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Cannabis – 1988

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ABSTRACT – In this updating review of research on cannabis particular attention has been paid to the increasing number of studies of the disposition of the components of cannabis in man, as well as possible effects on health. Specific binding sites for cannaboids have not been demonstrated. Approximately 80 metabolites of tetrahydrocannabiol (THC) have been discovered, of which 11-OH-THC is the main metabolite, but it contributes little to the overall effect when the drug is smoked or given intravenously. The minimum plasma level of THC associated with the psychotropic effect is 25 ng/ml.

Cannabis may produce directly an acute panic reaction, a toxic delirium, and acute paranoid state, or acute mania. Cannabis use may aggrevate schizophrenia, but it is much less certain whether it can lead to sociopathy or even to "amotivational syndrome". Despite widespread use of cannabis in virtually all parts of the world, no catastrophic effects on health have been noted. Cannabis appears to be relatively safe as compared with current social drugs. It is, however, still too early in the history of the present episode of cannabis use to be sanguine about possible bad effects.

A previous review of cannabis in 1974 brought matters regarding this social drug up to date (1). The purpose of the present review will be to assess the state of cannabis 14 years later. Particular attention will be paid to the increasing number of studies of the disposition of the components of cannabis in man as well as possible effects of the drug on health.

Source and chemistry

The collective name given to the terpenes found in cannabis is *cannabinoids*. Most of the naturally-occurring cannabinoids have now been identified. Three, cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC), and cannabinol (CBN) are the most abundant. The steps from CBD to THC to CBN represent the biosynthetic pathway in the plant. TCH is an optically active resinous material which is very lipid soluble and water-insoluble. These physical properties make pharmacological investigations difficult as various nonpolar solvents must be used (2).

Much more activity has been evident in chemical laboratories, where a variety of synthetic cannabinoids have been developed to exploit potentially useful pharmacological actions for therapeutic purposes. Ring modifications include removal of the methyl group and substitution of hydroxy or ketone groups and addition of substituents at C1. Side-chain variants include alkyl-substituted and oxygensubstituted compounds. Noncannabinoid phenanthrenes and phenanthridines have also been made. Most of these compounds have been synthesized as possible analgesics. One synthetic cannabinoid, nabilone, has been introduced as therapy for nausea and vomiting associated with cancer chemotherapy. THC itself has also been marketed for such use. Levonantradol has been under investigation for a variety of potential uses (3).

Attempts to modify the psychoactivity of can-

nabis by various chemical interventions on the part of users have been generally unsuccessful. The practice of soaking marijuana in formaldehyde, which leads to a product called AMP, may have changed the characteristics of intoxication. Smoking AMP causes more thought disorder, psychomotor retardation and clouded sensorium, as well as elevated blood pressure, rigidity and myoclonus than experienced with usual marijuana. The exact chemical contributions to these new actions are unknown (4).

Patterns of use

From the period of the late 1960s until a decade later, a remarkable increase in the use of cannabis was noted in many epidemiological surveys (5). However, during the last decade, use has shown only a slight increase overall with signs of decreasing use during the past several years.

Although perhaps 30 to 40 million persons in the US (and representative numbers in other countries) have tried cannabis, the rate of use varies considerably. Some persons use the drug only occasionally while others use it several times a day. Occasional use is still much more frequent than daily use. Even frequent users tend to reduce consumption over time (6).

Attempts to predict which young people will use cannabis have come up with a variety of predictors. Parents of users are less warm and supportive and tend to abuse drugs themselves. Peer and sibling influence is critical. Users tend to be somewhat alienated, higher on anxiety, poor school performers and tend toward greater use of alcohol and other drugs (7). Between 50 and 70% of 16–17 year old blacks in a Chicago ghetto had tried cannabis or hard liquor. Boys rather than girls used substances at an earlier age. Those who performed better on first-grade IQ and readiness tests started use at an earlier age. Girls who were rated by their teachers as shy or having learning problems initiated use at a later age (8). Peer influence was the strongest predictor. Users were also less likely to attend religious services, much more likely to miss school, and to be orientated towards their peers rather than their family (9). What emerges is that peer influence has much to do with attitudes towards drug use as it does with other aspects of life of adolescents.

Mechanism of action

The mechanism of action of psychoactive cannabinoids is still uncertain. In general, it is worth noting that cannabinoids have a multiplicity of actions which involve a number of organ systems. However, with the exception of the central nervous system, these actions may be due to an indirect action on the innervation of the organ rather than on the organ itself. In the brain, the action is more direct. **Another aspect of cannabinoids is that they have remarkably low toxicity. Lethal doses in man are unknown (10).**

A number of studies have indicated that the primary mode of action of psychoactive cannabinoids is through an interaction with lipid components of cell membranes. For instance, both THC and 11-OH-THC increase the fluidity of synaptic plasma membranes as tested by a fluorescence probe. At the same concentrations, CBD, CBN and other inactive cannabinoids have no such effect. Such evidence supports a membrane perturbant hypothesis of the mechanism of action (11). Although specific binding sites for cannabinoids have been suggested, whether or not these are true receptors has been open to much question (12). Another possibility has been that cannabinoids may act by increasing synthesis of prostaglandins. However, little difference has been shown between psychoactive and non-psychoactive cannabinoids in this regard (13).

THC and CBD, but not CBN, inhibit calcium uptake by brain synaptosomes, possibly by a direct effect in calcium channels. However, this action may be more relevant to the anticonvulsant actions than to the psychoactive effects (14). Regional cerebral blood flow, measured by the radiolabeled xenon technique, was decreased by 11% in heavy users of cannabis as compared with an age- and sex-matched non-using group. Such diminished blood flow was reversible when drug use was stopped. However, it is not likely that reduced blood flow accounts for the psychoactivity; rather, it may simply reflect a decreased level of brain function among chronic users (15).

Metabolism and kinetics: animals

In vitro metabolism of CBD by rat liver produced a variety of monohydroxylated and dioxygenated metabolites involving both the ring, a portion of the molecule as well as the side chain (16). No in situ metabolism of THC by rat brain was found (17). Metabolism of THC by the perfused dog lung revealed a number of hydroxylated metabolites. Liver microsomal metabolism produced additional side chain hydroxylated metabolites (18). Glucuronide metabolites of several cannabinoids were found in liver extracts of mice treated with the cannabinoids. CBD and CBN showed more extensive glucuronidation than THC (19).

The kinetics of THC in dogs was determined after intravenous injection of 14C-labeled THC. A biphasic disappearance from plasma was observed. Metabolites were totally and rapidly eliminated in the bile and urine with 10–15% undergoing enterohepatic circulation (20).

Metabolism: man

More than a decade of metabolic studies following identification of 11-OH-THC as the primary THC metabolite have now discovered approximately 80 metabolites of THC. "Primary" metabolites have usually been identified from *in vitro* experiments and have undergone one or two metabolic reactions, usually involving hydroxyl groups. Metabolites excreted in urine have often undergone several metabolic reactions.

About 2/3 of a dose is eliminated in feces and about 1/3 in urine, all as metabolites. Elimination is slow (21). The metabolite pattern in urine is more complex than feces, with 18 non-conjugated metabolites being excreted following oral ingestion of THC. The most abundant is delta-9-THC-lloic acid. This acid group at the 11-position may be combined with acidification or hydroxylation of the side-chain to yield multiple metabolites (22).

Following intravenous administration of radiolabeled THC in man, the 11-hydroxy metabolite and the 8-beta-hydroxy metabolite existed at about 10% of the concentration of THC itself. After oral administration the amount of 11-hydroxy metabolite is about equal to the amount of unchanged THC (23).

Because CBD and CBN lack appreciable psychoactivity, their metabolism has been less well studied. In general, the metabolic routes are similar to those of THC with 11-hydroxy metabolites being most abundant (24).

The psychoactivity of various cannabinoids and their metabolites has been systematically studied. The delta-8 isomer of THC has about 75% the activity of the delta-9 isomer. Whether this isomer occurs in nature is questionable. Side-chain variants of THC, such as tetrahydrocannabivarin, which has a three-carbon side chain, show approximately 25% the activity of THC. Delta-6a-THC, which has the double bond in a slightly different position, is only about 30% as active as THC; the same is true for its six-carbon side chain homolog, synhexyl. Among metabolites, 11-hydroxy-THC is somewhat more active, having about 120% of the activity of THC. The 8a- and 8b-hydroxy-THC metabolites have activity 20–25% of the parent compound (25). When given orally in substantial doses, neither CBN nor CBD show activity. An intravenous infusion of 18 mg of CBN showed definite activity, although only 10% that of THC itself (24). In general, psychoactivity is found only in compounds with THC-like structures.

One assumes that intravenous administration of THC, which can only be done under experimental conditions, affords total bioavailability. During smoking, bioavailability is limited by pyrolysis, loss through side stream smoke, less than total absorption through the lung, and possibly a small amount of metabolism in the lung. After oral administration, one would expect considerably less availability, not only due to degradation in the gut but also "first-pass" metabolism in the liver.

The systemic availability of smoked THC varies widely depending upon the expertise of the smoker. In a mixed group of smokers, it ranged between 8 and 24% (26). However, among heavy users the range was between 5 and 56%. Light users, as expected, showed a lower efficiency in delivering a dose, with bioavailability ranging between 2 and 22% (27, 28). THC administered orally in a chocolate cookie showed a mean availability of 8%, roughly one-third that from smoking. On the other

nd, when administered in an oily solution, bioailability increased to between 10 and 20%.

Following intravenous administration, plasma oncentrations rise quickly reaching about 22 g/ml three minutes after termination of the infuon. THC concentrations decline rapidly to about 5 ng/ml at 1 hour and about 3 ng/ml at 4 hours, resumably mostly due to distribution rather than etabolism. The usual symptoms of intoxication re almost completely gone by 3 hours (26). The urve of plasma concentration of THC following moking is parallel to that following intravenous dministration with about one-half the concentraions. THC is absorbed slowly and unreliaby from he gut after oral administration. Most subjects ave plasma peaks between 1 and 2 hours after ngestion. Peak concentrations are considerably ower than following smoking.

Although heavy users of marijuana tend to attain higher plasma concentrations following smoking than do light users, the difference must reside in more efficient smoking. The rates of disappearance are about the same, indicating little evidence of induction of drug metabolizing enzymes (28). Very little difference was found in the disappearance rates for THC in plasma between men and women (29).

The volume of distribution of THC is estimated to be about 10 l/kg (30). Such a large apparent volume is characteristic of a highly lipophilic drug. The high plasma clearance value is close to the hepatic blood flow of 800 ml/min. Some THC is bound to erythrocytes but the majority is bound to lipoproteins (31).

The active metabolite, 11-hydroxy-THC, probably contributes little to the overall effect of the drug when it is smoked or given intravenously. Under those conditions only about 10% of THC is in the form of the metabolite. After oral administration, the proportion of metabolite is equal to or may exceed that of THC itself, and thus contributes substantially to the effect. Qualitatively, the intoxication produced by the metabolite is identical to that of THC (29).

Urinary excretion of cannabinoid metabolites can be extremely long following discontinuation of smoking. Under strictly supervised abstinence, 86 chronic users showed a mean excretion time of 27 days for metabolites measured semi-quantitatively by the EMIT technique. Some subjects required as long as 77 days before urines became negative (as defined by the test) for 10 consecutive days. Sporadic episodes of positive urines were interspersed with episodes in which excretion was negative (32).

Passive inhalation of sidestream smoke from 4 and 16 marijuana cigarettes was studied in 5 subjects exposed for 1 h each day for 6 consecutive days. Subjective effects from exposure to 16 cigarettes were similar to those from smoking a single cigarette. Daily mean plasma concentrations of THC ranged from 2.4 to 7.4 ng/ml and some urines as measured by the EMIT test were positive (33).

Six smokers and 4 non-smokers of cannabis were placed in a small room while the smokers consumed a marijuana cigarette. No cannabinoids were found in the blood of those passively exposed for as long as 3 hours after exposure. However, urine samples were positive for cannabinoids up to 6 hours after passive exposure. Thus, urine tests may be falsely positive from passive inhalation (34). Progressively increased exposure to marijuana smoke in a closed environment for 1 hour only rarely produced a positive EMIT urine test and only minute amounts of THC in the plasma (35). These observations would indicate that while passive exposure can lead to mild intoxication and positive urine and blood tests, the degree of exposure to accomplish such results must be great.

The single dose kinetics of deuterium-labeled CBN were evaluated in 6 subjects. Systemic availability of smoked CBN varied between 6 and 65%. The volume of distribution was determinded to be about 50 l/kg. The apparent terminal plasma T1/2 was 32 hours after intravenous infusion and 43 hours after smoking (36). A similar study of single-dose kinetics of deuterium-labeled CBN revealed systemic bioavailability which ranged between 10 and 42% The plasma concentration curves for smoking were similar, but at lower concentrations, to intravenously administered CBD (37).

Drug-testing and forensic issues

Attempts to correlate plasma concentrations of THC with levels of psychomotor impairment

have met with only limited success. During the early stages of intoxication, plasma levels are very high while impairment is just beginning. After a rapid distributive phase, plasma concentrations begin to decline becoming quite low by 3–4 hours after smoking. During the period from 1–4 hours, some correlation can be found between plasma concentrations and impairment (38). The absolute levels associated with impairment are highly variable. One estimate is that only levels of 25 ng/ml or higher would be definitely associated with impairment in every case (39). Such levels would be attained only within 1-2 hours of smoking.

Urine testing is hardly useful for determining impairment. Metabolites are detectable for days to weeks following brief exposures to the drug. Unless urine concentrations were extremely high, it would be hazardous to make judgments regarding impairment. **It must be remembered that many therapeutic and social drugs are probably more likely than cannabis to produce impairment: sedative-hypnotics, opiates, antihistamines, PCP and LSD (40).**

Effect on health

The ambiguity currently surrounding the health hazards of cannabis may be attributed to a number of factors besides those which ordinarily prevail. First, it has been difficult either to prove or to disprove health hazards in man from animal studies. Second, cannabis is still used mainly by young persons in the best of health. Third, cannabis is often used in combination with tobacco and alcohol, among licit drugs, as well as a variety of other illicit drugs. Finally, the whole issue of cannabis use is so laden with emotion that serious investigations of the health hazards of the drug have been colored by the prejudices of the experimenter, either for or against the drug as a potential hazard to health.

Psychopathology

Cannabis may produce directly an acute panic reaction, a toxic delirium, an acute paranoid state, or acute mania. Whether it can directly evoke depressive or schizophrenic states, ore whether it can lead to sociopathy or even to th "amotivational syndrome" is much less certain

A variety of psychotic reactions have bee ascribed to cannabis use. Many are difficult to f into the usual diagnostic classifications. Twent psychotic patients admitted to a mental hospit with high urinary cannabinoid levels were com pared with 20 such patients with no evidence o exposure to cannabis. The former group wa more agitated and hypomanic but showed le affective flattening, auditory hallucination incoherence of speech, and hysteria than the 2 matched control patients. The cannabis patien improved considerably after a week, while th control patients were essentially unchanged (41 Thus, a self-limiting hypomanic-schizophreni like psychosis following marijuana has been do umented.

That cannabis use may aggravate schizo phrenia is beyond any question. Such worsenin followed acutely after use of cannabis by l schizophrenics, despite continued maintenen with antipsychotic drugs. Whether some dire interaction between the two types of drugs involved is questionable (42). Other adverse rea tions encountered among 70 patients in Swede included anxiety reactions, flashbacks, dysphor reactions and abstinence syndromes (43). Depe sonalization occurring both during and after u of cannabis provoked panic attacks and agor phobia in 6 users (44).

An early study, using pneumoencephalogr phy, suggested that young persons who use marijuanna regularly were likely to show bra atrophy. This study has never been confirme using more modern techniques of computerize tomography. Twelve heavy users of cannabis (a average of 1 g/day for over 10 years) were give complete neurological examinations and com puterized tomographic scans. Only one subjec who was also alcoholic, showed any abno malities (45).

Whether chronic use of cannabis changes th basic personality of users so that they becom less impelled to work and to strive for succe has been a vexing question. As with other que tions concerning cannabis use, it is difficult separate consequences from possible causes drug use. One cannot help being impressed

the fact that many promising youngsters change their goals in life drastically after entering the illicit drug culture, usually by way of cannabis.

One of the recurrent lures about social drugs is that they have positive effect on sexual performance and enjoyment. Such a reputation has developed for cannabis. A survey of cannabis users indicated that the majority of men and 40% of women reported enhanced qualtiy of orgasms. Neither the duration nor frequency of intercourse nor the number of orgasms was increased. The sense of touch was reported to be increased (46). What has been termed "chemical foreplay" with marijuana was studied among 1090 college students. Cannabis had no influence on sexual behavior among black students, but white women who used the drug had a more active sex life (47). The paradox is that while occasional use of cannabis in close proximity to sexual relations may have favorable effects, chronic use may actually diminish sexual desire (48).

Effect on driving an automobile

If marijuana is to become an accepted social drug, it would be important to know its effects on driving ability. Fully one-half of the fatal car crashes in the United States are associated with another social drug, alcohol. Neither experimental nor epidemiological approaches to the marijuana question have yet provided definitive answers.

Fifty-nine subjects smoked marijuana cigarettes until "high" and then were tested periodically by highway patrol officers on the roadside sobriety test. Overall, 94% of subjects failed to pass the test 90 min after smoking and 60% after 150 min, despite the fact that by then plasma concentrations of THC were rather low (29).

The exact prevalence of persons who might be picked up while driving under the influence of marijuana is uncertain. One survey found at least 5 ng/ml of THC in the blood specimens of 14.4% of a random sample of 1792 drivers detained for erratic driving. Many were also associated with blood levels of alcohol as well (49).

The incidence of drugs in dead motor vehicle operators was estimated in four separate studies involving 2610 fatalities. Alcohol was present in 1680 cases. THC was present in 351 but in 294 of these it was found in combination with alcohol. Plasma concentrations of THC were less than 5 ng/ml in 278 of these 351 instances. This evidence suggests that at present, THC plays a relatively minor role in fatal traffic accidents as compared with alcohol (50).

Flying an airplane is much more difficult than driving an automobile, but the general principles of impairment are similar. Ten certified pilots who smoked marijuana or placebo were tested on a simulator. The results were highly variable from pilot to pilot and from skill to skill. It was assumed that the pilots had regained full function after 4 h (51). Somewhat contrary results were obtained in another similar study which found, however, some degree of impairment in flying skills as long as 24 h after an exposure to marijuana. The subjects were unaware of any such impairment (52).

Cardiovascular problems

Tachycardia, orthostatic hypotension, and increased blood concentrations of carboxyhemoglobin from cannabis smoking would undoubtedly be deleterious for persons with heart disease due to arteriosclerosis of the coronary arteries or congestive heart failure.

Tachycardia is a consequence of almost every acute dose of cannabis, although some degree of tolerance develops to this effect. Evidence suggests that it is mainly due to an inhibition of vagal tone (53).

Smoking one cigarette containing 19 mg of THC decreased the exercise time until angina by 48%. Smoking a marijuana placebo cigarette decreased the exercise time until angina by only 9%. Thus, smoking marijuana increased myocardial oxygen demand and decreased myocardial oxygen delivery (54).

Clearly, smoking of any kind is bad for patients with angina, but the greater effect of cannabis as compared with tobacco in increasing heart rate makes this drug especially bad for such patients. Fortunately, few angina patients are devotees of cannabis.

Lung problems

Virtually all users of cannabis in North America take the drug by smoking. As inhaling any foreign material into the lung may have adverse consequences, well proven in the case of tobacco, this mode of administration of cannabis might also be suspect. Young, healthy volunteer subjects in a chronic smoking experiment had pulmonary function tests before and after 47 to 59 days of daily smoking of approximately five marijuana cigarettes a day. Decreases were found in forced expiratory volume in 1s, in maximal midexpiratory flow rate in plethysomographic specific airway conductance, and in diffusing capacity. Thus, very heavy marijuana smoking for 6 to 8 weeks caused mild but significant airway obstruction (55).

The issue of damage to lungs from cannabis is somewhat confounded by the fact that many cannabis users also use tobacco. As yet, it is far easier to find pulmonary cripples from the abuse of tobacco than it is to find any evidence of clinically important pulmonary insufficiency from smoking of cannabis.

Endocrine and metabolic effects

Changes in male sex hormones have been a source of controversy ever since the first report of a cannabinoid-induced decrease in serum testosterone level. Decreased levels were associated with morphological abnormalities in sperm and with decreased sexual functioning (56).

A review of literature on this subject concluded that no significant effect was found in regard to serum testosterone and that sperm production was decreased but without evidence of infertility. Ovulation was inhibited, and luteinizing hormone was decreased. Cannabinoids had no evidence of estrogenic activity, which had been postulated earlier (57).

Data on the effects of cannabis on the female reproductive system are sparse. Preliminary unpublished data indicate that women who use cannabis 4 times a week or more have more anovulatory menstrual cycles than do non-users of the same age. Animal work tends to support this observation. THC administered to rats suppressed the cyclic surge of LH secretion and of ovulation (58).

Although cannabis has been said in the past to cause hypoglycemia, this error has been pointed out in numerous studies. On the contrary, some subjects showed impaired glucose tolerance following experimentally administered i.v. doses of 6 mg of THC (57).

Immunity

A number of *in vitro* studies, using both human and animal material, suggest that cell-mediated immunity may be impaired after exposure to cannabis. Clinically, one might assume that sustained impairment of cell-mediated immunity might lead to an increased prevalence of opportunistic infections or an increased prevalence of malignancy, as seen in the current epidemic of acquired immune deficiency syndrome (AIDS). No such clinical evidence has been discovered.

Immunosuppression was shown in animals by prolonged allogenic skin graft survival, inhibited primary antibody production to sheep erythrocytes, and a diminished blastogenic response (60). Other studies cast doubt on some of the earlier positive observations of impaired cellular immunity. Dinitrochlorobenzene is used as a skin test for intact delayed hypersensitivity, mediated by cellular immunity. No differences were observed in 34 chronic marijuana smokers as compared with 279 nonsmokers (61). The conflicting evidence between *in vitro* and *in vivo* studies of immune function has been reviewed recently (62).

Chromosomal damage

A significant increase (3.4 versus 1.2%) of chromosomal abnormalities was reported in marijuana users as compared with nonusers (63). Changes were largely breaks or translocations of chromosomes. More of the latter were found in chronic cannabis users than in nonusers, but when breaks were included in the counts, the differences vanished (64). After 72 days of chronic smoking of cannabis, no increase in break frequency was found over that which existed prior to the study (65).

Dysmorphogenesis

A large study involved 12,424 women of whom 1,246 (11%) were marijuana users. Lower birth weights, a shorter gestation period, and more major malformations were found among the offspring users (66). While no definite clinical association has yet been made between cannabis use during pregnancy and fetal abnormalities, such events are likely to be rare at best and could easily be missed.

The effects of cannabis on reproductive functions remain obscure. Pregnancies of 35 cannabis users were compared with 36 matched non-users. Meconium staining was significantly more frequent (57% versus 25%) among the users. The latter also had significantly longer labors. In view of the lack of knowledge, it seems prudent to recommend that women who wish to become pregnant avoid cannabis use, as also those with any problems with fertility and young persons who are not fully sexually mature (68).

Therapeutic use

For many centuries, cannabis was used as a treatment, but only during the 19th century did a particularly lively interest develop for exploiting its therapeutic potential. Cannabis was reported to be effective in treating tetanus, convulsive disorders, neuralgia, migraine, dysmenorrhea, postpartum psychoses, senile insomnia, depression, and gonorrhea, as well as opium or chloral hydrate addiction. In addition, it was used to stimulate appetite and to allay the pain and anxiety of patients terminally ill with cancer.

Antiemetic for patients in cancer chemotherapy

Cancer chemotherapy, especially with the agent cisplatin, produces severe nausea and vomiting, which is extremely difficult to treat with ordinary antiemetic drugs, such as prochlorperazine. This complication is so severe that many patients forego effective cancer chemotherapy. The antiemetic effects of cannabis had been suggested as early as 1972. THC was compared with two other antiemetics, thiethylperazine and metoclopramide, in a controlled cross-over trial. No difference was found betwen the antiemetic effect of these three agents. However, adverse effects of THC were sufficiently greater than those from the other two drugs, which raised questions about its clinical utility (69). When THC was compared with prochlorperazine and placebo, the latter two treatments were not found to differ, but THC was superior to either one (70).

A synthetic homolog of THC, nabilone, was developed in 1972 and has been tested extensively for antiemetic activity. A cross-over study comparing nabilone with prochlorperazine in 113 patients revealed significantly greater response rates following nabilone therapy. However, side effects from nabilone were also more common (71).

The potential role of THC as an antiemetic may have been mooted by recent developments. Metoclopramide has been found to be effective when given in high intravenous doses. Lorazepam and dexamethasone are also useful as parenteral agents. These drugs are often used in various combinations which meet most requirements. Thus, THC may be superseded even before it has had widespread clinical trial.

Glaucoma

Discovery of the ability of cannabis to lower intraocular pressure was more or less fortuitous. Intraocular pressure was measured as part of a multifaceted study of the effects of chronic smoking of large amounts of cannabis. Intraocular pressure was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking (72). When patients with ocular hypertension or glaucoma were tested, 7 of 11 showed a fall in intraocular pressure of 30%. Confirmatory evidence was obtained from a trial in which i.v. injection of THC in doses of 22 μg/kg and 44 μg/kg produced an average fall in intraocular pressure of 37%, with some decreases as much as 51% (73).

The exploitation of cannabinoids for treatment of glaucoma will require much further developmental work to ascertain which cannabinoid will be lastingly effective and well tolerated topically.

Miscellaneous uses

Cannabinoids have been found to have analgetic activity and efforts are being made to synthesize new compounds that separate this action from the others. They have also been used as muscle relaxants, for treating bronchial asthma and as anticonvulsants. Thusfar, none of these additional potential therapeutic uses has been established.

Conclusion

Progress continues to be made trying to understand more about our new social drug. The search is never-ending. During the past 14 years, some of the anxieties that sorrounded the appearance of a new social drug in Western society have abated. Despite widespread use of cannabis in virtually all parts of the world, no catastrophic effects on health have been noted. Indeed, as we learn more about cannabis, it appears increasingly to be relatively safe as compared with current social drugs. However, it is still too early in the history of the present episode of cannabis use to be sanguine about possible bad effects. Meanwhile, we try to learn more.

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