HEALTH ASPECTS OF CANNABIS USE

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I. INTRODUCTION

This topic is extremely broad and embraces both the adverse consequences of chronic use of cannabis as well as the potential application of cannabinoids or their homologs as therapeutic agents. Each year the National Institute on Drug Abuse issues a review, "Marijuana and Health", directed to the United States Congress (1). These comprehensive reviews are more detailed than that which can be presented here. Short reviews of the subject have also been published in the past few years (2,3).

II. ADVERSE EFFECTS ON HEALTH

A. General Considerations

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. When such studies of cannabis reveal possible harmful effects, the doses used are often large although drug administration is generally short. Second, use of cannabis by humans is still mainly by young persons in the best of health. Fortunately, the pattern of use is more often one of intermittent rather than regular use, the doses of drug usually being relatively small. This factor might lead to anunderestimate of the potential impact of cannabis on health. Third, canna-

bis is often used in combination with tobacco and alcohol, as well as with a variety of other illicit drugs. Thus, potential health hazards from cannabis may be difficult to distinguish from those concomitantly used 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 of health.

B. Chronic Use of Cannabis

The acute effects of cannabis, taken by a variety of routes, have been well described (4,5). The effects of chronic use of cannabis are more to the point when considering the issues of its status as a possible social drug. Three large-scale field trials of cannabis users have been implemented, but the results of these trials have done little to allay apprehensions about the possible ill effects of chronic use. Once again, objections have been made about the small samples used, the sampling techniques and the adequacy of the studies performed.

If field studies fail to provide evidence of harm from prolonged use of cannabis, it is unlikely that experimental studies will do better, and such has been the case.

Experimental studies suggest that tolerance develops rapidly, that a mild withdrawal reaction may occur, and that some acute effects may be reversed (for instance, a slow heart rate with chronic use rather than a rapid one as seen with acute use). Other effects of chronic cannabis use are related in a specific publication of the New York Academy of Sciences on Chronic Cannabis Use (6). On the whole, we must rely heavily on experiments of nature to determine possible adverse effects.

C. Psychopathology

Cannabis may directly produce an acute panic reaction,a toxic delirium, or an acute paranoid state. Whether it can directly evoke depressive or schizophrenic states, or whether it can lead to sociopathy or even to the "amotivational syndrome" is much less certain. The existence of a specific cannabis psychosis, postulated for many years, is still not established. The fact that users of cannabis may have higher levels of various types of psychopathology does not infer a causal relationship. Indeed, the evidence rather suggest that virtually every diagnosable psychiatric illness among cannabis users began before the first use of the drug. Use of

alcohol and tobacco, as well as sexual experience and "acting-out" behavior, usually antedated the use of cannabis (7). Thus, it seems likely that psychopathology may predispose to cannabis use rather than the other way around.

It would seem reasonable to assume that cannabis might unmask latent psychiatric disorders and that this action probably accounts for the great variety that have been described following its use. On the other hand, evidence for a specific type of psychosis associated with its use is still elusive. Needless to say, use of cannabis should be discouraged (as would probably be the case with most socially used psychoactive drugs) in any patient with a history of prior emotional disorder (8).

Whether chronic use of cannabis changes the basic personality of the user so that they become less impelled to work and to strive for success has been a vexing question. As with other questions concerning cannabis use, it is difficult to separate consequences from possible causes of drug use. It has been postulated that the apparent loss of motivation seen in some cannabis users is really a manifestation of a concurrent depression, for which cannabis may have been a self-prescribed treatment (9).

If this syndrome is so difficult to prove, why does concern about it persist? Mainly because of clinical observations. One cannot help being impressed by the fact that promising youngsters change their goals in life drastically after entering the illicit drug culture, usually by way of cannabis. While it is clearly impossible to be certain that these changes were caused by the drug (one might equally argue that the use of drug followed the decision to change life style), the consequences are often sad. With cannabis as with most other pleasures, moderation is the key word. Moderate use of the drug does not seem to be associated with this outcome, but when drug use becomes a preoccupation, trouble may be in the offing.

D. Brain Damage

The startling report of cerebral atrophy in ten young men who were chronic users of cannabis aroused a great deal of controversy (10). Two studies using computerized tomography have effectively refuted the original claim of brain atrophy (11,12).

A model in monkeys chronically smoking cannabis produced EEG abnormalities from deep electrodes and postmortem histopathological alterations of the brain. EEG abnormalitiesand ultrastructural changes were reported in animals chronically exposed to amount of cannabis consistent with human use (13).

Thus, the issue of brain damage is not totally resolved, although the original observation of brain atrophy seems to have been disproven. The issue is of tremendous importance and probably can only be settled by some suitable animal model, as studies in man are confounded by too many other variables.

E. Tolerance/Dependence

The demonstration of tolerance in man was delayed by ethical restrictions on the amount of exposure permissible to human subjects. For instance, in an early study subjects were exposed only to a test oral dose of 20 mg of delta-9-tetrahydrocannabinol (THC) and then given the same dose or placebo repeated at bedtime for four more days followed by the same THC dose as a challenge on the fifth day. Using such small doses and relatively infrequent intervals, it was impossible to show tolerance to the psychic effects of the drug, although tolerance to the tachycardia and dizziness produced by the drug was evident (14).

Definite evidence of tolerance to the effects of THC in man was adduced only when it became permissible to use comparably large doses over longer periods of time. Subjects in one 30-day study were given high oral doses (70 to 210 mg/day) of THC around the clock. Tachycardia actually became bradycardia and a progressive loss of "high" was noted (15). Similar tolerance to cannabis smoking was observed in a 64-day study in which at least one cigarette daily had to be smoked with smoking as desired later in the same day. Additionally, in this study tolerance developed to the respiratory depressant effect of THC (16).

In man, mild withdrawal reaction was uncovered after abrupt cessation of doses of 30 mg of THC given every 4 hours orally for 10 to 20 days. Subjects became irritable, had sleep disturbances, and had decreased appetite. Nausea, vomiting and occasionally diarrhea were encountered. Sweating, salivation and tremors were autonomic signs (15). Relatively few reports of spontaneous withdrawal reactions from suddenly stopping cannabis use have appeared, despite the extraordinary amount of drug consumed. Five young persons experienced restlessness, abdominal cramps, nausea, sweating, increased pulse rate and muscle aches when their supplies of cannabis were cut off. Symptoms persisted for one to three days (60). The rarity of reports of these reactions may reflect the fact that they are mild and seldom is a user completely cut off from additional drug.

F. 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, as is well proven by tobacco, this mode of administration of cannabis might also be suspect.

Young, healthy volunteers 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 one second, in maximal mid-expiratory flow rate, in plethysomographic specific airway conductance, and diffusing capacity. Thus, very heavy marijuana smoking for six to eight weeks caused mild but significant airway obstruction (17).

Quite possibly such dramatic early changes are not progressive with continued smoking (18). Compared with tobacco, cannabis smoking yields more residue ("tar") but the amount of smoke inhaled is very likely to be considerably less. The study in which five cigarettes daily were consumed represented heavy use of the drug, compared with 20 to 40 tobacco cigarettes which might be consumed by a heavy tobacco smoker. The issue of damage to lungs from cannabis is also 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.

G. Cardiovascular Problems

Tachycardia, orthostatic hypotension and increased blood concentrations of carboxyhemoglobin from cannabis smoking would undoubtedly have deleterious effects on persons with heart disease due to arteriosclerosis of the coronary arteries or congestive heart failure. A direct test of the effects of marijuana smoking in exercise-induced angina proved this harmful effect of the drug. Smoking one cigarette containing 19 mg of THC decreased the exercise time until angina by only 9%. Thus, smoking marijuana increased myocardial oxygen demand and decreased myocardial oxygen delivery (19).

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

H. Endocrine and Metabolic Effects

Changes in male sex hormones have been a source of controversy every since the first report of a decreased serum testosterone level. Decreased levels were associated with morphological abnormalities in sperm and with decreased sexual functioning (20). One possible cause for the lowered serum testosterone levels might be an impairment of synthesis of testosterone in the testis (21). Another possibility might be an increased conversion of testosterone peripherally to estrogens, a factor that might be pertinent to other endocrine side effects.

Data on the effects of cannabis on the female reproductive system are sparse. Preliminary unpublished data indicate that women who use cannabis four 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 ovulation (22).

The endocrine changes may be of relatively little consequence in adults, but they could be of major importance in the prepubertal male who may use cannabis. If the pattern of hormonal changes that induces puberty is altered by cannabis use, then permanent alterations in bodily and psychosexual development could ensue. Should use of cannabis in early adolescence delay physical growth, could this lead to adverse psychosocial consequences? The questions are not academic, as recent surveys of cannabis use indicate that some boys (and girls) may be exposed to it even as early as the pre-pubertal years.

I. Pregnancy and Fetal Development

This is another area of great uncertainty about the meaning of data. Virtually every drug that has been studied for dysmorphogenic effects has been found to have them, if the doses are high enough or if enough species are tested or if treatment is prolonged. The placenta is no barrier to the passage of most drugs, so the assumption should be made that they will reach the fetus if taken during pregnancy.

Studies in primates, still unpublished, indicate that "reproductive efficiency" is reduced when one or both parents have been treated chronically with cannabis, that is, the number of completed pregnancies per mating is reduced. Only variable and nonspecific abnormalities have been found in the aborted offspring, and these were not much different from the findings in spontaneously aborted offspring.

It is still good practice in areas of ignorance, such as the effects of drugs on fetal development, to be prudent. The current admonition against using cannabis during pregnancy is based more on ignorance than on definite proof of harm. While no 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 belated recognition of the harmful effects on the fetus of smoking tobacco and drinking alcoholic beverages indicates that the same caution with cannabis is wise.

J. Miscellaneous Problems

1. Cell Metabolism. Virtually all the changes reported have been in vitro and tend to indicate both slowing of the cell cycle as well as increased mitotic activity (22,23). These conflicting findings are difficult to relate to clinical findings.

2. Chromosomal Abnormalities. A slight increase (3.4% versus 1.2%) of chromosomal abnormalities was reported in marijuana users as compared with non-users (24). Theclinical significance of such changes is unknown.

3. Immunity. Impaired cellular immunity was reported early on in chronic users of marijuana, but later studies have failed to confirm this observation (25,26). Once again, the clinical significance of such impairment is questionable.

4. Contaminants. Contamination of cannabis withinsecticides, fungi, bacteria and insects is entirely possible, given the conditions of its growth. A few cases of pulmonary disease have resulted from such contamination, althoughthe frequency is rare.

5. Possible Accumulation of Drug. Being highly lipophilic, THC should be expected to be sequestered in fatty tissues. Metabolites of the drug are excreted in urine long after exposure to the last dose. The excretion of these metabolites is not associated with any cannabis-like effects, however. Nor has any recognized health hazard been attributed to such accumulation.

K. Summary of Adverse Reactions

It has been remarked facetiously that the most adverse consequence of cannabis use is getting caught up in the crimi-

nal justice system because of such use. That observation may still be true. Yet, it is reasonable to assume that drug-taking, especially by young persons, may seriously interfere with their maturation process. Further, evidence from all drugs, both social as well as therapeutic, indicates that side effects of consequence are inevitable. One will have to make risk-benefit judgements in the case of cannabis just as one does with other drugs.

III. THERAPEUTIC ASPECTS

The therapeutic aspects of cannabis have been the subject of two reviews in recent years (27,28). In this review, we shall consider some potential uses of cannabis currently under investigation, somewhat in order of their importance and promise.

A. Antiemetic for Patients in Cancer Chemotherapy

Nausea and vomiting which accompanies the use of cancer chemotherapeutic agents is extremely difficult to treat with ordinary antiemetic drugs, such as prochlorperazine. This drug, as well as many others, acts specifically at chemoreceptor trigger zones in the medulla sensitive to chemical stimuli that induce vomiting, e.g. apomorphine. For reasons still not clear, the vomiting induced by anticancer drugs does not always respond to such antiemetics even though it is chemically induced.

The first serious trial of THC as an antiemetic was a controlled comparison of this drug with placebo in 20 patients undergoing cancer chemotherapy. Doses of 15 mg of THC every four hours were given orally as gelatin capsules in which THC was dissolved in sesame oil. Doses were started two hours before chemotherapy and repeated two and six hours later. Results were outstanding. Fourteen of 20 patients in whom an evaluation could be made had an antiemetic effect from THC while none was observed from placebo during 22 courses (29).

These favorable findings have been largely, but not totally, confirmed. An open study in 53 patients refractory to other treatments, revealed that ten had complete control of vomiting by THC administered prior to chemotherapy and for 24 hours after, 28 had 50% or more reduction in vomiting, and only 15 had no therapeutic effect. Four patients were dropped from the study because of adverse effects (30). A controlled crossover trial comparing doses of 15 mg of THC versus 10 mg of prochlorperazine in 84 patients was done by he original

group who proposed THC as treatment. Response was complete to THC in 36 of 79 courses but to prochlorperazine in only 16 or 78 courses. Of 25 patients who received both drugs, 20 preferred THC. However, of the 36 courses of THC that resulted in a complete antiemetic response, 32 were associated with a "high" (31). Additional controlled studies have confirmed the antiemetic efficacy. One hundred sixteen patients were randomized to receive 15 mg of THC, 10 mg of prochlorperazine or placebo. Many patients given THC found it to be unpleasant (32). Fifteen patients were treated with courses of either THC or placebo, patients acting as their own controls. The THC regimen produced more relief of nausea and vomiting than placebo in 14 of these 15 patients who had received high-dose methotrexate (33). Plasma concentrations of greater than 10 mg/ml of THC were associated with best results. A crossover controlled trial of THC, thiethylperazine and metoclopramide found no difference in the antiemetic effect of the three agents. Adverse effects of THC were sufficiently greater than those of the other two drugs to question its utility (34). A comparison of THC, prochlorperazine and placebo found the latter two treatments not to differ, THC being superior to either (35).

Nabilone, a synthetic homolog of THC developed in 1972, has been tested for antiemetic activity. One hundred thirteen patients were treated in a crossover study with either nabilone or prochlorperazine. Response rates were significantly greater with nabilone therapy, but side effects were also more common (36). This drug has not succeeded in totally eliminating the objectionable mental effects of cannabinoids. Two other synthetic THC homologs, levonantradol and BRL 4664 have been found in open studies to have antiemetic effects (37,38). It remains to be seen whether any of these synthetics will be appreciably better than THC itself. In the meantime, extremely promising results have been obtained with intravenous doses, somewhat larger than usually given, of metoclopramide. A comparison of this drug with prochlorperazine and placebo showed it to be more effective than either, the only disturbing side effect being sedation (39). Using doses of 1 mg/kg of metoclopramide intravenously before and several times after treatment with cisplatin (perhaps the most emetic anticancer drug), protection was "total" in 48% of courses and "major" in another 23% (40).

Thus, the present situation is that while THC and some of its homologs are undoubtedly antiemetics, they have drawbacks, particularly the mental effects so desired by social users. The advent of newer antiemetics with few mental effects, such as metoclopramide and maybe domperidone, may make the issue moot.

B. Glaucoma

A survey of possible ocular effects of cannabis was added to a multifaceted study of the effects of chronic smoking of large amounts of the drug. Decreases of intraocular pressure up to 45% were found in nine of 11 subjects after 30 minutes of smoking (41). This effect lasted for four to five hours after smoking a single cigarette. Its magnitude was unrelated to the total number of cigarettes smoked. Thus, it appeared that a maximal effect was produced by the amount of THC absorbed from a single cigarette containing 19 mg of THC. In patients with ocular hypertension or glaucoma, seven of 11 patients showed a fall in intraocular pressure of 30%. The effect is real, for it has been confirmed. Intravenous injection of THC in doses of 22 mcg/kg and 44 mcg/kg produced an average fall in intraocular pressure of 37%, with some decreases as much as 51% (42). Similar experiments in rabbits, using several routes of administration have also confirmed the reduction in pressure.

Smoking cannabis or taking it intravenously are hardly reasonable recommendations to make for patients with glaucoma, many of whom are elderly. If the drug could beadministered topically, however, any impediments to its use would be overcome. Thus far, all experiments have been done in rabbits, a traditional animal model for studying topical eye medications. The problem of high lipid solubility of THC has been overcome by developing mineral oil as the vehicle for instillation in the eye. The degree of lowering of pressure is at least as great as with the conventional eye drops, such as pilocarpine, and the duration of effect is often longer. A minimal systemic absorption of the drug occurs when it is applied to the conjunctivae, but it is of no consequence in producing mental effects. Besides THC, other cannabinoids, such as cannabinol or THC metabolites, such as 8alpha- and 8beta,11-dihydroxy-delta-9-THC have shown this effect in rabbits (43,44). As these agents have no mental effects, they are of considerable interest for this purpose.

An extract prepared from the non-psychoactive components of cannabis has been used alone and in combination with timolol eye-drops with success. The effects of the two agents are additive and are said to be effective when other measures have failed. The composition of this extract is still uncertain (45). A synthetic THC homolog, BW 146Y, was given orally to treat glaucomatous patients. Although intraocular pressures were reduced, mild orthostatic hypotension and subjective effects were noted (46).

The outlook for this exploitation of cannabinoids in treatment is still promising. It will take a considerable amount of further developmental work to be sure that whichever

cannabinoid is selected for clinical use will be lastingly effective and well tolerated. Nonetheless, the potential benefit will be great, for glaucoma treatment still does not prevent blindness as often as it might. Further, the effects of cannabinoids may be additive with those of other drugs, so that the overall benefit to patients may be greater than is currently possible.

C. Analgesia

THC in single oral doses of 10 and 20 mg was compared with codeine (60 and 120 mg)in patients with cancer pain. The larger THC dose was comparable to both doses of codeine, but the smaller dose, which was better tolerated, was less effective than either dose of codeine (47). When the THC was given intravenously in doses of 44 mcg/kg to patients undergoing dental extraction, an analgesic effect was demonstrated. It was not as good as that achieved by doses of 157mcg/kg of diazepam intravenously. Anxiety and dysphoria were produced in these patients, several of whom actually preferred the placebo to the dose of 22 mcg/kg of THC (48).

In the chronic spinal dog model, THC, nantradol and nabilone shared some properties with morphine. They increased the latency of the skin twitch reflex and suppressed withdrawal abstinence. These actions were not antagonized by naltrexone, suggesting that they are not mediated through opiate receptors (49). A single clinical study compared intramuscular levonantradol and placebo in postoperative pain and confirmed a significant analgesic action. However, no dose-response was observed and the number of side effects were rather high (50.

Considering the present array of very effective new analgesics of the agonist-antagonist type, as well as the prospect of others that may be even more selective on specific opiate receptors, it seems unlikely that any THC homolog will prove to be the analgesic of choice. But it is really too early to be sure.

D. Muscle Relaxant

The aroma of cannabis smoke is often found around wards housing patients with spinal cord injuries. Part of the streetlore is that cannabis helps to relieve the involuntary muscle spasms that can be so painful and disabling in this condition. Some confirmation of a muscle relaxant, or antispastic, action of THC came from an experiment in which oral doses of 5 of 10 mg of THC were compared with placebo. The 10 mg dose of THC reduced spasticity by clinical measurement

(51). A single small study such as this can only point to the need for more study of this potential use of THC, or possibly of some of its homologs. Presently used muscle relaxants, such as diazepam, cyclobenzaprine, baclofen and dantrolene have major limitations.

E. Anticonvulsant

Anticonvulsant activity was one of the first therapeutic uses suggested for cannabis and was documented experimentally many years ago (52). Subsequently, a great many studies in various animal species have validated this action.

Despite all these various lines of evidence supporting an anticonvulsant action of various cannabinoids, clinical testing has been rare. A single case report of better control of seizures following regular marijuana smoking was not very convincing (53). A clinical trial in 15 patients not adequately controlled by anticonvulsants added cannabidiol in doses of 200 or 300 mg/day or placebo to their treatment. Control of seizures was somewhat better in those patients receiving cannabidiol (54). As this cannabinoid has little psychoactivity, it would be the obvious one to try in future clinical studies.

F. Miscellaneous Uses

1. Bronchial Asthma. Bronchodilation from marijuana smoke was discovered during a general study of the effects of the drug on respiration. Normal volunteer subjects were exposed to marijuana smoke calculated to deliver 85 mcg/kg or 32 mcg/kg. The high-dose group showed a fall of 38% in airway resistance and an increase of 44% in airway conductance (55). Ten stable asthmatic patients were treated in another study with aerosols of placebo-ethanol, of THC 200 mcg in ethanol, or of salbutamol 100 mcg. Forced expiratory volume in 1 second, forced vital capacity and peak flow rate were measured on each occasion. Salbutamol and THC significantly improved ventilatory function. Improvement was more rapid with salbutamol but the two treatments were equally effective at the end of one hour (56). Whether effective doses of THC delivered by aerosol would be small enough to avoid the mental effects is uncertain. The fact that THC increases airway conductance by a mechanism of action that may be different from the usual beta adrenergic stimulants makes further inquiry necessary.

2. Insomnia. Although early speculation had suggested that THC might differ from conventional hypnotics in not reducing rapid eye movement (REM) sleep, study of the drug in

the sleep laboratory showed that it did (57). Another sleep laboratory study showed that a dose of 20 mg of THC given orally decreased (REM) sleep. Abrupt discontinuation of THC after 4 to 6 nights of use produced a mild insomnia but no marked REM rebound. The lack of effect on REM rebound seen with low doses of THC was not apparent when very high doses (70 to 210 mg) were given orally. REM was reduced during treatment and marked REM rebound was observed after withdrawal (58).

These studies indicate that the sleep produced by THC does not differ much from that of most currently used hypnotics. The side effects of the drug before sleep induction as well as the hangover effects make the drug less acceptable than the currently popular benzodiazepines, such as flurazepam. As many other effective hypnotics are currently being developed, it seems unlikely that THC will find a place in treatment of insomnia.

3. Hypertension. THC itself occasionally produces orthostatic hypotension (5). The development of effective antihypertensive drugs has been one of the outstanding achievements of pharmacology over the past 30 years. The prospect of a new antihypertensive based on orthostatic hypotension, perhaps the least desirable mode of lowering blood pressure, is hardly very enticing (59). Further, it is by no means certain that the mental effects of any homolog of THC can be completely eliminated without losing many of the desired pharmacological actions as well. The issue seems hardly worth pursuing.

G. Prospects as a Therapeutic Agent

Cannabis and THC homologs should be treated like any other investigational new drug as the search for a clinical use in medicine goes on. We should expect neither less nor more in regard to safety and efficacy than we would from other new agents. At present, cannabis has not yet made its way back into the formularies. It is unlikely that it ever will. The ingenuity of pharmaceutical chemists in developing THC analogs may yet find a way to exploit some of these potential therapeutic uses without the side effects that make cannabis itself undesirable. Modern inquiry into this drug spans less than decades, which is hardly enough time to settle the issue.

IV. SUMMARY

Both the adverse consequences of social use of cannabis as

well as the potential therapeutic use of cannabinoids or their homologs are still uncertain. It seems likely that adverse consequences will be fully documented and that therapeutic uses may be found. Only the former concern the chronic user of cannabis, who must still make a personal decision whether the risks outweigh the benefits from the drug.

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