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Medicinal Applications of Delta-9-Tetrahydrocannabinol and Marijuana

Eric A. Voth, MD, and Richard H. Schwartz, MD

The use of crude marijuana for herbal medicinal applications is now being widely discussed in both the medical and lay literature. Ballot initiatives in California and Arizona have recently made crude marijuana accessible to patients under certain circumstances. As medicinal applications of pure forms of delta-9-tetrahydrocannabinol (THC) and crude marijuana are being considered, the most promising uses of any form of THC are to counteract the nausea associated with cancer chemotherapy and to stimulate appetite.

We evaluated the relevant research published between 1975 and 1996 on the medical applications, physical complications, and legal precedents for the use of pure THC or crude marijuana. Our review focused on the medical use of THC derivatives for nausea associated with cancer chemotherapy, glaucoma, stimulation of appetite, and spinal cord spasticity. Despite the toxicity of THC delivered in any form, evidence supports the selective use of pure THC preparations to treat nausea associated with cancer chemotherapy and to stimulate appetite. The evidence does not support the reclassification of crude marijuana as a prescribable medicine.

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From The International Drug Strategy Institute, Topeka, Kansas; University of Kansas School of Medicine, Kansas City, Kansas; and Fairfax Hospital, Falls Church, Virginia. For current author addresses, see end of text.

Marijuana has been widely used for hundreds of years as an intoxicant or an herbal remedy. Pure delta-9-tetrahydrocannabinol (THC) is the major active ingredient in marijuana and is 1 of 66 cannabinoid constituents of marijuana. It is now available by prescription as dronabinol. The use of crude marijuana as a medicine would entail smoking the drug or creating herbal preparations of it. Crude marijuana, an undefined herb containing approximately 480 substances (1), has not been approved by the U.S. Food and Drug Administration for use as a medicine.

We examine the use of THC for medicinal applications in various forms, including pure THC (given orally or as suppositories) and crude marijuana. We also consider the therapeutic benefits and drawbacks of THC.

Methods

Resources discussing the medicinal applications of pure THC and marijuana were identified from our personal libraries and by searching MEDLINE for research published between 1975 and 1996. We used the following MEDLINE search terms: *cannabis*, *cannabinoids*, *marijuana*, and *marijuana smoking*; the search yielded 6059 titles. These titles were then cross-searched with the following terms: *therapeutic use*, *antiemetics*, *glaucoma*, *cachexia/appetite*, *multiple sclerosis*, *palliative care*, or *terminal care*. This search yielded 194 titles on antiemetic properties, 56 on glaucoma, 10 on multiple sclerosis, 23 on appetite, and 11 on palliative or terminal care. Editorials, opinion statements, abstracts, and studies not done in humans were eliminated. Any clinical trials that involved the use of crude marijuana were included. We identified no recent clinical trials of medicinal applications (other than antiemetic properties) done in humans. Thus, we included case reports and summary articles for glaucoma, enhancement of appetite, and multiple sclerosis.

Studies on the physical effects of THC or marijuana were selected from among those that primarily involved human participants, presented recent or new data, and provided information that would illustrate potential complications related to different modes of THC delivery. These studies were also organized to illustrate risks associated with short- or long-term exposure. Most research has focused on either THC or crude marijuana.

Therapeutic Indications for Delta-9-Tetrahydrocannabinol

Nausea Associated with Cancer Chemotherapy

By far, most research on THC has involved the use of oral THC (dronabinol), which does not naturally occur in crude marijuana (2, 3). The studies that we evaluated examined a wide and heterogeneous representation of tumors and chemotherapy regimens (**Table 1**). We found no pattern of THC efficacy for any one type of tumor or chemotherapy. None of the studies compared any form of THC

Table 1. Studies That Used Delta-9-Tetrahydrocannabinol as an Antiemetic Agent for Patients with Cancer Receiving Chemotherapy*

Study (Reference)	Dosage and Form of THC	Patients	Design	Patient Age	Results
		n		*y*	
Sallan et al. (4)	15 mg or 10 mg/m² body surface area orally every 4 hours for 3 days	10	Randomized, double-blind, cross-over	29.5†	THC better than prochlorperazine
Sallan et al. (5)	10 mg/m² orally every 4 hours for 3 days	46	Randomized, double-blind, cross-over	32.5‡	THC better than prochlorperazine
Chang et al. (6)	10 mg/m², orally and smoked, every 3 hours for 5 days	15	Randomized, cross-over	24†	THC better than prochlorperazine
Frytak et al. (7)	15 mg orally	116	Prospective, double-blind	61†	THC equal to prochlorperazine and both drugs better than placebo
Kluin-Neleman et al. (8)	10 mg/m² orally	11	Double-blind, cross-over	34.6†	THC better than placebo
Ekert et al. (9)	10 mg/m² orally compared with metoclopramide	33	Double-blind, cross-over	5–19	THC better than prochlorperazine or oral metoclopramide
Lucas and Laszlo (10)	5–15 mg/m² orally every 4–6 hours 24 hours after chemotherapy	53	Randomized, cross-over	Adults	THC effective
Orr et al. (11)	7 mg/m² orally every 4 hours for 3 days	55	Randomized, double-blind, cross-over	46‡	THC better than prochlorperazine and both drugs better than placebo
Gralla et al. (12)	10 mg/m² orally every 3 hours for 5 days compared with intravenous metoclopramide	27	Randomized, double-blind	Adults	Metoclopramide better than THC
Ungerleider et al. (13)	7.5–12.5 mg orally	214	Randomized, double-blind, cross-over	47‡	THC equal to prochlorperazine
Levitt et al. (14)	Oral THC and smoked marijuana	20	Randomized, double-blind	54.5‡	Oral THC better than smoked THC
Vinciguerra et al. (15)	Approximately 5 mg of smoked marijuana per m²	56	Prospective, uncontrolled	40‡	Smoked THC effective; no controls used
Lane et al. (16)	10 mg oral THC plus prochlorperazine	60	Randomized, double-blind	55‡	Combination more effective than individual drugs

* THC = delta-9-tetrahydrocannabinol.
† Median age.
‡ Mean age.

with the serotonin antagonists ondansetron or granisetron. In fact, numerous safe and effective noncannabinoids are available for the control of chemotherapy-associated nausea (**Table 2**); this is an important point, given the side effects found in studies of THC.

Oral THC has generally been found to be as effective or more effective for nausea than prochlorperazine. Studies by Ungerleider (13), Sallan (4, 5), Frytak (7), and Chang (6) and their colleagues support this conclusion. Because of their uncertainty about the drug being used, 75 of 214 participants withdrew from the study by Ungerleider and colleagues. The other three studies, however, give useful information about side effects and dosage. In the studies by Sallan and colleagues (5, 6), negative side effects occurred in 81% of patients. Nine percent of these patients experienced hallucinosis, distortion of reality, and mental depression. The effectiveness of THC was usually correlated to the onset of a "high" or intoxicated feeling. Frytak and colleagues (7) determined that 32% of patients had toxicity during their study, in which peak levels of THC ranged from 2.7 to 6.3 ng/mL. However, the median age of this study group was 61 years, whereas the median age of the groups in Sallan and colleagues' study was 29.5 years. This older age may explain the increased toxicity seen by Frytak and colleagues.

According to the study by Chang and colleagues (6), plasma THC levels of at least 10 ng/mL were effective in preventing nausea. If nausea occurred after the initial treatment, patients were assigned to smoked THC or placebo. Absorption by the oral and smoked routes varied. The efficacy of the drug with either route is difficult to interpret because the two routes were mixed. However, both THC and prochlorperazine were found to be more effective than placebo.

Placebo was also found to be less effective than THC in the studies by Kluin-Neleman and colleagues (8) and Orr and colleagues (11). Kluin-Neleman and colleagues found the toxicity of THC to be so profound that most patients preferred nausea to THC. Some of the plasma THC levels were high (300 ng/mL), but they were consistent with levels that marijuana users may reach during intoxication (17) and levels that are easily obtainable through smoked or high oral doses. Orr and colleagues studied patients who were refractory to other antiemetic regimens and found that THC was superior to prochlorperazine. The latter, in turn, was superior to placebo. The selection of refractory patients, how-

ever, introduces bias against the regimens that do not include THC.

Patients refractory to other agents were also studied by Lucas and Laszlo (10). The initial dose, 15 mg of THC per m^2 of body surface area, was too toxic and thus was reduced to 5 mg/m^2. Even at the lower dose, nausea completely or partially resolved in 72% of patients.

Although Ekert and colleagues (9) found that oral THC was more effective than oral metoclopramide and prochlorperazine, Gralla and associates (12) (in the only study that used intravenous metoclopramide) found that metoclopramide provided more protection than did THC. Ekert and colleagues found that drowsiness, the major side effect in their study, was more common with THC than with either metoclopramide or prochlorperazine.

In one of the few studies that actually used smoked marijuana to treat nausea caused by cancer chemotherapy, Vinciguerra and colleagues (15) found that smoked marijuana controlled nausea in patients in whom other conventional forms of antiemetic therapy had failed. Persons who responded to smoked marijuana tended to have previously used marijuana. This study was uncontrolled, and patients themselves evaluated the results. Smokers were required to inhale deeply and hold the smoke for 10 seconds; this technique was used to completely smoke four cigarettes during each day of chemotherapy. Twenty-five percent of the patients refused to smoke the marijuana. More than 20% of the patients dropped out of the smoking group before the end of the study, and 22% of the remaining patients reported no benefit from smoking marijuana. Dosing also varied because the dose was rounded to the nearest one fourth of a marijuana cigarette, and THC levels were not checked for consistency of dose response.

In a randomized, double-blind study comparing pure THC with smoked marijuana, Levitt and colleagues (14) found that pure THC was more effective for nausea than smoked marijuana in 35% of patients. Forty-five percent of patients voiced no preference between the two.

Lane and associates (16) compared dronabinol plus prochlorperazine with single antiemetic agents. The combination regimen seemed to slightly mitigate the toxic effects of THC. However, 23% of the 60 patients withdrew from the study because of adverse effects (which were psychotropic effects in all but 1 patient who withdrew).

In summary, oral THC doses of 5 to 15 mg/m^2 have been effective in treating nausea associated with cancer chemotherapy if patients are pretreated and doses are then repeated every 3 to 6 hours for approximately 24 hours. Efficacy is often associated with a sensation of intoxication.

Table 2. Noncannabinoid Medications Used for Nausea Associated with Cancer Chemotherapy*

Phenothiazines
Prochlorperazine (Compazine)
Chlorpromazine (Thorazine)
Thiethylperazine (Torecan)
Perphanazine (Trilafon)
Promethazine (Phenergan)
Corticosteroids
Dexamethasone (Decadron)
Methylprednisolone (Medrol)
Anticholinergics
Scopolamine (Transderm Scop)
Butyrophenones
Droperidol (Inapsine)
Haloperidol (Haldol)
Domperidone (Motilium)
Benzodiazepines
Lorazepam (Ativan)
Alprazolam (Xanax)
Substituted benzamides
Metoclopramide (Reglan)
Trimethobenzamide (Tigan)
Alizapride (Plitican)
Cisapride (Propulsid)
Antihistamines
Diphenhydramine (Benedryl)
Serotonin antagonists
Ondansetron (Zofran)
Granisetron (Kytril)
Tropisetron (Navoban)
Dolasetron

* Adapted with permission from Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. N Engl J Med. 1993;329:1790-6.

Appetite Stimulation

The appetite-stimulating effect of THC may be beneficial for patients with wasting related to the acquired immunodeficiency syndrome (AIDS) and those with severe cancer-related anorexia. The literature contains few studies with objective data on the use of either pure THC or crude marijuana for appetite stimulation. This issue is complex because appetite stimulation is a surrogate measure for useful weight maintenance or gain and for effective calorie intake, which are far more important measures than appetite alone. In one trial (18), appetite improved in patients with terminal cancer who received low-dose oral THC (2.5 mg twice daily, 1 hour after meals). Twenty-two percent of patients withdrew from the trial because of typical cannabinoid toxicity. Only low doses of oral THC were necessary, a factor that helped avoid the toxicity of the typically higher doses received from smoked marijuana. This study was a prospective, unblinded, uncontrolled study; controlled studies are needed.

In a double-blind, placebo-controlled, parallel-group study (19), 2.5 mg of oral THC twice daily effectively stimulated appetite in patients with AIDS. The investigators did not evaluate muscle mass or total body fat but did find that in patients who received oral THC, weight was maintained or increased slightly.

Mattes and colleagues (20) compared the effects of oral and rectal suppository preparations of THC

on appetite stimulation and calorie intake with those of smoked marijuana in healthy persons. All participants in this double-blind, placebo-controlled study were experienced marijuana users; thus, the drug acceptance rate was relatively high. Smoked marijuana was no more effective than suppository THC in stimulating appetite, as measured by calorie intake. Rectal suppositories and oral THC were given at a dosage of 2.5 mg twice daily. Patients assigned to smoked marijuana had to inhale for 3 seconds and hold the smoke deeply in their lungs for 12 seconds; this process was continued until the cigarette was smoked to a stub. The plasma THC levels peaked more quickly with the inhaled THC but also decreased more quickly; in contrast, the levels achieved with suppository THC were more sustained.

Glaucoma

Along with other cannabinoids, THC has been shown to reduce intraocular pressure in laboratory animals and humans who have glaucoma (21–23). Cannabinol, nabilone, THC, and delta-8-tetrahydrocannabinol have been found to decrease intraocular pressure, whereas cannabidiol had no effect. Merritt and colleagues (24) concluded that such side effects as hypotension, tachycardia, palpitations, and altered mental status precluded the use of these drugs in the general population with glaucoma. Intraocular pressure is reduced only if patients stay under the effects of THC almost continuously. Although the reduction in pressure may suggest that THC is beneficial for the treatment of glaucoma, no evidence indicates that either pure THC or crude marijuana affects or arrests the underlying disease.

In summarizing the therapeutic potential of cannabis for glaucoma, Mechoulam and colleagues (25) observed that

> the cannabinoids tested so far appear to be of limited use in the treatment of glaucoma. They appear to act only against a primary symptom of the disease rather than against the underlying disease process, which remains uncertain. The side-effects of those cannabinoids particularly effective in lowering intraocular pressure restrict their clinical usefulness.

Multiple Sclerosis

Anecdotal reports (25) and a case report (26) have suggested that THC has benefits for patients with the spasticity of multiple sclerosis. Objective data on the efficacy of THC or crude marijuana are scant. However, a double-blind, randomized, placebo-controlled study of the effect of smoking marijuana in patients with multiple sclerosis (27) showed that posture and balance were negatively affected by the treatment and were actually worse than at baseline. These findings are consistent with the deterioration of mental, motor, and postural functions seen in normal volunteers by Kiplinger and colleagues (28).

Complications of Delta-9-Tetrahydrocannabinol Use

The toxic or negative effects of exposure to THC largely depend on the route of delivery, the duration of exposure, and the patient's age and immunologic status. For the treatment of nausea, exposure to THC would be brief but repetitive and dependent on the chemotherapy regimen. Short- or long-term use often affects the central nervous system. Both smoked and oral THC have been associated with distortion of reality, euphoria, dysphoria, and changes in coordination and concentration (4–8, 10, 15). Some investigators have found more serious toxic effects, including hallucinosis (7), depersonalization (8), and paranoia (11).

Concentration, motor coordination, memorization, memory retrieval, and the ability to sort unimportant information are all adversely affected by the use of crude marijuana (29–36). One study (17) showed that short-term use impairs driving performance; the performance of complex tasks, such as flying, is also negatively affected (37, 38). Marijuana seems to play a major role in vehicular trauma and impaired driving (39–44). Psychosis is more commonly associated with heavy marijuana use, but serious dysphoria and even hallucinosis have been reported with brief use (45–47).

Such cardiac effects as tachycardia and hypotension are commonly noted with short-term exposure to THC (6, 7, 16, 24). Although this effect may be of minimal consequence to younger persons, elderly patients tend to have worse tolerance of THC (7). It can be anticipated that long-term use in patients with such a disorder as glaucoma would not be well tolerated and might be dangerously toxic.

Respiratory problems are often prevalent in patients with cancer, and persons with AIDS may be harmed by smoking any substance. Smoking marijuana exposes patients to 50% higher levels of the procarcinogen benz-α-pyrene than does smoking tobacco (48). Marijuana smoking results in carboxyhemoglobin levels that are five times higher and tar levels that are three times higher than those produced by tobacco smoking (49). Numerous pathogenic bacteria (such as *Klebsiella*, *Enterobacter*, group D *Streptococcus*, and *Bacillus* species) (50) have been cultured from marijuana, and infections with salmonella (51) and fungi (52) have been associated with marijuana use. Thus, immunosuppressed patients (such as those receiving chemotherapy and those with AIDS) are at particular risk.

As access to marijuana broadens with such legis-

lative actions as proposition 200 in Arizona and proposition 215 in California, various age and demographic groups could have long-term exposure. In addition, if THC or marijuana is used for such applications as treating glaucoma or multiple sclerosis or enhancing appetite in patients with wasting related to AIDS, the patient faces long-term exposure. The possibility of central nervous system, pulmonary, cardiac, and infectious toxicities are of course greatly increased during the repetitive exposure of long-term therapy. Researchers have shown that long-term exposure to smoked marijuana is associated with many adverse effects, including impaired lung function (53–55), reduced specific conductance and increased airway resistance (56), heightened alveolar cellular response (57), and pathologic bronchial abnormality (58). In vitro studies have demonstrated DNA damage to human alveolar macrophages (59) and suppression of antiherpes activity by alveolar macrophages (60). Long-term marijuana smokers have also been found to use health care resources at an increased rate because of respiratory problems (61). Several researchers have voiced concern about the effects of marijuana or THC on systemic immune function (62–64) and other biochemical functions (65).

The long-term use of marijuana by young women for medicinal applications may affect the offspring of these women. In utero exposure to marijuana has been linked to changes in birth length, changes in birth weight, and neurologic abnormalities in newborns (66–71); prevalence of nonlymphocytic leukemia in offspring (72); negative effects on measures of intelligence among 3-year-old children (73); sleep disruption (74); and increased problems with behavior, language, sustained memory, and sustained attention in 4-year-old children (75).

Long-term and repetitive use of THC derivatives, especially by young persons, poses the problem of addiction (76–81). Although this is of minimal concern in patients with terminal cancer, it could be a major problem for persons with glaucoma and those intending to use marijuana as a household herbal remedy.

Medicinal Uses of Crude Marijuana: Past, Present, and Future

The use of marijuana as an intoxicant and its use as an herbal remedy are two separate issues that have become intertwined. The salient questions about the medicinal uses of marijuana are 1) is marijuana safe and effective as medicine and 2) what actually constitutes a medicine?

At the request of the U.S. Congress, the National Institutes of Health (Lee PR. Letter to Congressman Dan Hamburg; 13 July 1994) reviewed the preclinical and human data on the use of crude marijuana as a medicine. The summary opinion stated that

> This evaluation indicates that sound scientific studies supporting these claims are lacking despite anecdotal claims that smoked marijuana is beneficial. Scientists at the National Institutes of Health indicate that after carefully examining the existing preclinical and human data, there is no evidence to suggest that smoked marijuana might be superior to currently available therapies for glaucoma, weight loss associated with AIDS, nausea and vomiting associated with cancer chemotherapy, muscle spasticity associated with multiple sclerosis, or intractable pain.

Supporters of the use of crude marijuana as a medicine have proposed that marijuana be made available as a prescribable medication (82) for the treatment of a wide variety of illnesses, including those discussed here and such conditions as headache, dysentery, menstrual cramps, pain, and depression. The anecdotes supporting the use of crude marijuana as a medicine are not usually submitted to independent medical or scientific evaluation of efficacy or toxicity (83).

Since the early 1970s, supporters of crude marijuana as a medicine have pursued a petition to force the U.S. Drug Enforcement Administration to reschedule marijuana under the Controlled Substances Act from Schedule I (high abuse potential, not available to prescribe) to Schedule II (high abuse potential). In our MEDLINE search, we found almost no evidence of studies on the use of marijuana for medicinal applications that were done before this petition was filed.

Because of long-standing controversy about the rescheduling issue, administrative law judge Francis Young was asked by the Drug Enforcement Administration in 1988 to comment on the merits of rescheduling marijuana (84). Young suggested that marijuana be rescheduled for nausea associated with cancer chemotherapy. He also concluded that the evidence was insufficient to warrant the use of crude marijuana for glaucoma or pain. The administrator of the Drug Enforcement Administration rejected Young's opinion and stated that Young had relied mostly on anecdotal information and ignored the prevailing scientific opinion (85).

The rescheduling petition was then appealed to

Table 3. Criteria for a Drug To Be Considered a Medicine*

The chemistry of the drug must be known and reproducible
Adequate safety studies must have been done
Adequate and well-controlled studies must have proven the efficacy of the drug
The drug must be accepted by qualified experts
The scientific evidence must be widely available

* Information obtained from reference 86.

the U.S. Court of Appeals for the District of Columbia. In rejecting the petition to reschedule marijuana (86), the Court determined that only rigorous scientific proof can satisfy the requirement of "currently accepted medical use," which is necessary for a substance to be considered a medicine (**Table 3**). All potential medicines are submitted to this standard.

Several surveys have examined oncologists' choices of therapy for the nausea caused by chemotherapy. Doblin and Kleiman (87) surveyed 2430 oncologists (response rate, 43%) and found that 44% of the respondents had recommended illegal marijuana to at least one patient having chemotherapy. The results of this survey have been widely misquoted (88, 89). For example, Grinspoon and Bakalar (89) incorrectly stated in a major medical journal that "44% of oncologists," rather than 44% of oncologists responding to the survey, had recommended marijuana to their patients. The results actually corresponded to 6% of practicing oncologists.

Schwartz and Beveridge (90) surveyed oncologists practicing in the Washington, D.C., area to determine their preferences for the treatment of nausea caused by chemotherapy. Oral THC or smoked marijuana ranked ninth out of nine choices for mild nausea and sixth out of nine for severe nausea. Approximately 25% of the respondents who treated their patients with marijuana reported that the patients had adverse side effects.

We posed the same question to 1500 clinical adult oncologists in a survey conducted in 1994 (91) that had a 75% response rate. The choice of serotonin receptor antagonists was also considered in the survey. More than 88% of respondents had never recommended crude marijuana to a patient. Only 1% estimated that they had recommended crude marijuana more than five times a year.

In November 1996, ballot initiatives in California and Arizona allowed physicians to either recommend (California) or prescribe (Arizona) crude marijuana. These initiatives placed no limitations on age or on the disorders for which crude marijuana could be used. The medical significance of these initiatives is that they circumvent the U.S. Food and Drug Administration process for assuring safety and efficacy and that they may expose patients to the delivery of a crude herbal substance through smoking.

Conclusions

The literature suggests that pure THC is useful for nausea associated with cancer chemotherapy and that it may be useful in low doses for appetite stimulation in patients with the AIDS wasting syndrome. Both marijuana and pure THC may have toxic effects, and the therapeutic benefits of these substances must be carefully weighed against these effects.

Research has recently defined the presence of a cannabinoid receptor and the existence of an endogenous cannabinoid, anandamide (92). It has also shown that cannabinoids have affinity for various locations in the brain. It is conceivable that synthetic cannabinoids could be developed to minimize toxicity and maximize therapeutic benefits, and active research into these possibilities seems appropriate. New delivery systems (such as suppositories [20] or nasal inhalers) for the administration of pure THC, as well as the current availability of numerous effective antiemetic agents, precludes the perceived need to smoke crude marijuana for medicinal purposes. Pure THC is already available as a prescription medication. Crude marijuana does not qualify as a medicine and remains a Schedule I drug.

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Requests for Reprints: Eric A. Voth, MD, The International Drug Strategy Institute, 901 Garfield, Topeka, KS 66606.

Current Author Addresses: Dr. Voth: The International Drug Strategy Institute, 901 Garfield, Topeka, KS 66606.
Dr. Schwartz: 410 Maple Avenue, Vienna, VA 22180.

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