum Disorders

It is important to differentiate between OCD and the putative obsessive-compulsive spectrum disorders, such as body dysmorphic disorder, hypochondriasis, or Tourette's syndrome (Stein and Hollander 1993). Although standard anti-OCD treatments are often used in these disorders, alternative pharmacotherapy and psychotherapy approaches are indicated in the treatment of conditions such as Tourette's syndrome. Furthermore, it is important to rule out general medical conditions that may present with obsessive-compulsive symptoms; Sydenham's chorea and other neurologic disorders with basal ganglia lesions and obsessive-compulsive symptoms may require specific interventions in addition to anti-OCD treatments (Cummings and Cunningham 1992).

Case Example

A 7-year-old boy with difficulty in keeping up with schoolwork was brought to a family physician. The family noted that the patient had motor tics and occasionally made barking or grunting noises. The physician was aware of the link between tics and OCD and received a positive response to her inquiries about the presence of obsessions and compulsions. Treatment with fluoxetine was initiated and the child reported feeling less anxious. However, there was no improvement in school functioning and the child was referred to a psychiatrist. The psychiatrist made a diagnosis of Tourette's syndrome with both attention deficit/hyperactivity disorder (ADHD) and subclinical obsessions and compulsions and initiated a treatment that was focused on the ADHD.

History of Previous Pharmacologic Treatments

Patients' pharmacotherapeutic histories should be adequately assessed, such as whether they have been treated with SRI trials of adequate dose and duration. Although not all studies of OCD demonstrate a linear dose–response curve (Greist et al. 1995a, 1995b) it is generally accepted that in OCD it is appropriate to aim for doses that are much higher than those used in ordinary cases of major depression (e.g., clomipramine 250 mg, citalopram 60 mg, fluoxetine 80 mg, fluvoxamine 300 mg, paroxetine 60 mg, sertraline 200 mg) (March et al. 1997). Similarly, given the relatively slow response of OCD to pharmacotherapy, current recommendations are that OCD medication trials should be at least 10–12 weeks in duration (March et al. 1997).

Treatment Resistance

Definition

How many failed trials of medication are necessary before a patient's OCD can be termed *treatment-resistant*? There is certainly some evidence that patients with OCD who do not respond to one SRI may respond to another (Pigott et al. 1990). It is therefore probably premature to label a patient who has failed only one SRI trial as having treatment-resistant OCD. However, there is also evidence that patients who have previously failed to respond to an SRI are less likely to respond to another SRI trial than medication-naïve patients (Greist et al. 1995b). Thus, patients with OCD who have not responded to trials of two or more SRIs may fall into the treatment-resistant category.

Selective Serotonin Reuptake Inhibitors and Clomipramine

There is no evidence from head-to-head comparison studies that any particular SRI is more effective than any other. Nevertheless, the finding in several meta-analyses that clomipramine has the largest effect size of the SRIs in OCD (Greist et al. 1995b; Stein et al. 1995) and the possibility that tricyclic antidepressants are more effective than selective serotonin reuptake inhibitors (SSRIs) in some patients with certain types of depression (Hollander et al. 1991; Roose et al. 1994) arguably suggest that a trial of clomipramine should at least be initiated before a patient's OCD can be considered treatment resistant. Certainly, several authors have suggested that clomipramine should be considered for patients with OCD who have not responded to one or more trials of an SSRI.

Behavior Therapy

Given the evidence for the efficacy of behavioral therapy in OCD, it also seems unwise to characterize a patient's OCD as treatment resistant unless an attempt at treatment with this modality has been made. It is important to ascertain whether the patient received a clear rationale for the implementation of exposure and response prevention, whether instructions about exposure were given and followed, and whether "dosing" (sufficient exposure) and duration of behavioral therapy were adequate. Behavior therapy may fail because patients simply feel unable to follow through with therapists' instructions or because anxiety continuously fails to diminish after exposure and response prevention.

Partial Responders

A final question in the diagnosis of treatment-resistant OCD is the extent to which the patient has in fact improved since treatment began. In clinical trials, a 25%–35% decrease in OCD symptoms on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al. 1989a, 1989b) is taken to be a treatment response. Although such patients continue to have symptoms, they may experience significant improvement in function. Nevertheless, when there is sufficient clinical distress or functional impairment, it would seem appropriate to classify such patients as partial responders and to institute additional treatment.

Assessment of the Patient with Treatment-Resistant Obsessive-Compulsive Disorder

A thorough clinical assessment of patients with treatment-resistant OCD is the first step in planning possible interventions. All DSM-IV-TR (American Psychiatric Association 2000) axes should be thoroughly evaluated. In addition, the OCD symptoms themselves should be carefully assessed. Certain OCD symptoms may, for example, be more refractory to pharmacotherapy or psychotherapy. Thus, there is some evidence that hoarding is more likely than other OCD symptoms to fail to respond to treatment (Black et al. 1998). Similarly, obsessional slowness may predict poor response to both pharmacotherapy and psychotherapy (Veale 1993).

Comorbid Axis I Diagnoses

On Axis I, it is particularly important to consider the presence of any comorbid disorders. The presence of comorbid melancholic depression argu-

ably suggests that clomipramine will be more effective than the more selective SRIs (Hollander et al. 1991; Roose et al. 1994). Comorbid anxiety disorders such as social phobia may suggest the need for medications (e.g., monoamine oxidase inhibitors [MAOIs]) that are not used as first-line agents in OCD (Carrasco et al. 1992). Subtle psychotic symptoms may have been overlooked but may nevertheless require specific antipsychotic treatments. Comorbid substance abuse similarly may not respond to standard anti-OCD treatments and may continue to exacerbate the disorder.

Comorbid Axis II Diagnoses

Patients with OCD not infrequently have comorbid Axis II conditions (Baer et al. 1992). Several personality disorders have been associated with a relatively poor outcome of OCD to standard psychotherapy and pharmacotherapy, and total number of abnormal personality disorder traits has been associated with worse outcome in some studies. Although comorbid personality disorder traits may also respond during standard anti-OCD management, they may necessitate the use of specific interventions other than anti-OCD treatments. For example, comorbid borderline personality disorder may require intensive psychotherapeutic interventions focused on interpersonal relationships (Hermesh et al. 1987). Patients with comorbid schizotypal personality disorder may require pharmacotherapeutic interventions that focus not only the serotonin system but also on the dopamine system (Jenike et al. 1986).

Comorbid Medical Problems

We have already mentioned the importance of ruling out general medical disorders that may account for the pathogenesis of OCD. It is also important to assess patients with OCD for the presence of comorbid tics; these predict relatively poor response to SRIs (McDougle et al. 1993). Finally, it may be useful, particularly in children and adolescents, to inquire into the temporal relationship between OCD and streptococcal infections (Swedo et al. 1998) to determine whether the patient belongs to the subgroup of OCD sufferers with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). This group of patients may respond to specific immune therapies (see below).

Psychosocial Stressors

Psychosocial factors in the pathogenesis of OCD have received relatively short shrift in recent decades. Nevertheless, there is literature documenting exacerbation of OCD symptoms in response to stressors. In addition,

the principles of behavioral theory suggest that family members may play a role in exacerbating OCD symptoms by helping the patient reduce exposure to feared stimuli. Thus, a careful evaluation of ongoing stressors in the patients' lives as well as of their families' responses to these stressors is crucial (see also Chapter 9). For patients with children, it is also important to inquire about the impact of OCD symptoms on the children.

Pharmacotherapy Augmentation

Several different approaches to pharmacotherapy augmentation have been undertaken in OCD. These include augmentation with serotonergic agents, dopaminergic agents, and various other agents as well as alternative forms (e.g., increased doses) or routes (e.g., intravenous administration) of SRI administration.

Serotonergic Augmentation

Although there is no evidence that serotonergic dysfunction exists in OCD, several studies have demonstrated that SRIs are selectively effective in the treatment of this disorder (Zohar and Insel 1987). Furthermore, a range of data, including that of reduction of the serotonin metabolite 5-hydroxyindoleacetic acid in cerebrospinal fluid during successful SRI treatment of OCD (Thoren 1980) and of exacerbation of OCD symptoms by administration of serotonin agonists such as m-chlorophenylpiperazine or sumatriptan (Zohar and Insel 1987), suggests the importance of serotonin in mediating OCD symptoms.

Thus, several augmentation strategies in OCD rely on the addition of a second serotonergic agent to an SRI. Fenfluramine, a serotonin releaser and reuptake inhibitor, has been found to be effective in open trials but can no longer be recommended because of possible adverse cardiologic effects. Similarly, tryptophan, a precursor of serotonin, is no longer available for augmentation purposes because of safety concerns. Buspirone, a serotonin-1A agonist, has been effective in open studies but again seems relatively inadvisable in view of negative controlled studies.

An interesting recent idea is to add a low dose of clomipramine to an SSRI or vice versa. This runs the risk of increasing clomipramine to dangerous levels, however, and therefore requires careful monitoring of drug levels and electrocardiographic effects (Szegedi et al. 1996). Nevertheless, in a large recent trial, addition of sertraline to clomipramine 150 mg was more effective and more tolerable than increasing the dose of clomipramine to 250 mg (Ravizza et al. 1996).

Dopaminergic Augmentation

Several theoretical rationales exist for the addition of a dopaminergic agent to an SSRI. First, dopamine agonists may exacerbate stereotypies in animal models or OCD symptoms in humans (Goodman et al. 1990). Second, many patients with OCD have tics, and there is substantial evidence that OCD and Tourette's syndrome (for which dopamine blockers are useful) have overlapping neurobiologic underpinnings, perhaps at the genetic level (Pauls et al. 1986). Finally, there are important interactions between the dopamine and serotonin systems (Kapur and Remington 1996). Certainly, the presence of tics in patients with OCD predicts lower rates of response to SSRIs (McDougle et al. 1993). Furthermore, a controlled study found that haloperidol, a typical antipsychotic agent with dopamine-blocking effects, was significantly more effective than placebo in the augmentation of an SSRI. Notably, haloperidol was most effective in patients with comorbid tics (McDougle et al. 1994). Dosing is typically begun at 0.5 mg and increased every 4–7 days to a maximum of 2–4 mg/day as clinically indicated (McDougle 1997). The introduction of the atypical antipsychotics, which have a superior side effect profile, raises the question of whether these agents are useful in the augmentation of SRIs in treatment-resistant OCD.

Several open trials have in fact provided evidence for the efficacy of low doses of risperidone (0.5–1.0 mg twice daily) (McDougle et al. 1995; Stein et al. 1997), and other atypicals may also be useful (Potenza et al. 1998). Patients should be carefully monitored for the emergence of side effects such as depression. Interestingly, to date it is not clear that positive response to risperidone augmentation requires the presence of comorbid tics. Clozapine, although an atypical antipsychotic, is not recommended for use for this indication because it runs the risk of agranulocytosis. Some case reports have shown an exacerbation of obsessive-compulsive symptoms with clozapine (Hwang et al. 1993), although not all studies are consistent in this regard (Ghaemi et al. 1995). SRIs with atypical antipsychotics may also be useful in putative obsessive-compulsive spectrum disorders, such as Tourette's syndrome and trichotillomania (Hawkridge et al. 1996; Stein et al. 1997).

Case Example

A 34-year-old man presented with OCD (primarily hand-washing compulsions) that was unresponsive to several trials of SRIs (including clomipramine) of adequate dose and duration. There was no history of tics, but the patient's father had multiple motor and vocal tics. Risperidone, 1 mg/day was added to his regimen of fluvoxamine 300 mg/day. After 2 weeks,

the patient reported a decrease in OCD symptoms, and this clinical improvement continued for the next several weeks. Some increase in sedation also occured, which was helped by taking the risperidone late at night.

Alternative Strategies

To date, double-blind studies with buspirone and lithium augmentation in patients with treatment-resistant OCD have had negative results despite encouraging open studies (Pigott et al. 1991, 1992). Controlled trials with pindolol augmentation have also not been uniformly positive (Mundo et al. 1998). Several other agents have been found useful in anecdotal reports or small open trials of SRI augmentation in treatment-resistant OCD, including aminoglutethimide, clonazepam, and gabapentin (Chouinard et al. 1996; Leonard et al. 1994). Tramadol, an opioid, may be a particularly promising agent (Shapira et al. 1997). However, in the absence of positive controlled trials, such augmentation strategies cannot be recommended unreservedly unless the patient with OCD also has a comorbid disorder for which these strategies have been demonstrated to be useful (e.g., lithium augmentation in OCD with comorbid depression).

There is growing evidence that intravenous clomipramine may be useful in patients with OCD who cannot tolerate or who fail to respond to oral SRIs (Fallon et al. 1998; Koran et al. 1997). It is possible that intravenous dosing allows first-pass hepatic metabolism to be bypassed, thus resulting in higher blood levels of the active metabolite. Nevertheless, use of intravenous clomipramine has mostly been confined to research centers, and careful cardiologic monitoring during infusions of the medication would seem advisable. Once the patient has responded to intravenous clomipramine (e.g., 14 infusions, starting at 25 mg/day and increasing to 250 mg/day), he or she can be converted to oral dosing (see also Chapter 2).

Similarly, although the use of megadoses of SRIs does not strictly fall within the category of augmentation, there are anecdotal reports that the use of very high doses can be effective in the treatment of some patients (Bystritsky et al. 1996). The efficacy and safety of these kinds of dosing strategies have not, however, been documented in controlled trials. Such research does seem warranted.

Psychotherapy Augmentation

Exposure and response prevention therapy may be augmented in several ways. It may be helpful, for example, for therapists to expose themselves

to the feared stimulus as well (i.e., participant modeling). Similarly, exposure and response prevention sessions may need to occur outside of the consulting office to obtain maximal effect. Self-help books and portable computer programs may also be valuable in promoting adherence to exposure and response prevention programs.

There may be a need for specialized or creative exposure techniques to deal with less usual forms of OCD such as obsessional slowness, lack of overt rituals, or hoarding. Such symptoms may predict a poor outcome in response to standard forms of behavioral therapy. Referral to a specialist may be useful. For example, prompting and shaping may be helpful for patients with obsessional slowness. Patients who present with obsessions and neutralizing thoughts but without overt rituals may require a variety of techniques, such as thought stopping (a distracting technique aimed at interrupting obsessions), saturation (repeating obsessions until associated distress lessens), or stimulus control (confining obsessions to a specified amount of time).

There has recently been a focus on psychotherapeutic interventions other than exposure and response prevention in the treatment of OCD. In particular, cognitive therapy techniques may be useful in some patients (Salkovskis 1985). More cognitively based interventions may perhaps be useful in patients with exaggerated responsibility, unrealistic threat appraisal, and other cognitive distortions (Salkovskis 1985). Nevertheless, the extent to which such techniques are useful in patients who have failed to respond to standard behavioral therapy is not clear. Again, referral to a practitioner experienced in cognitive and behavioral therapy should be strongly considered for patients with apparently refractory OCD.

As suggested earlier, it is possible that for exposure and response prevention techniques to succeed, family intervention must also take place. Family members need psychoeducation about the nature of the disorder, they need to be instructed not to become involved in the patient's rituals, and they need information about how best to "coach" patients in exposure exercises. Ongoing meetings with the family may be needed to ensure compliance of all parties with exposure homework (see Chapter 9).

Case Example

A 48-year-old man presented with a two-decade history of excessive hand washing and cleaning of the bathroom. There was only minimal response to a trial of a SRI. During treatment it was revealed that his wife was an extreme perfectionist, and although she did not appear to suffer from clinical OCD, throughout their marriage she had in fact encouraged his rituals. For example, she had been unwilling to have pets in the house,

for fear that they would cause mess. The patient only began to improve after his wife was persuaded to come into the therapy and to change her expectations.

A useful form of psychotherapy augmentation is the referral of the patient to a consumer advocacy organization such as the Obsessive Compulsive Foundation (OCF) and to internet sites (e.g., www.ocfoundation.org) or mailing lists (e.g. ocd-l@vm.marist.edu) devoted to OCD (Stein 1997) A survey of one such mailing list found that most subscribers were extremely satisfied with the quality of information and the level of support that they had received. We know of many patients who have found such support groups (real and virtual) extremely valuable in furthering their treatment.

Psychotherapy may be augmented by partial or full hospitalization. In some patients, rituals may be present only within certain environments (e.g., their own house). However, for many patients, hospitalization allows an intensive focus on exposure and response prevention. A multidisciplinary approach, with input from psychology, nursing, and occupational therapy, may provide the necessary momentum to successfully complete behavioral therapy. Several authors have documented the success of their intensive programs in the management of treatment-refractory OCD (Byerly et al. 1996; Drummond 1993).

Alternative Interventions

Other Medications

There is a good deal of evidence that OCD is a heterogenous disorder (Baer 1994). Not only do various kinds of symptoms seem to cluster together, but different phenomenologic subtypes of OCD also may be characterized by specific and contrasting neurobiologic underpinnings. Findings that not all patients respond to serotonergic pharmacologic challenges in the same way (Zohar and Insel 1987) and that SRIs are effective in only a proportion of patients (Stein et al. 1995), together with research on the role of other neurotransmitters in OCD, suggest that agents other than the SRIs perhaps should also be considered for patients with refractory OCD.

Monoamine Oxidase Inhibitors

There are several anecdotal reports of patients with OCD responding to MAOIs. Nevertheless, controlled trials are conflicting; one trial showed equal efficacy with an SRI, whereas another trial failed to show any benefit

over placebo (Jenike et al. 1997; Vallejo et al. 1992). In general, we suggest that irreversible MAOIs may be worth considering in patients who have failed to respond to multiple medication interventions.

Newer Antidepressants

Several of the newer antidepressants with some serotonergic activity may also be worth considering in treatment-refractory OCD. Nefazodone has been reported to be effective in some patients with OCD, but no controlled trials support its use. Venlafaxine has been demonstrated to be useful in treatment-refractory depression, and there are reports that it may also be useful in some patients with treatment-refractory OCD (Ananth et al. 1995). Further controlled trials on this agent seem warranted.

Antiandrogens

Antiandrogens have been suggested by some researchers as effective in OCD (Casas et al. 1986). However, no controlled trials currently support this intervention. Although some authors have suggested that OCD has a low placebo response rate, given that controlled trials in this disorder often have not supported preliminary open data, we recommend caution for all interventions that have not been studied using rigorous designs.

Inositol

Inositol is a glucose precursor that was found useful in a controlled crossover design in 15 patients with OCD (Fux et al. 1996). Interestingly, inositol has proven useful in several mood and anxiety disorders (e.g., panic, major depression), but not in several other disorders (Levine 1997). Its mechanism of action remains uncertain, but presumably it acts on the second messenger pathway. We treated 10 patients with OCD, each of whom had failed several previous SRI trials, with inositol augmentation of their current SRI (Seedat and Stein, unpublished data). Unfortunately, only a minority responded, suggesting that response to inositol may be superior in treatment-naïve patients with OCD.

Immune Suppressors

Another group of agents currently under study for OCD are those that act on the immune system (Swedo et al. 1998). In particular, such interventions are being researched in patients who demonstrate post–streptococcal infection autoimmune neuropsychiatric disorders. Ultimately, this work may suggest new ways of intervening with particular subgroups of patients with treatment-resistant OCD. At present, however, such interventions remain experimental.

Electroconvulsive Therapy and Transcranial Magnetic Stimulation

There is little evidence that electroconvulsive therapy (ECT) is effective for OCD. However, ECT can be considered for patients with a severe comorbid major depression that proves unresponsive to standard pharmacotherapies. Ongoing research on transcranial magnetic stimulation in OCD may ultimately provide a new method of treatment.

Neurosurgery

The neuroanatomy of OCD has become increasingly well understood in recent years. Early evidence for basal ganglia involvement in OCD emerged during the influenza epidemic at the start of the twentieth century, when patients with postencephalitic parkinsonism were documented to have OCD symptoms. More recently, several structural brain imaging studies have suggested basal ganglia abnormalities in OCD. Finally, functional imaging studies have now clearly documented corticostriatal dysfunction in OCD, with subsequent normalization after both pharmacotherapy and behavioral therapy (Baxter et al. 1992).

The rationale for neurosurgery is to interrupt the corticostriatal circuits thought to be crucial in mediating OCD symptoms. Several different surgical procedures have been described (e.g., cingulotomy, anterior capsulotomy); these are under active study at a number of specialized centers in the United States, Sweden, and elsewhere (Jenike 1998). Although not a panacea, neurosurgery appears worth considering in patients with severe OCD who have not responded to more conventional treatments.

Summary

Treatment-resistant OCD provides an important challenge for clinicians and researchers. For clinicians, OCD can at times be an intractable illness. Nevertheless, there is a growing number of management options, including both pharmacotherapy and psychotherapy augmentation, alternative strategies such as intravenous clomipramine, and alternative interventions including agents other than the SRIs and neurosurgery.

For researchers, treatment-resistant OCD underscores the complexity of this illness and raises questions about the biologic heterogeneity of the disorder. How are the subtypes of OCD best defined? What is the relationship between phenomenologic heterogeneity and underlying neurobiologic mechanisms? Ultimately, the investigation of such heterogeneity will, it is hoped, lead to improvements in the treatment options for this intriguing disorder.

References

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revision. Washington, DC, American Psychiatric Association, 2000

Ananth J, Burgoyne K, Smith M, et al: Venlafaxine for treatment of obsessive-compulsive disorder. Am J Psychiatry 152:1832, 1995

Baer L: Factor analysis of symptom subtypes of obsessive-compulsive disorder and their relation to personality and tic disorders. J Clin Psychiatry 55S:18–23, 1994

Baer L, Jenike MA, Black DW, et al: Effects of axis II diagnoses treatment outcome with clomipramine in 55 patients with obsessive-compulsive disorder. Arch Gen Psychiatry 49:862–866, 1992

Baxter LR, Schwartz JM, Bergman KS, et al: Caudate glucose metabolic rate changes with both drug and behavior therapy for OCD. Arch Gen Psychiatry 49:681–689, 1992

Black DW, Monahan P, Gable J, et al: Hoarding and treatment response in 38 nondepressed subjects with obsessive-compulsive disorder. J Clin Psychiatry 59:420–425, 1998

Byerly MJ, Goodman WK, Christensen R. High doses of sertraline for treatment-resistant obsessive-compulsive disorder. Am J Psychiatry 153:1232–1233, 1996

Bystritsky A, Munford PR, Rosen RM, et al: A preliminary study of partial hospital management of severe obsessive-compulsive disorder. Psychiatr Serv 47:170–174, 1996

Carrasco JL, Hollander E, Schneier FR, et al: Treatment outcome of obsessive compulsive disorder with comorbid social phobia. J Clin Psychiatry 53:387–391, 1992

Casas M, Alvarez E, Duro P, et al: Antiandrogenic treatment of obsessive-compulsive neurosis. Acta Psychiatr Scand 73:221–222, 1986

Chouinard G, B'elanger MC, Beauclair L, et al: Potentiation of fluoxetine by aminoglutethimide, an adrenal steroid suppressant, in obsessive-compulsive disorder resistant to SSRIs: a case report. Neuropsychopharmacol Biol Psychiatry 20:1067–1079, 1996

Cummings JL, Cunningham K: Obsessive-compulsive disorder in Huntington's disease. Biol Psychiatry 31:263–270, 1992

Drummond LM: The treatment of severe, chronic, resistant obsessive-compulsive disorder: an evaluation of an in-patient programme using behavioural psychotherapy in combination with other treatments. Br J Psychiatry 163:223–229, 1993

Fallon BA, Liebowitz MR, Campeas R, et al: Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. Arch Gen Psychiatry 55:918–924, 1998

Fux M, Levine J, Aviv A, et al: Inositol treatment of obsessive-compulsive disorder. Am J Psychiatry 153:1219–1221, 1996

Ghaemi SN, Zarate CA Jr, Popli AP, et al: Is there a relationship between clozapine and obsessive-compulsive disorder? A retrospective chart review. Compr Psychiatry 35:267–270, 1995

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part I: development, use, and reliability. Arch Gen Psychiatry 46:1006–1011, 1989a

Goodman W, Price L, Rasmussen S, et al: The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), part II: validity. Arch Gen Psychiatry 46:1012–1016, 1989b

Goodman WK, McDougle CJ, Price LH, et al: Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? J Clin Psychiatry S51:36–43, 1990

Greist JH, Chouinard G, DuBoff E, et al: A double-blind comparison of three doses of sertraline in outpatients with OCD. Arch Gen Psychiatry 52:289–295, 1995a

Greist JH, Jefferson J, Koback K, et al: Efficacy and tolerability of serotonin transporter inhibitors in OCD: a meta-analysis. Arch Gen Psychiatry 52:53–60, 1995b

Hawkridge S, Stein DJ, Bouwer C: Combining neuroleptics with serotonin specific reuptake inhibitors in Tourette's syndrome (letter). J Am Acad Child Adolesc Psychiatry 35:703–704, 1996

Hermesh H, Shahar A, Munitz H: Obsessive-compulsive disorder and borderline personality disorder. Am J Psychiatry 144:120–121, 1987

Hollander E, Mullen L, DeCaria CM, et al: Obsessive compulsive disorder, depression, and fluoxetine. J Clin Psychiatry 52:418–422, 1991

Hwang MY, Stein DJ, Simeon D, et al: Clozapine, obsessive symptoms, and serotonergic mechanisms. Am J Psychiatry 150:1435, 1993

Jenike MA: Neurosurgical treatment of obsessive-compulsive disorder. Br J Psychiatry 35(suppl):79–80, 1998

Jenike MA, Baer L, Minichiello WE, et al: Concomitant obsessive-compulsive disorder and schizotypal personality disorder. Am J Psychiatry 143:530–532, 1986

Jenike MA, Baer L, Minichiello WE, et al: Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry 154:1261–1264, 1997

Kapur S, Remington G: Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 153:466–476, 1996

Koran LM, Sallee FR, Pallanti S: Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. Am J Psychiatry 154:396–401, 1997

Leonard HL, Topol D, Bukstein O, et al: Clonazepam as an augmenting agent in the treatment of childhood-onset obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 33:792–794, 1994

Levine J: Controlled trials of inositol in psychiatry. Eur Neuropsychopharmacol 7:147–155, 1997

March JS, Frances A, Carpenter D, et al (eds): Treatment of obsessive-compulsive disorder. J Clin Psychiatry S4:1–72, 1997

McDougle CJ: Update on pharmacological management of OCD: agents and augmentation. J Clin Psychiatry S58:11–17, 1997

McDougle CJ, Goodman WK, Leckman JF, et al: The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder. J Clin Psychopharm 13:354–358, 1993

McDougle CJ, Goodman WK, Leckman JF, et al: Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder: a double-blind placebo-controlled study in patients with and without tics. Arch Gen Psychiatry 51:302–308, 1994

McDougle CJ, Fleischmann RL, Epperson CN, et al: Risperidone addition in fluvoxamine-refractory obsessive-compulsive disorder: three cases. J Clin Psychiatry 56:526–528, 1995

Mundo E, Guglielmo E, Bellodi L: Effect of adjuvant pindolol on the antiobsessional response to fluvoxamine: a double-blind, placebo-controlled study. Int Clin Psychopharmacol 13:219–224, 1998

Pauls DL, Towbin KE, Leckman JF, et al: Gilles de la Tourette's and obsessive compulsive disorder: evidence supporting a genetic relationship. Arch Gen Psychiatry 43:1180–1182, 1986

Pigott TA, Pato MT, Bernstein SE, et al: Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 47:926–932, 1990

Pigott TA, Pato MT, L'Heureux F, et al: A controlled comparison of adjuvant lithium carbonate or thyroid hormone in clomipramine-treated OCD patients. J Clin Psychopharmcol 11:242–248, 1991

Pigott TA, L'Heureux F, Hill JL, et al: A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated OCD patients. J Clin Psychopharmacol 12:11–18, 1992

Potenza MN, Wasylink S, Longhurst JG, et al: Olanzapine augmentation of fluoxetine in the treatment of refractory obsessive-compulsive disorder. J Clin Psychopharmacol 18:423–424, 1998

Ravizza L, Barzega G, Bellino S, et al: Therapeutic effect and safety of adjunctive risperidone in refractory obsessive-compulsive disorder (OCD). Psychopharmacol Bull 32:677–682, 1996

Roose SP, Glassman AH, Attia E, et al: Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry 151:1735–1739, 1994

Salkovskis P: Obsessional-compulsive problems: a cognitive-behavioral analysis. Behav Res Ther 23:571–583, 1985

Shapira NA, Keck PE Jr, Goldsmith TD, et al: Open-label pilot study of tramadol hydrochloride in treatment-refractory obsessive-compulsive disorder. Depress Anxiety 6:170–173, 1997

Stein DJ: Psychiatry on the internet: survey of an OCD mailing list. Psychiatr Bull 21:95–98, 1997

Stein DJ, Hollander E: The spectrum of obsessive-compulsive related, in Obsessive-Compulsive Related Disorders. Edited by Hollander E. Washington, DC, American Psychiatric Press, 1993

Stein DJ, Spadaccini E, Hollander E: Meta-analysis of pharmacotherapy trials for obsessive compulsive disorder. Int Clin Psychopharm 10:11–18, 1995

Stein DJ, Bouwer C, Hawkridge S, et al: Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. J Clin Psychiatry 58:119–122, 1997

Swedo SE, Leonard HL, Garvey M, et al: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 146:264–271, 1998

Szegedi A, Wetzel H, Leal M, et al: Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. J Clin Psychiatry 57:257–264, 1996

Thoren P, Åsberg M, Bertilsson L, et al: Clomipramine treatment of obsessive-compulsive disorder, II: biochemical aspects. Arch Gen Psychiatry 37:1289–1294, 1980

Vallejo J, Olivares J, Marcos T, et al: Clomipramine versus phenelzine in obsessive-compulsive disoder, a controlled clinical trial. Br J Psychiatry 161:665–670, 1992

Veale D: Classification and treatment of obsessional slowness. Br J Psychiatry 162:198–203, 1993

Zohar J, Insel TR: Obsessive-compulsive disorder: psychobiological to diagnosis, treatment, and pathophysiology. Biol Psychiatry 22:667–687, 1987

This page intentionally left blank

Page numbers printed in **boldface** type refer to tables or figures.

CONTENTS

ISBN 0-88048-779-8

9 780880 487795 59000

CLINICAL PRACTICE
Judith H. Gold, M.D., F.R.C.P.C.
Elissa P. Benedek, M.D.
Series Editors

American Psychiatric Publishing, Inc.