Marijuana (Cannabis) as Medicine

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ABSTRACT. The modern published literature on the therapeutic potentials of cannabis has been reviewed. A pure preparation of the major active component, delta-9-tetrahydrocannabinol (THC), Marinol® or dronabinol, is available for treating nausea and vomiting associated with cancer chemotherapy and as an adjunct to weight loss in patients with wasting syndrome associated with AIDS. Although such approval currently applies only to orally administered THC, for practical purposes smoked marijuana should also be expected to be equally effective.

Promising leads, although often fragile, suggest possible uses for treating chronic pain syndromes, neurological disease with spasticity and other causes of weight loss. These possible indications require more study.

KEYWORDS. Cannabis, marijuana, THC, dronabinol, vomiting, spasticity, anorexia, pain, seizures, glaucoma, asthma, insomnia

INTRODUCTION

Marijuana has been used medically for millennia and in the United States for over 150 years. It was in the US Pharmacopoeia until 1942 when it was removed because of federal legislation making the drug

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illegal. The number of potential indications ranged so widely as to rival those of patent medicines of the time (Table 1). Like the latter, all the proposed indications were based on anecdote and folklore. A few studies of the medical utility of a material thought to be similar to the active component of marijuana, synhexyl (parahexyl), were made during the 1940's and 1950's (Himmelsbach et al. 1994; Loewe, 1946; Stockings, 1947; Pond, 1948; Parker and Wrigley, 1950; Thompson and Proctor, 1953). However, it was not until the isolation and synthesis of delta-9-tetrahydrocannabinol (THC) as the active component during the mid 1960's that more formal pharmacologically based studies became possible (Gaoni and Mechoulam, 1964; Isbell et al. 1964). Nonetheless, a comparison of synhexl and THC revealed them virtually identical in clinical effects, except that synhexyl was less potent and slower in onset of action (Hollister et al. 1968). Curiously, almost all studies of medical marijuana have employed THC or its homologs rather than smoked marijuana. This oversight has created the current climate of controversy about the medical uses of marijuana.

During the past 25 years, a number of reviews have appeared touching upon the therapeutic aspects of marijuana (Nahas, 1973; Bhargava, 1978; Zinberg, 1979; AMA Council, 1980; AMA Council, 1981; Ungerleider and Andrysiak, 1985; Hollister, 1986; Hall et al., 1994; Grinspoon and Bakalar, 1995; Voth and Schwartz, 1997). As with

TABLE 1. Proposed Therapeutic Indications of Marijuana

*Antiemetic	Melancholia
*Appetite Stimulation	Neuralgia
*Antispasmodic, muscle relaxant	Antitussive
*Analgesic	Antineoplastic
*Bronchodilator	Antipyretic
*Anticonvulsant	Topical antibiotic
Sedative-hypnotic	Anti-inflammatory
Opiate, alcohol withdrawal	Obsessive-compulsive
Antihypertensive	Dysmenorrhea

*some suggestive evidence for efficacy

most issues surrounding use of marijuana, interpretation of the medical literature has been filled with controversy, ranging from those who believed it to be a panacea provided by Nature to alleviate the ills of mankind to those who believe that any acceptance of medical use will send the wrong message to young people, for whom marijuana is considered to be a menace and a stepping-stone to the use of more dangerous drugs. This reviewer will try assiduously to avoid bias as well as to place the possible medical uses of marijuana in the context of currently available alternative treatments for the same indication.

The present review will focus primarily on clinical studies evaluating proposed medical uses of marijuana published in refereed medical journals. The various indications will be discussed in the order of the amount of evidence currently available to support each. Readers may then form their own opinion regarding the overall quality of the evidence. Medical indications are divided into two categories, those with enough available evidence to merit further study and those for which evidence is so lacking or so poor as to merit little serious further consideration. Most studies will involve THC rather than smoked marijuana. The argument has been made that smoked marijuana, which contains almost 300 chemicals, few of which have been studied, might therefore have superior utility over the pure material. Although a number of cannabinoids have been found in marijuana, most with similar effects to those of THC itself, they are uniformly weaker and far less abundant than THC. Thus, customarily doses of raw marijuana have been calibrated to their THC content (Hollister 1974).

INDICATIONS WITH EVIDENCE FOR MEDICAL EFFICACY

Antiemetic Action

The antiemetic action of marijuana was not anticipated despite anecdotal reports over the years. The story is that a young patient being treated with chemotherapy for leukemia reported to his oncologists that smoking a marijuana cigarette before and during the chemotherapy ameliorated the nausea and vomiting which is routinely produced. These side effects of cancer chemotherapy are so noxious that patients may refuse life-saving treatment rather than endure them. Over time, repeated experiences of nausea and vomiting may be conditioned, so

that this adverse effect is evoked by the mere anticipation of a round of chemotherapy.

Although an antiemetic effect of THC had been suggested as early as 1972, the first report of a placebo-controlled trial came in 1975 from one of the top oncology centers in the USA. THC in the form of gelatin capsules, in which the drug was dissolved in sesame seed oil, was given in doses of 15 to 20 mg to 20 patients undergoing cancer chemotherapy. Three doses were given, 2 h before and 2 and 4 h after chemotherapy. Fourteen of the 20 patients in whom an evaluation could be made reported a definite antiemetic effect from the THC, while none was observed from placebo during 22 courses (Sallan et al. 1975).

Another comparison of THC with placebo was made in 15 patients with 11 acting as their own control. Fourteen of the 15 patients given THC obtained more relief of nausea and vomiting than from placebo during a course of high-dose methotrexate chemotherapy (Chang et al. 1979). Best results were obtained when plasma concentrations of THC were more than 12 mg/ml. Such concentrations would ordinarily be expected to produce rather definite mental effects (Hollister et al. 1981).

A larger uncontrolled study was done several years later confirming these results. Fifty-three patients refractory to other treatments were studied in an uncontrolled fashion. Ten had complete control of vomiting when THC was administered before chemotherapy and for 24 h thereafter. Twenty-eight had 50% or more reduction in vomiting, and only 15 patients showed no therapeutic effect whatsoever. However, four patients were dropped from the study because of adverse effects (Lucas et al. 1980).

In yet another comparison of THC and placebo, the former treatment was superior, but the side effects were so profound that the patients preferred avoiding treatment. However, doses were far in excess of what might be needed for efficacy, obtaining plasma concentration of 300 ng/ml of THC, several times those required (Kluin-Neleman et al. 1979).

Several studies followed with the next logical step, a comparison of THC with prochlorperazine, which was then the favored antiemetic. One of the first was by the group making the original controlled trial. Doses of 15 mg of THC were compared with 10 mg doses of prochlorperazine in a controlled crossover trial in 84 patients. THC produced

complete response in 36 of 79 courses, while prochlorperazine was effective in only 16 of 78 courses. Twenty-five patients received both drugs, of whom 20 preferred THC. Of the 36 courses of THC that resulted in complete antiemetic response, 32 were associated with mental effects characterized as a ''high'' (Sallan et al. 1979).

Another comparison between THC in 15 mg doses and prochlorperazine in 10 mg doses versus a placebo control was made in 116 patients who received oral doses 3 times a day. The THC regimen was equal to prochlorperazine, and both were superior to placebo. However, many patients who received THC found it unpleasant (Frytak et al. 1979). When THC was compared with prochlorperazine and placebo, the latter two treatments were found to differ, but THC was superior to either one (Orr et al. 1980). A controlled crossover design compared oral doses of THC 7.5 to 12 mg with oral doses of prochlorperazine in 214 patients and concluded that the two treatments were equal (Ungerleider et al. 1982).

Comparisons with other antiemetics have also been made. THC was found to be superior to either prochloperazine or metoclopramide in pediatric cancer patients. An increase in drowsiness, appetite and ''high'' were reported in patients treated with THC (Ekert et al. 1979). A crossover comparison of THC and haloperidol for treatment of 52 patients with nausea and vomiting from cancer chemotherapy compared oral doses of 10 mg/day of THC with 2 mg/day of haloperidol given alternately in two-week courses. Both drugs were equally effective. Some patients who did not respond to one drug responded to the other. Although no serious side effects were reported, THC toxicity was less well tolerated than that of haloperidol (Neidhart et al. 1981).

An uncontrolled study used 56 patients undergoing cancer chemotherapy that had not responded to standard treatment for prevention of nausea and vomiting. After being allowed four marijuana cigarettes daily during the course of chemotherapy, 78% benefited. Young age and previous experience with cannabis were predictors of good response. Sedation and dry mouth were the only side effects (Vinciguerra et al. 1988).

A review of dronabinol (oral THC) cancer chemotherapy patients treated for nausea and vomiting indicated that combination with prochloperazine was more effective than either drug alone. Among 750 courses of therapy with THC, about one-third each of patients had considerable response, partial response or no response. In open studies

of appetite stimulation among patients with either cancer or symptomatic HIV infections, doses of 2.5 mg twice daily were effective in stabilizing weight and improving appetite (Plasse et al. 1991).

Although smoked marijuana is often preferred, whether it is superior to orally administered THC has not been tested in controlled comparisons. It may very well be those pharmacokinetic differences between orally administered THC and smoked marijuana might explain the preference for the latter route. Orally administered THC is slow in onset of action though longer in duration. Smoked marijuana produces a THC concentration that mimics the pattern of intravenously administered THC (Agurell et al. 1986). This immediate effect might be perceived by patients as more desirable. For those patients who have this perception, smoked marijuana may be the drug of choice. Smoking marijuana cigarettes, even at street prices, would certainly be less expensive than using conventional antiemetic drugs.

An oral preparation of THC (Marinol®, dronabinol) has attained approval for two indications. Nausea and vomiting associated with cancer chemotherapy are still something of a problem with usual anti-nauseants and THC has been shown to be an effective treatment compared with prochlorperazine (Lane et al. 1991). Severe weight loss associated with the wasting syndrome experienced by patients with AIDS is another indication less well established. No comparisons have been made with other possible treatments, either 5-HT_3 receptor antagonists or anabolic steroids, such as testosterone.

A survey that questioned members of the American Society of Clinical Oncology obtained responses from 1,035 members. About 44% of the responders told of using illegal marijuana for the treatment of at least one patient and almost one-half would prescribe marijuana were it to be made legal. Respondents also were of the opinion that marijuana itself was more effective than THC or semisynthetic cannabinoids (Doblin and Kleiman 1991).

A later survey of oncologists in 1993 by means of questionnaire obtained replies from 141 physicians. The major question was how they would rank available antiemetics for such use (Schwartz 1994). The four favored drugs were metoclopramide, lorazepam, dexamethasone or other corticosteroids, and prochlorperazine or promethazine. Marijuana or oral THC (dronabinol) was rated sixth in preference. Of those oncologists who had prescribed marijuana or THC for their patients, the drug was considered efficacious in about 50% of patients.

However, one in four patients complained of bothersome side effects. By the time of the survey, prescriptions for marijuana had declined. Few oncologists reckoned that they would prescribe the drug more frequently were it made legal and freely available. This survey was completed before the availability of 5-HT_3 antagonists, such as ondansetron, which would currently be the first choice in treatment. Neither did it consider the efficacy of combinations of antiemetics, which have often surpassed the efficacy of single drugs.

In summary, one can conclude that marijuana, both taken orally as THC or smoked, is effective in controlling nausea and vomiting associated with cancer chemotherapy being comparable in efficacy to some currently used antiemetics. As this indication is already approved for the oral form, and as no evidence indicates that the effects from smoking are qualitatively different, one might accept the use of smoked marijuana for the same indication. The choice of dosage form could then be made based on whether a rapid-acting short-lived effect was preferable to a slow-onset, longer duration of action. One might even imagine scenarios in which both dosage forms might be used together. Although evidence for efficacy of the smoked form is less than optimal, in part due to less opportunity for such studies, it is now at least as convincing as was the evidence for orally administered THC. The admission of smoked marijuana as an acceptable treatment for this specific indication would be justified on the basis of present knowledge and would save both much effort and expense by avoiding the need for their elegant proof of efficacy demanded for drugs with the less well-known efficacy and safety.

Very likely, the major drawback would be the psychoactive effects, which, while sought out by those who use marijuana socially, are unwanted effects when the drug is used therapeutically. This difficulty might be met if one could find a cannabinoid that retained the antiemetic action without causing any mental changes. As isomer of the synthetic cannabinoid, 7-hydroxy-delta-6-tetrahydrocannabinol, is devoid of psychoactivity. Yet, in pigeons treated with the anticancer drug cisplatin, a drug most likely to cause vomiting, it showed antiemetic effects (Feigenbaum et al. 1989). Thus, the goal of separating these effects may be within reach. However, the number of drugs now shown useful for control of vomiting has increased greatly since cannabinoids were first considered as useful. The issue may have become

moot, unless such cost considerations prevail more in the future than they have in the past.

Appetite Stimulation

Frequent anecdotal reports by users of cannabis testify to the development of a ravenous appetite with a craving for sweets, especially chocolate. An experimental study, using a standardized chocolate milkshake, tested this idea. Subjects were treated with oral doses of THC 0.5 mk/kg, as well as placebo, alcohol and dextroamphetamine as a negative control. Of 12 fasted subjects, 7 who received THC increased their intake, 2 showed no change and three consumed less as compared with placebo. As expected, dextroamphetamine decreased intake. Alcohol, despite the calories provided, produced little change. When 12 subjects were fed before the test, 7 increased food intake, and 5 showed no change. Results were inconstant, both within and between subjects (Hollister 1971).

After 21 days of inpatient marijuana smoking, both body weight gain and caloric consumption were higher in casual and heavy users than in the control subjects (Greenberg et al. 1976). The psychological toxicological effects of chronic administration (0.1-0.34 mg/kg po qid) of THC were studied in cancer patients on in-and-out patient bases. The clinical observations demonstrated that THC slows or reverses weight loss and possesses some antiemetic and analgesic properties (Regelson et al. 1976).

The wasting syndrome associated with AIDS has made the search for drugs that might stimulate appetite more meaningful. THC in the form of dronabinol has been most often studied. An open pilot study of dronabinol in patients with AIDS-associated cachexia showed it effective in increasing weight as well as being well tolerated. Ten men received doses of 2.5 mg three times daily for periods of 4 to 20 weeks. Eight patients gained weight an average of 0.6 kg/month while 2 showed no gain. Initially, patients had been losing weight at the rate of 0.93 kg/month. Increasing the dose to 5 mg three times daily did not enhance weight gain (Plasse 1991).

A randomized double-blind comparison of dronabinol 2.5 mg twice daily with placebo over a 6 week period was completed in 88 patients. Before the study, patients were at least 2.3 kg below their ideal weight. Among the dronobinol-treated patients, the mean weight gain was 0.1 kg from baseline compared with a loss of 0.4 kg among the placebo

group. Side effects were not severe enough to merit discontinuation of treatment (Beal et al. 1995). Following the controlled study, patients entered an open study of one year's duration. Doses could vary between 2.5 and 20 mg/day according to response. A weight gain of 2 kg was found in those patients who completed three months of treatment. No evidence of the development of tolerance was noted. Side effects were not a major problem.

A phase 2 study of dronabinol in patients with cancer-associated anorexia and weight loss, revealed that low doses (2.5 mg twice daily after meals) improved appetite. Despite the low dose, 22% of patients withdrew from therapy because of side effects (Nelson et al. 1994). In a letter concerning this subject, the authors responded that dronabinol was safe and effective for appetite stimulation during chemotherapy, but that they considered metoclopramide, megestrol and dexamethasone better (Nelson and Walsh 1995). As the latter drugs are mainly used as antiemetics, one wonders whether whatever weight gain they might have provided was due to that action.

Four studies explored the role of age, gender, satiety state, and route of drug administration and dose on appetite stimulation in normal men. Increased food intake was found only after chronic dosing with rectally administered THC 2.5 mg three times daily for 3 days. Orally administered THC in the same dose did not increase appetite. Nor did inhalation of marijuana smoke. The conclusion was that appetite stimulation from cannabinoids was highly variable (Mattes et al. 1994).

An experimental approach to determine the effect of marijuana smoking on appetite used 7 men who were sequestered during observation. A single marijuana cigarette smoked during a period of isolation and work had no effect. However, 2-3 cigarettes smoked during a period of socialization increased caloric intake. The intake was largely in the form of snacks rather than increased consumption at mealtime (Foltin et al. 1986).

Testosterone enanthate, a long-acting injectable form, given in doses of 200 mg IM every 3 weeks, increased weight gain in AIDS patients, most particularly in the form of increased lean body mass. It should be noted that all these patients showed a low serum testosterone level at baseline, which may limit this beneficial effect to such patients (Grinspoon et al. 1998). Nonetheless, testosterone, other anabolic steroids, and human growth hormone might be reasonable competitors of THC for this indication.

Spasticity

It is said around our hospital if you want to know what marijuana smoke smells like, you should drop by the spinal cord injury ward. Such patients think that marijuana is helpful for relieving the pain and muscle spasm secondary to spinal cord injuries.

Ten patients who admitted using marijuana after spinal cord injury perceived a decrease in pain and spasticity as reported on a questionnaire (Dunn and Davis 1974). Another questionnaire given to 43 patients also with spinal cord injury reported decreased spasticity following marijuana use. Current use was related to past use and to use by peers, suggesting some possible bias in reporting (Hanigan et al. 1986).

The effects of oral THC 35 mg/day on muscle resistance, deep tendon reflexes and spasticity was evaluated in 5 patients with traumatic paraplegia. Two patients showed beneficial effects of THC, two had no real benefit and the fifth withdrew from the study because of the mental side effects (Malec et al. 1990).

A double-blind study was performed comparing 5 mg of THC orally, 50 mg codeine orally, and placebo in a patient with spasticity and pain due to spinal cord injury. The three conditions were applied 18 times each in a randomized and balanced order. THC and codeine both had an analgesic effect in comparison with placebo. Only THC showed a significant beneficial effect on spasticity. In the dosage used, no altered consciousness occurred (Maurer et al. 1990).

An antispastic action of THC was confirmed by the first clinical study. Oral doses of 5 and 10 mg of THC were compared with placebo in patients multiple sclerosis. The 10 mg dose reduced spasticity by clinical measurement (Petro and Ellenberger 1989).

A short-term trial of oral THC in 13 patients with multiple sclerosis and spasticity refractory to standard drugs revealed that a dose of 7.5 mg/day was the minimally effective dose. At this dose, subjective spasticity scores were less for THC than placebo. However, on objective measurements, there were no differences. A dose of 7.5 g/day was also highest tolerated; none of the patients in the trial requested continuation after the blind condition was abandoned (Meinck et al. 1989). A study of one patient with multiple sclerosis and another with spinal cord injury showed that doses of 5 mg/day of THC produced some relief of symptoms. Improvement in a 30-year-old man with multiple

sclerosis after smoking a marijuana cigarette was confirmed by electromyography of the flexor muscles of the leg and measurement of hand action tremor (Ungerleider et al. 1987). Administration of oral THC 5 to 10 mg to eight severely disabled multiple sclerosis patients yielded mild subjective improvement in tremor and sense of well being among two patients (Clifford 1983). The overall impression is that THC has some beneficial effect on spasticity, but tolerance to the side effects of the drug may be idiosyncratic.

On the other hand, a group that started with the premise that marijuana would reduce the spasticity of patients with multiple sclerosis and permit better postural control found the opposite. Ten adult patients with that disease were compared with 10 normal volunteers after smoking a marijuana cigarette. Both groups suffered a decrease in posture and balance as measured by a computer-controlled dynamic posturographic platform. No differences were observed between them (Greenberg et al. 1994). The medical treatment of spasticity with drugs such as diazepam, cyclobenzaprine, baclofen and dantrolene leaves much to be desired. In this case, smoking marijuana, which produces a sudden rise of THC levels, might not be the best route of administration. Further studies with oral dosing are required before this indication is written off.

A questionnaire concerning the effects of marijuana in 122 patients with multiple sclerosis revealed a generally beneficial profile of perceived effects. In descending order, the following symptoms were reported as being relieved: spasticity (97%), chronic pain in extremities, acute paroxysmal phenomenon, tremor, emotional dysfunction, anorexia/weight loss, fatigue, double vision, sexual, bowel and bladder dysfunction, and visual dimness (30%). Thus, we are faced with a substantial conflict between patients' perceptions and objective studies (Consroe et al. 1997).

Cannabidiol, another naturally occurring cannabinoid, was given in doses increasing from 100 to 600 mg/day to five patients with idiopathic dystonias, along with previously administered treatments. Dose-related improvement ranging from 20% to 50% was noted in all patients. However, in two patients with coexisting Parkinson syndromes, doses of over 300 mg/day exacerbated the hypokinesia and resting tremor, indicating an aggravating action in such patients (Consroe et al. 1986).

Analgesic Effects

Preclinical evidence of an analgesic effect of cannabinoids is strong. THC and the synthetic homologues, nantradol, and nabilone, shared some properties with morphine in the chronic spinal dog model. Latency of the skin twitch reflex was increased, and withdrawal abstinence was suppressed. Naltrexone did not antagonize these actions, suggesting that they are not mediated through opiate receptors which might suggest the eventual combination of opiate and cannabinoids (Gilbert 1981).

Both THC and a synthetic cannabinoid induced an antinociceptive effect in spinally transected rats, indicating a supraspinal mechanism of analgesia. Previously the same investigators had found evidence of a spinal site mediated through spinal alpha-adrenergic receptors (Lichtman and Martin 1991).

There is clinical support for an analgesic action as well. Single oral doses of 10 mg and 20 mg of THC compared with codeine (60 mg and 120 mg) in patients with cancer pain. A 20 mg dose of THC was comparable to both doses of codeine. The 10 mg dose, which was better tolerated, was less effective than either dose of codeine (Noyes et al. 1975). THC given IV in doses of 44 ng/kg to patients undergoing dental extraction produced an analgesic effect, which was less than that achieved from intravenous doses of 157 μg of diazepam. Several of these patients actually preferred placebo to the dose of 22 μg of THC per kg because of anxiety and dysphoria from the latter drug (Raft et al. 1977). Intramuscular levonantradol was compared with placebo in postoperative pain, and a significant analgesic action was confirmed. No dose-response relationship was observed, and the number of side effects from levonantradol was rather high (Jain et al. 1981).

Paradoxically, smoking of material estimated to deliver 12 mg of THC increased sensitivity to an electric shock applied to the skin of normal volunteers (Hill et al. 1974). The apparent paradox is that the biphasic action of THC (initial stimulation followed by sedation) both increases and decreases pain. Traditionally, aspirin-like drugs, which work peripherally by inhibiting the synthesis of prostaglandins, are used to treat pain derived from the integument. The initial mental stimulation from THC might increase sensitivity to this kind of pain. Visceral pain, such as that of cancer patients, is usually treated by

opiates having both peripheral and central sites of action. Recent evidence suggests that opiates may act directly on pain pathways in the spinal cord as well as reducing the affective response that accompanies pain. Thus, when the two types of pain are distinguished from each other and viewed in the context of the sequential biphasic action the apparent paradox is solved.

Because THC and other cannabinoids seem to be relatively safe (no deaths from overdose) and produce at best only a mild form of dependence, the notion of producing a synthetic cannabinoid with few other actions than analgesia has stimulated a great deal of interest on the part of various pharmaceutical companies. While it seems unlikely that THC itself will ever be used as an analgesic, synthetics may ultimately fulfill this role. Such drugs might be expected to act primarily on peripheral cannabinoid receptors rather than on those abundant in the CNS.

INDICATIONS WITH SPARSE EVIDENCE OF EFFICACY

Glaucoma

Discovery of the ability of cannabis to lower intraocular pressure (IOP) 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. IOP was found to decrease as much as 45% in 9 of 11 subjects, 30 min after smoking (Hepler and Frank 1971). Lowered intraocular pressure lasted 4 to 5 h after smoking a single cigarette. Its magnitude was unrelated to the total number of cigarettes smoked. The maximal effect on IOP was produced by the amount of THC absorbed in a single cigarette containing 19 mg of THC. When patients with ocular hypertension or glaucoma were tested, 7 of 11 showed a fall of intraocular pressure of 30%. Confirmatory evidence was obtained from a trial in which intravenous injection of THC in doses of 22 μg/kg and 44 μg/kg produced an average fall in IOP of 37%, with some decreases as much as 51% (Cooler and Gregg 1977).

The effects of intravenously administered cannabinoids on IOP were measured in 12 normal volunteers. Half received intravenous doses of THC, cannabidiol and cannabinol, the other half received doses of delta-8-THC, 11-hydroxy-THC, and 8-beta-hydroxy-del-

ta-9-THC. Total dose of THC and its 11-hydroxy metabolite was 3 mg; delta-8-THC was given in total dose of 6 mg, 8-beta-hydroxy-THC to a total of 9 mg, cannabinol and cannabidiol to total of 20 mg. Significant reductions in IOP were produced by the THC, delta-8-THC, and 11-hydroxy-THC, all of which are psychoactive compounds while the other cannabinoids had little or no such activity. Thus, it seemed impossible to separate mental effects, which were considerable for the effective drugs, from lowering of IOP (Perez-Reyes et al. 1976).

Orally administered THC (20 or 25 mg) lowered IOP about 8 mm Hg among 17 patients with heterologous glaucomas. No such lowering was found in patients who received only 5 or 10 mg doses. All patients who received the higher doses experienced severe mental effects. One patient, who received only a 5 mg dose, experienced severe tachycardia and orthostatic hypotension (Merritt et al. 1980).

Similar findings were reported from the same group after having 16 patients smoke marijuana cigarettes weighing 900 mg (amount of THC unspecified). Compared with placebo, IOP was lowered for 3-4 hours following the smoke. However, rapid heart rate and lowering of blood pressure which preceded this action were quite large and would not be tolerated by many patients among the age group who suffer glaucoma (Merritt et al. 1980).

As treatment for glaucoma is a lifetime proposition, systemic therapy has never been seriously considered. Topical therapy, properly used, has been generally satisfactory. Unfortunately, attempts to make a tolerable topical preparation of THC or other cannabinoids have been impossible to date. One hears tales of patients with glaucoma whose vision is spared only by smoking marijuana cigarettes; remarkably, no case reports, along with objective measurements, even of a few such patients, have appeared. As glaucoma occurs most often in older patients, one has difficulty imagining such patients embracing a lifetime of possible marijuana intoxication. This possible indication has elicited no literature during the past 12 years.

Anticonvulsant

One of the therapeutic uses suggested for cannabis was as an anticonvulsant. Such an effect was documented experimentally many years ago (Loewe and Goodman 1947). Studies in various animal species have shown cannabidiol effective in many animal-screening tests for anticonvulsants (Wada et al. 1973; Turkanis et al. 1974).

Clinical testing has been rare, despite all these various lines of evidence supporting an anticonvulsant effect of cannabinoids. Better control of seizures following regular marijuana smoking was reported in a not very convincing single case (Consroe et al. 1975).

Cannabidiol (CBD), a non-psychoactive cannabinoid, was tested in 15 epileptic patients poorly controlled by usual drugs. Patients were randomly assigned to a dose of 300 mg of CBD or placebo and treated for as long as 4 1/2 months, while continuing their past anticonvulsant drugs. Of 8 CBD-treated patients, 4 remained free of seizures, 3 showed partial improvements and 1 showed no response. Of 7 placebo-treated patients, only 1 showed improvement. The drug was well tolerated (Cunha et al. 1980). As cannabidiol has little if any psychoactivity, it is a good candidate for this use.

The number of effective anticonvulsants has increased since the original interest in cannabidiol. Consequently, no further clinical studies have been reported.

Bronchial Asthma

A general study of the effects of marijuana on respiration revealed a bronchodilating action in normal volunteer subjects. Marijuana smoke delivered by smoking cigarettes containing 2.6% THC caused fall of 38% in airway resistance and an increase of 44% in airway conductance, with less change when a 1% THC cigarette was smoked. The low-dose group showed lesser changes, but they were still significant as compared with baseline (Vachon et al. 1973).

Asthma was deliberately induced by either inhalation or methacholine or exercise in asthmatic patients. They were then treated with inhalation of placebo marijuana, of saline, of isoproterenol, or of smoke derived from 500 mg of marijuana containing 2% THC. Both marijuana smoke and isoproterenol aerosol effectively reversed both methacholine- and exercise-induced asthma while saline and placebo marijuana had no effect (Tashkin et al. 1975).

Aerosols of placebo-ethanol, THC (200 μg) in ethanol, or of salbutamol (100 μg) were tested in another study of 10 stable asthmatic patients. Forced expiratory volume in 1 s, forced vital capacity, and peak flow rates were measured on each occasion. Both salbutamol and THC significantly improved ventilatory function. Improvement was more rapid with salbutamol, but two treatments were equally effective at the end of 1 h (Williams et al. 1972).

While it is conceivable that an aerosol preparation could be made, those currently used (corticosteroids and beta-adrenergic agonists) are well established. Although treatment of asthma in the past has employed smoked drugs (stramonium [*Datura* spp.] cigarettes known as cubebs were used until 60-70 years ago), it seems intuitively wrong to treat a pulmonary condition with a method of drug administration that increases inflammation. As treatment of bronchial asthma has shifted towards emphasis on alleviating the inflammatory aspects, there is little support for using smoked marijuana. Consequently, interest in the indication is currently non-existent.

Insomnia

THC does not differ from conventional hypnotics in reducing rapid eye movement (REM) sleep (Pivik et al. 1972). THC in doses ranging from 61 to 258 μg/kg produces in normal subjects increments in stage four sleep and decrements in REM sleep, but without the characteristic REM rebound which follows chronic treatment with an hypnotic. When THC was administered orally as a hydroalcoholic solution in doses of 10, 20, and 30 mg, subjects fell asleep faster after having mood alterations consistent with a ''high.'' Some degree of ''hangover'' the day following was noted from larger doses (Cousens and Dimascio 1973). Another sleep laboratory study showed that a dose of 2 mg of THC given orally decreased REM sleep. After 4-6 nights of use, abrupt discontinuation of THC produced a mild insomnia but not marked REM rebound (Freemon 1974). REM rebound may not be apparent after low doses of THC; however, very high doses (70 to 210 mg) reduced REM sleep during treatment and were followed by marked REM rebound after withdrawal (Feinberg et al. 1976). The sleep produced by THC does not seem to differ much from that of most currently used hypnotics. Side effects before sleep induction as well as hangover effects make the drug less acceptable than currently popular benzodiazepines. No further studies have been reported.

Early on, synthetic cannabinoids were tried as antianxiety and antidepressant drugs. Diazepam 5 mg was superior to the synthetic cannabinoid nabilone 2 mg for treating experimentally induced anxiety in highly anxious people. Thus, even aside from the marijuana-like effects of nabilone, it was not acceptable (Nakano et al. 1978). Following a favorable report from use of synexyl for treatment of depression, a further study found it to be of no benefit (Parker and Wrigley 1950).

Again, cannabinoid-like drugs were of little use in these psychiatric conditions. Nor has there been any attempt to exploit them in this fashion over the succeeding decades.

DISCUSSION

Among the many possible therapeutic uses of marijuana, a few have enough supporting evidence to justify further studies. Greatest support has been elicited for using the drug, mainly in the form of orally administered THC, for the control of nausea and vomiting. This use has been further legalized by the switch of synthetic oral THC to Schedule III of the Controlled Substances Act. Capsules (Marinol® or dronabinol) containing THC dissolved in oil have been marketed for this purpose. Demand for such preparations has not been great, however, probably because of the reluctance of physicians to prescribe a drug that so recently was considered illegal and possibly also to the fact that many other antiemetics have been developed during the past decade which obviate the mental side effects of THC. The remaining issue is whether smoked marijuana might be superior, as such administration permits rapid and close titration of dose. This issue has not been resolved and would take a large, expensive clinical trial to settle. Thus far, no support has been offered for such a trial.

As appetite stimulants are not very effective, this possible action of marijuana is certainly worth consideration. Data suggest that stimulation is inconstant and mild. All of the studies have involved oral THC, which would seem to be the most appropriate route for this purpose, its slower but more prolonged duration of action being consonant with the aims of treatment. Anabolic steroids offer another approach to this indication. Comparisons between these and THC would be required.

Available medications to relieve muscle spasticity are generally somewhat disappointing. Whether the few reports of benefit from marijuana improve the situation is questionable. The incoordinating effects of this drug might aggravate the underlying neurological condition.

Development of cannabinoids as analgesics is attractive, but it seems obvious that neither oral THC nor smoked marijuana is the best approach. If synthetic cannabinoids could be developed which retain the analgesic action but minimize the mental effects, this indication would be more promising.

Other potential medical uses, such as treatment for glaucoma, asthma, seizures and insomnia or anxiety, not only have very little experimental support but also would seem adequately treated with existing drugs. During the past dozen years, little interest in exploring these is apparent in the medical literature.

A major unresolved issue is the comparison between orally administered THC and smoked marijuana. Many users aver that smoke marijuana may have active ingredients other than THC, as perhaps 300 or so chemicals are present in the plant or in the smoke. As few of these have ever been studied alone (nor will they be), the argument cannot be settled directly. On the other hand, except for some THC-like structures, which are present in marijuana in much smaller amounts, and with far less potency than that of THC, no other active material has been found. Thus, it appears unlikely that some panacea is being missed. As for the kinetic advantages of smoking, immediate effects might be desirable for situations in which immediate action is preferable; most drugs are used for longer-lived conditions in which sustained effects are more essential.

CONCLUSION

It is surprising that more than 35 years after the synthesis of THC, and the resulting capability of clinical pharmacological studies, little published literature has tested various potential therapeutic uses of the drug. Earliest studies were more concerned with the actions of the drug on various organ systems and were not concerned with therapeutic actions. For part of the past 15 years, an increasing literature explored this aspect but has recently dropped off. Therapeutic use has become entwined with the political and legal moves that have polarized investigators. The consequence is that legal steps have been taken which are poorly supported by medical evidence.

For those of us who like to have new treatments accepted on the basis of evidence rather than plebiscite, it has been a discouraging period. The solutions proposed by the recent Institute of Medicine Report would seem to be even more discouraging than those which were obtained before. In view of the fact that marijuana and its constituents may be among the safest materials one can be exposed to, it would seem reasonable to make its testing less, rather than more difficult.

Meanwhile, we must ponder the question, "Are we missing a therapeutic advance or is the lore of the past only folklore that has no place in modern science?" Innovation is desperately needed if we are to settle the question before all chances for proper appraisals are lost.

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