Medical Marijuana for Cancer

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Marijuana has been used for centuries, and interest in its medicinal properties has been increasing in recent years. Investigations into these medicinal properties has led to the development of cannabinoid pharmaceuticals such as dronabinol, nabilone, and nabiximols. Dronabinol is best studied in the treatment of nausea secondary to cancer chemotherapy and anorexia associated with weight loss in patients with acquired immune deficiency syndrome, and is approved by the US Food and Drug Administration for those indications. Nabilone has been best studied for the treatment of nausea secondary to cancer chemotherapy. There are also limited studies of these drugs for other conditions. Nabiximols is only available in the United States through clinical trials, but is used in Canada and the United Kingdom for the treatment of spasticity secondary to multiple sclerosis and pain. Studies of marijuana have concentrated on nausea, appetite, and pain. This article will review the literature regarding the medical use of marijuana and these cannabinoid pharmaceuticals (with emphasis on indications relevant to oncology), as well as available information regarding adverse effects of marijuana use. **CA Cancer J Clin 2015;65:109-122. © 2014 American Cancer Society.**

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Introduction

As more states pass laws legalizing marijuana for medical use, the need for accurate information regarding the therapeutic effects of marijuana grows. Patients and clinicians currently face choices regarding the therapeutic use of both pharmaceutical and nonpharmaceutical cannabinoid products.

To inform these choices, a review of the published peer-reviewed literature regarding marijuana and cannabinoid pharmaceuticals was undertaken. This review of cannabinoid pharmaceuticals is relevant to patients and clinicians living in areas where these agents are approved by the US Food and Drug Administration (FDA) or corresponding agencies of other nations. This review of marijuana is intended to guide decisions of patients and clinicians living in areas where the recommendation, purchase, possession, and/or use of marijuana are not subject to criminal penalty. This is not meant as a recommendation for the use (or not) of marijuana, or of the legal and regulatory policies surrounding such use.

Background

Marijuana

Marijuana, the dried leaves of the Cannabis sativa plant, has long been used both recreationally and as a medicine.[1] (Although more than one species of Cannabis can be used for its psychoactive properties [such as C. afghanica or indica, used to make hashish[2]] for the purposes of this document, the term "cannabis" will be used to mean Cannabis sativa.) Its use in the United States was curtailed in the early 20th century, first by various state laws and then in 1937 by the Marihuana Tax Act, a federal law. Since that time, although the specific applicable law has changed, the manufacture, importation, possession, use, and distribution of marijuana has remained illegal under federal law. At this time, the US Drug Enforcement Administration lists marijuana and its cannabinoids as Schedule I controlled substances, which means that they cannot legally be prescribed under federal law. Schedule I drugs are said to: 1) have a high potential for abuse; 2) have no currently accepted medical use in treatment in the United States; and 3) have a lack of accepted safety for use under medical supervision. Other Schedule I drugs include heroin and 3,4-methylenedioxy-N-methylamphetamine (MDMA or ecstasy), whereas cocaine is a Schedule II controlled substance.[3] Although cannabinoids from marijuana are Schedule I substances, some synthetic cannabinoids are not (these are discussed later).

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Because marijuana is a Schedule I controlled substance, physicians and other health care professionals who write prescriptions for it can be prosecuted under federal law. A number of states have passed laws allowing for the medical use of marijuana. In those states, a health care practitioner provides an "authorization" for that use that, based on previous court action, is considered by the federal courts to be protected physician-patient communication.[1]

Marijuana can be used to make hashish and hash oil, which contain concentrated cannabinoids (cannabinoids are discussed below). Both marijuana and hash oil can be consumed by inhalation (smoking and vaporizing) and by mouth (drinking it as a tea or eating after it is mixed into foods, such as baked goods).

In addition to the cannabinoids responsible for its psychoactive effects, marijuana smoke contains many of the same chemical constituents as tobacco smoke. Some of these, such as 4-aminobiphenyl, arsenic, benzene, cadmium, formaldehyde, and lead, are known human carcinogens (for some of these, marijuana smoke contains more or less than the smoke of tobacco cigarettes). The smoke also contains toxicants such as ammonia, carbon monoxide, hydrogen cyanide, and tar. Unlike tobacco smoke, marijuana smoke does not contain nicotine or tobacco-specific nitrosamines (which are derived from nicotine).[4] Although in mutagenicity assays marijuana smoke condensates had comparable or even somewhat less mutagenicity than tobacco smoke condensates,[5] smoking marijuana is linked to higher carboxyhemoglobin levels, inhaled tar, and tar retained in the lungs compared with smoking filter-tipped cigarettes.[6] This may be due to observed differences in smoking behavior, such as puff volume, depth of inhalation, and breath holding.[6,7]

Vaporizing marijuana by heating it to temperatures between 180°C and 200°C releases substantial amounts of cannabinoids with only trace amounts of a few other chemicals.[8,9] Vaporization has become an alternative to smoking as a means of inhaling marijuana.

Cannabinoid Receptors and Cannabinoids

Cannabis sativa contains a number of chemical compounds, some of which are classified as cannabinoids. "Cannabinoid" was the term originally used for C21 terpenophenolic compounds originally found in this plant. These compounds were found to activate cannabinoid receptors in the brain, and now this term is also used to describe other compounds that activate those receptors, even if they do not have a similar chemical structure.[10] Two major types of cannabinoid receptors have been characterized: CB1 and CB2. CB1 receptors are found mainly in central and peripheral neurons, whereas CB2 receptors are found most often in immune cells. Nevertheless, CB1 receptors can be found in immune cells, whereas CB2 receptors can be found in neurons.[10] These receptors, along with endogenous cannabinoid receptor agonists (endocannabinoids, molecules naturally found in and produced by the body that activate these receptors), are known collectively as the endocannabinoid system.[10]

Although there are more than 60 cannabinoids in marijuana,[10] 2 in particular have been the subjects of most studies examining medicinal uses: delta-9-tetrahydrocannabinol (Δ9-THC, often referred to just as THC) and cannabidiol (CBD).

THC is often called the major psychoactive component of marijuana because it appears to be responsible for the feeling of "high" reported by consumers of marijuana. In addition to euphoriant properties, it also has analgesic, antiemetic, antiinflammatory, and antioxidant properties.[10]

CBD is another major cannabinoid found naturally in the marijuana plant. Although CBD has low affinity for CB1 and CB2 receptors, at low concentrations it can antagonize CB1/CB2 agonists and may even behave as an inverse agonist.[11] Although in the past it was called "nonpsychoactive," CBD has anxiolytic and antipsychotic properties. It also has anticonvulsive properties and can counteract some of the psychoactive effects of THC.[10,12] It also has reported efficacy in the treatment of pain, although this may be due more to its anticonvulsive effects than an antinociceptive effect.

Based on a study of marijuana seized in California, the content of THC in marijuana by weight has increased over time, with a median potency increasing from 4.18% in 1996 to 13.95% in 2008. In contrast, the CBD content has gone down, with a resultant increase in the THC:CBD ratio.[13] Strains of marijuana with high CBD content and low THC content have been cultivated and have been used by some to treat forms of refractory childhood epilepsy.[14,15] Formal clinical trials of this, however, are lacking.[16]

Because marijuana is a Schedule I controlled substance, marijuana used for research must be obtained through the National Institute of Drug Abuse (NIDA). Any limits in terms of the strains available through the NIDA limits the research that can be conducted. In July 2014, a representative from the NIDA reported that the THC content in the strains of marijuana currently available for clinical trials ranged from 0.001% to 13%. None of the marijuana available at that time through the NIDA had a "high CBD content," and was not expected to be available until 2015 (H. Singh, personal communication, July 2014).

Delta-9-tetrahydrocannabinol

THC is highly lipophilic and is water insoluble. It is rapidly absorbed into the blood from inhaled marijuana smoke, with plasma levels becoming detectable within seconds and peak plasma levels noted in fewer than 10 minutes. Peak plasma levels are directly related to the THC content of the marijuana that is smoked.[7] The bioavailability of THC from smoking marijuana varies based on depth of inhalation, puff, and

breath-holding duration, and is estimated to be between 10% to 35%, with higher systemic bioavailability for heavy users than occasional users. Smoking marijuana through a pipe instead of a cigarette can result in higher THC absorption because this results in less THC loss in sidestream smoke.[7]

A human study of vaporization of marijuana found that this delivery method yielded similar plasma THC levels compared with marijuana smoking, with lower carbon monoxide levels.[9]

Characterization of absorption of THC after oral administration has largely been based on studies of the pharmaceutical dronabinol (see below), although there have been a few studies of marijuana in baked goods. Absorption after oral administration has been described as "slow and erratic," resulting in "low and irregular" plasma levels. THC can be degraded by acid, which could potentially lower the amount available to be absorbed by the stomach. It is known to undergo extensive first-pass metabolism.[17] After oral ingestion, plasma levels usually peak after 60 to 120 minutes, although in some subjects it can take as long as 4 hours or more to observe peak plasma levels. Some subjects can even have more than one peak after a single oral dose.[7] Bioavailability after oral ingestion is approximately 6%, but with high variability between subjects.[7]

THC can also be administered via the oral mucosa. Mean plasma levels reached the threshold of detection at 45 minutes after sublingual administration of a whole-plant cannabis extract containing THC (range, 30-120 minutes; the mean peak plasma levels were noted 100-130 minutes after administration [higher concentration drops showed a later peak]).[18] In a study comparing the pharmacokinetics of oral THC with those of THC in a whole-plant cannabis extract (nabiximols), the time to maximal concentration was increased in the latter, although the difference was not statistically significant. Delivery via the oral mucosa resulted in slightly increased bioavailabilty compared with ingestion.[19] The bioavailability of THC, in terms of peak plasma level and area under the curve, is increased if the oral mucosal spray is administered during a fed state.[20]

In the blood, 90% of THC is distributed to the plasma, and is mainly bound to plasma proteins such as lipoproteins and albumin. Approximately 10% of THC in the blood is distributed in red blood cells. THC rapidly penetrates highly vascularized tissues including the liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland. Only approximately 1% of a dose of THC given intravenously is found in the brain at the time when the psychoactive effects are peaking. Oxidative metabolism of THC yields an active metabolite, 11-hydroxy-delta 9-tetrahydrocannabinol (11-OH-THC). Over time, THC accumulates in less vascularized tissues and finally in body fat, although the exact composition in body fat is not known and may include hydroxyl metabolites and fatty acid conjugates.[7]

When marijuana is smoked, THC levels peak within 6 to 10 minutes, whereas 11-OH-THC levels peak within 9 to 23 minutes. After inhalation, maximal psychotropic effects occur after 20 to 30 minutes and continue for 45 to 60 minutes or longer depending on the THC concentration of the marijuana.[7]

Levels differ after oral ingestion, with peak THC levels occurring hours after ingestion and 11-OH-THC levels that can exceed THC levels. Psychotropic effects are noted within 30 to 90 minutes, peak within 2 to 4 hours, and decline to low levels after 6 hours.[7]

THC crosses the placenta and can be found in small amounts in breast milk.[7]

Cannabidiol

CBD is also highly lipophilic. The absorption and kinetics of CBD from inhaled marijuana smoke have been described as being similar to those of THC, with an average systemic bioavailability of 31% in marijuana smokers (range, 11%-45%).[7] Again, similar to THC, CBD oral bioavailability is poor, in the range of 13% to 19%.[21] Peak plasma levels in one study occurred after 1.3 hours.[19] Peak plasma levels are similar when CBD is administered as an oral mucosal spray along with THC; however, the time to maximal concentration is longer.[19] The bioavailability of CBD, in terms of peak plasma level and area under the curve, is increased if the oral mucosal spray is administered during a fed state.[20]

Pharmaceutical Forms of Cannabinoids

Two cannabinoids are approved by the FDA and therefore can be legally prescribed in the United States according to federal law. One, dronabinol, contains the trans isomer of THC dissolved in sesame oil contained within a gelatin capsule. The THC for this drug is synthetically derived. This drug is approved by the FDA approved for 2 indications: 1) chemotherapy-induced nausea and vomiting (CINV); and 2) anorexia associated with weight loss in patients with the acquired immunodeficiency syndrome.[22] The second, nabilone, is a synthetic cannabinoid that mimics the action of THC. It is approved by the FDA to treat CINV.[23] Both drugs are only available as capsules. Nabilone is classified as a Schedule II controlled substance, whereas dronabinol is classified as a Schedule III controlled substance. The usefulness of these drugs for treating acute nausea and vomiting is hampered by the need for oral administration and absorption from the stomach, as well as the length of time to reach peak plasma levels.

Another cannabinoid pharmaceutical of note is nabiximols. Nabiximols is a whole-plant extract of marijuana, and contains THC and CBD in a 1.08:1.00 ratio. It is administered as an oral mucosal spray.[19] This drug is currently in clinical trials in the United States for the treatment of pain,

and is approved for use in Canada and parts of Europe for the treatment of spasticity from multiple sclerosis. It is also approved in Canada under the Notice of Compliance with Conditions program for the treatment of some types of pain.

A liquid containing cannabidiol without THC will also soon become available in the United States through a clinical trial to treat Lennox-Gastaut syndrome[24] and Dravet syndrome,[25] rare forms of childhood-onset epilepsy. A phase 2 clinical trial of this drug in patients with schizophrenia is currently ongoing.[26]

Review of Potential Medical Uses for Marijuana and Cannabinoids in Cancer

Although categorization of marijuana as a Schedule I controlled substance can make broad-based research difficult, marijuana, THC, and cannabinoid pharmaceuticals have been studied for a number of medical applications, including the treatment of nausea, pain, anorexia and weight loss, seizures, spasticity, and glaucoma. This review concentrates on the uses of marijuana and cannabinoids that most directly impact the patient with cancer: nausea, pain, and anorexia and weight loss. This is followed by a short review of clinical trials of cannabinoids as anticancer agents.

Methods

To review the evidence for medical uses of marijuana and cannabinoids, a search of PubMed was performed using the search terms "marijuana," "cannabis," "delta-9-tetrahydrocannabinol," "dronabinol," "nabilone," "nabiximols," and "cannabidiol." The PubMed search was initially limited to English-language articles that were clinical trials. The abstracts and articles were then reviewed by hand to find clinical trials that evaluated the use of marijuana or cannabinoids for the treatment of the following: nausea and vomiting, pain, or poor appetite and weight loss. To augment the PubMed search, the reference sections from review articles, meta-analyses, and practice guidelines were reviewed to find additional clinical trials.

Nausea and Vomiting

Marijuana

A search of PubMed found only 2 studies of smoked marijuana in the treatment of CINV. These studies were of similar design, comparing smoked marijuana with placebo with each patient serving as his or her own control. In one study, 15 patients who had been treated with high-dose methotrexate were given both oral THC and smoked marijuana. The THC and smoked marijuana were effective in reducing nausea and vomiting in 14 of 15 patients compared with placebo. This study also examined plasma levels of THC and found a correlation between higher levels and antiemetic effect.[27] The second study of 8 patients who received chemotherapy with doxorubicin and cyclophosphamide did not demonstrate an improvement in nausea and vomiting with marijuana and oral THC compared with placebo.[28]

In 2001, an article by Musty and Rossi reviewed a number of studies of marijuana for the treatment of CINV that had been conducted by state health departments, but which had not been reported in publications indexed in PubMed. For some studies, patients were given oral THC supplemented with smoked marijuana. In some studies, oral THC was compared with smoked marijuana. Some studies were not controlled and one had an active control (a phenothiazine) or the active control was oral THC. In these studies, smoked marijuana was found to be more effective than previous treatments for CINV. It was at least as effective as oral THC or a phenothiazine (Table 1).[27-29]

Pharmaceuticals

The efficacy of oral THC in patients with CINV has been demonstrated in a number of studies of dronabinol. Some of these studies were placebo controlled[30-33] and in 2 studies each patient acted as his or her own control.[30,32] In some studies, dronabinol was compared with an active control (prochlorperazine,[31,33-38] haloperidol,[37,39] metoclopramide,[34,40] or ondansetron[41]). In one study, although dronabinol was effective, some patients preferred the placebo due to side effects.[32] The combination of dronabinol and prochlorperazine was found to be more helpful than either drug alone in one study,[42] whereas the combination of dronabinol and ondansetron was not found to be better than either drug alone for delayed emesis in another study.[41] Dronabinol was also efficacious for nausea secondary to radiotherapy in one study.[43]

The effect of nabiximols on delayed emesis after chemotherapy (generally moderately emetogenic regimens) was examined in a placebo-controlled study of 16 patients. In this pilot study, nabiximols was superior to placebo for delayed emesis, but was no more helpful than placebo for acute emesis (ie, emesis occurring within the first 24 hours of chemotherapy).[44]

The efficacy of nabilone in patients with CINV has also been explored in a number of studies. Many of these studies used a crossover design. Nabilone was found to be superior to placebo in 3 studies.[45-47] A number of studies also compared single-agent nabilone with active controls such as metoclopramide,[48] prochlorperazine,[49-55] domperidone,[56,57] and alizapride,[55,58] and found that nabilone was at least as effective and sometimes more effective than the control drug. However, nabilone was associated with more severe central nervous system side effects than the comparator drugs such as

TABLE 1. Effect of Smoked Marijuana on Chemotherapy-Induced Nausea and Vomiting

STUDY	DESIGN	SUBJECTS	N	HOW ADMINISTERED	CONTROL	RESULTS
Chang 1979[27]	RCT/crossover	Patients receiving high-dose methotrexate	15	Smoked marijuana plus oral THC	Placebo (self)	14 of 15 patients had a reduction in nausea and vomiting compared with placebo
Chang 1981[28]	RCT/crossover	Patients receiving doxorubicin and cyclophosphamide	8	Smoked marijuana plus oral THC	Placebo (self)	No improvement in nausea and vomiting compared with placebo
Reported in Musty & Rossi 2001[29]						
State of Tennessee	Single arm	Patients treated with cancer chemotherapy and refractory to other antiemetics	28	Smoked	None	22 patients (80%) rated marijuana as very or moderately effective and 23 (85%) rated their side effects as mild
State of Michigan	RCT with crossover possible	Patients treated with cancer chemotherapy	165	Smoked	Thiethylperazine	Little difference compared with control
State of Georgia	RCT	Patients treated with cancer chemotherapy unresponsive to usual antiemetics	119	Smoked	Oral THC	Oral THC and smoked marijuana found to be equally effective
State of New Mexico (1983)	RCT	Patients treated with cancer chemotherapy	142	Smoked	Oral THC	More patients found smoked marijuana more effective than previous agents compared with those receiving oral THC
State of New Mexico (1984)	RCT initially, with crossover and combined treatment possible	Patients treated with cancer chemotherapy	174	Smoked	Oral THC	Few patients continued with oral THC alone; the majority switched to smoked marijuana or combined treatment, which was better than previous therapy for >90% of subjects
New York Department of Health	Single arm	Patients treated with cancer chemotherapy	199	Smoked	None	Smoked marijuana judged to be more effective than previous therapy 93% of time

N, number of subjects in the study; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol.

drowsiness, postural dizziness and hypotension, lightheadedness, euphoria,[53,56,58,59] and, rarely, hallucinations.[49,55]

Administering nabilone in combination with dexamethasone was found to be superior to nabilone alone in the treatment of CINV. The combination also had fewer side effects.[59] However, the combination of nabilone and prochlorperazine was not found to be superior to nabilone alone in one study.[60] This combination was inferior to dexamethasone plus metoclopramide for emesis after cisplatin-containing chemotherapy in another study.[61]

Nabilone was also found to be as effective as metoclopramide for the treatment of radiation-induced emesis in one study, although nabilone treatment was linked to an increased incidence and severity of adverse reactions.[62] In another study, it was found to be as effective as metoclopramide in the treatment of postoperative nausea and vomiting in women who underwent abdominal hysterectomies.[63]

Pain

Marijuana

A few studies to date have explored the effects of smoked marijuana on experimentally induced pain. Smoked marijuana improved pain tolerance in one study.[64] In another study, smoked marijuana decreased pain sensitivity and intensity and improved pain tolerance in pain induced by the cold pressor test, in which the subject places his or her hand in water at a temperature of 4°C.[65] In another study, smoked marijuana had antinociceptive effects based on increased latency of finger withdrawal from radiant heat stimulation compared with placebo.[66] In a study that induced pain by injecting capsaicin intradermally, medium-dose marijuana decreased pain, whereas a higher dose increased pain (Table 2).[64-72]

Studies of smoked marijuana in patients with pain that was not experimentally induced have concentrated on those

TABLE 2. Effect of Smoked Marijuana on Pain

STUDY	DESIGN	SUBJECTS	N	HOW ADMINISTERED	CONTROL	TEST	RESULTS
Milstein 1975[64]	RCT	Both experienced marijuana users and non-users of marijuana	32	Smoke inhaled via smoking device	Placebo	Pain tolerance: pressure algometer (metal rod putting pressure on the thumb)	Increased pain tolerance with marijuana compared with placebo, with a larger effect for experienced users compared with nonexperienced
Cooper 2013[65]	RCT	Daily marijuana smokers	30	Smoked marijuana and oral THC	Placebo	Cold pressor test	Marijuana and oral THC decreased pain sensitivity, increased pain tolerance, and decreased subjective ratings of pain intensity
Greenwald & Stitzer 2000[66]	RCT	Male regular marijuana users	5	Smoked	Placebo	Finger withdrawal from radiant heat stimulation	Significant dose-dependent antinociception (increased finger withdrawal latency)
Wallace 2007[67]	RCT	Healthy volunteers	15	Smoked	Placebo	Intradermal capsaicin	No effect with marijuana that was 2% THC by weight, decreased pain with marijuana that was 4% THC by weight, and increased pain with marijuana that was 8% THC by weight
Ware 2010[68]	RCT	Adults with posttraumatic or postsurgical neuropathic pain	21	Smoked	Placebo		A single inhalation of 25 mg of 9.4% THC marijuana 3 times daily for 5 d reduced the intensity of pain and improved sleep
Ellis 2009[69]	RCT/crossover	Adults with HIV-associated distal sensory predominant polyneuropathy refractory to at least 2 previous analgesic classes	28	Smoked	Placebo		Greater pain relief with marijuana than placebo and more subjects had at least 30% pain relief with marijuana compared with placebo (46% vs 18%)
Abrams 2007[70]	RCT	Adults with painful HIV-associated sensory neuropathy	50	Smoked	Placebo	Brush and von Frey hair stimuli	Marijuana reduced daily and chronic pain more than placebo; also reduced hyperalgesia as measured by brush and von Frey hair stimuli tests
Wilsey 2013[71]	RCT/crossover	Adults with central and peripheral neuropathic pain	39	Vaporized	Placebo		Analgesia with both 3.53% THC-by-weight marijuana and 1.29% THC-by-weight marijuana compared with placebo with no significant difference noted between the doses/concentrations
Abrams 2011[72]	Single arm	Adults with chronic pain being treated with slow-release opiates	21	Vaporized	None		Pain decreased with no effect on plasma opioid levels

HIV, human immunodeficiency virus; N, number of subjects in the study; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol.

with neuropathic pain. In one study, the pain was postsurgical or posttraumatic.[68] In others, study subjects had painful human immunodeficiency virus (HIV)-associated sensory neuropathy.[69,70] In all of these studies, smoked marijuana was found to be better than placebo in relieving pain. Another study examined the effects of marijuana that was vaporized (and not smoked) and found that it too was better than placebo at relieving neuropathic pain (patients

had central or peripheral neuropathic pain that was resistant to standard treatments).[71] A small study examined the effects of vaporized cannabis on pain in individuals taking extended-release opiates for chronic pain. It found that pain improved with the administration of vaporized cannabis, whereas there was no change in plasma opioid levels.[72]

Pharmaceuticals

Only a few studies using nabiximols to treat cancer pain have been published to date. One study randomized patients with cancer pain despite treatment with opioids to either nabiximols, oromucosal THC, or placebo and found that nabiximols improved pain scores better than placebo, whereas the difference between THC and placebo did not reach statistical significance.[73] In a continuation of this study, patients receiving nabiximols continued to have pain relief, as well as improvements in insomnia and fatigue, without a need to increase their doses over time.[74] Another study of patients with advanced cancer with pain refractory to opioids found that patients receiving low and medium doses reported improved analgesia compared with placebo.[75]

For neuropathic pain, the results of studies of nabiximols have been mixed. In a double-blind, placebo-controlled, crossover pilot trial, nabiximols was not found to be superior to placebo for the treatment of chemotherapy-induced neuropathic pain. However, because 5 of the 16 patients reported significant pain relief (greater than 2 points on a numeric scale), the authors concluded that further study was warranted.[76] The effect of nabiximols on central neuropathic pain was considered to be equivocal in one randomized study, because it was not significantly better than placebo during the treatment phase but showed superiority over placebo in the withdrawal phase.[77] Nabiximols did improve central neuropathic pain from multiple sclerosis in another randomized trial,[78] and pain relief persisted in the open-label continuation study.[79] This drug was not better than placebo in the treatment of painful diabetic peripheral neuropathy in one study.[80] It was, however, better than placebo in the treatment of neuropathic pain that was unilateral and peripheral in origin in another study.[81] In that study, the origins of the neuropathy included trauma, postinfectious neuropathy, vascular neuropathy, and idiopathic neuropathy.

In a study of patients with rheumatoid arthritis, nabiximols was found to improve pain and sleep quality better than placebo.[82]

Dronabinol has also been studied for pain. In one small study, 5 of 13 patients with chronic nonmalignant pain reported "adequate response" to dronabinol.[83] Another study of patients with chronic nonmalignant pain who were already being treated with opioids found that dronabinol provided additional pain relief and was better than placebo.[84] A study of patients with cancer pain found that THC at a dose of 10 mg had a mild analgesic effect.[85] In a placebo-controlled dose escalation study, pain relief over that of the placebo was noted only at doses of 15 mg and 20 mg. These doses produced substantial sedation and "mental clouding."[86] This drug was not found to be better than placebo, however, in the treatment of postoperative pain in a study of women after abdominal hysterectomy.[87]

An open-label study of dronabinol among patients with neuropathic pain did not find that the drug was beneficial in terms of pain relief, allodynia, quality of life, anxiety/depression, or function.[88] A small pilot study of 7 patients found that dronabinol was no better than diphenhydramine for the treatment of central neuropathic pain from spinal cord injury.[89] This drug was, however, better than placebo in treating central neuropathic pain from multiple sclerosis.[90] In patients with spasticity and pain from spinal cord injury, THC was compared with codeine and placebo. Both THC and codeine improved pain, but only THC improved spasticity.[91]

THC when given intravenously had variable effects on pain caused by dental extraction in a small study. The majority of subjects preferred placebo over THC in this study due to side effects.[92]

Nabilone improved pain from diabetic neuropathy in one placebo-controlled study.[93] Another study compared nabilone with gabapentin as add-on treatment for peripheral neuropathic pain, and found that both treatments improved pain to a similar extent.[94] This drug was not better than placebo in treating chronic neuropathic pain in one study.[95] Nabilone was more helpful than ibuprofen in treating headaches from medication overuse.[96] It was also more helpful than placebo in treating pain related to fibromyalgia.[97]

Nabilone reduced spasticity-related pain in patients with upper motor neuron disease in a placebo-controlled, double-blind, crossover trial.[98] The drug also reduced spasticity in a small randomized, double-blinded, crossover pilot study of patients with spinal cord injury.[99]

The drug was not, however, helpful in the treatment of patients with acute postoperative pain, and in fact was linked to worsening of pain scores.[100] It was also not found to be helpful in the treatment of capsaicin-induced pain and hyperalgesia.[101] In another study of experimentally induced pain, it was only helpful in one aspect (reduced temporal summation) in women but not in men.[102]

Treatment of Poor Appetite and Weight Loss

Marijuana

Smoked marijuana caused an increase in caloric intake in studies of healthy volunteers.[103,104] Studies of the effects of smoked marijuana on appetite have focused on individuals with HIV. HIV-positive clinic patients who report using marijuana indicate that it helps with appetite and nausea

TABLE 3. Effect of Smoked Marijuana on Appetite and Weight Loss

STUDY	DESIGN	SUBJECTS	N	HOW ADMINISTERED	CONTROL	RESULTS
Foltin 1986[103]	RCT/crossover	Healthy volunteers	9	Smoked	Placebo	Single marijuana cigarette had no effect on caloric intake, but 2 to 3 cigarettes were found to increase the average daily caloric intake
Hart 2002[104]	Staggered double-dummy	Healthy marijuana smokers	11	Smoked	Oral THC and placebo	Both smoked marijuana and oral THC were found to increase food intake
Woolridge 2005[105]	Cross-sectional questionnaire	HIV-positive outpatients	523			27% of patients surveyed used marijuana; 97% reported that marijuana improved appetite
Haney 2005[106]	Staggered double-dummy	HIV-positive marijuana smokers with and without muscle wasting	30 (15 in each group)	Smoked	Oral THC and placebo	Smoked marijuana and oral THC improved caloric intake compared with placebo in the group with muscle wasting but not in the group without muscle wasting
Haney 2007[107]	RCT/crossover	HIV-positive marijuana smokers	10	Smoked	Oral THC and placebo	Smoked marijuana and oral THC increased caloric intake and weight in a dose-dependent manner compared with placebo

HIV, human immunodeficiency virus; N, number of subjects in the study; RCT, randomized controlled trial; THC, delta-9-tetrahydrocannabinol.

(as well as other symptoms).[105] In placebo-controlled studies of HIV-positive chronic marijuana smokers, smoking marijuana led to an increase in food intake.[106,107] This may be mediated through increases in the hormones ghrelin and leptin, as well as decreases in peptide tyrosine tyrosine, which help regulate appetite (Table 3).[103-108]

Oral THC (as dronabinol) has been studied in the treatment of anorexia and wasting associated with HIV. It seemed to be comparable to smoked marijuana in its effect on food intake and body weight in previous studies.[106,107] In a study comparing it with megestrol acetate, it was inferior to the 750-mg dose of megestrol acetate and was not linked to weight gain.[109] In a study comparing it with a placebo in patients with HIV, many of whom had experienced weight loss, this drug was linked to improvements in appetite and nausea, although there was no significant effect on weight noted.[110] In a continuation of that study, weight remained stable in patients being treated with dronabinol.[111]

In patients with cancer, one study indicated that dronabinol could improve altered taste sensations.[112] In a phase 2 study, it did seem to help with appetite in patients with cancer, but it did not prove to be better than placebo in a double-blind trial.[113] In a study of patients with cancer who were undereating or had weight loss in which dronabinol was compared with megestrol acetate, a greater percentage of patients treated with megestrol acetate reported appetite improvement and weight gain compared with patients treated with dronabinol.[114]

Dronabinol also improved food intake and decreased disturbed behavior in a small study of elderly patients with presumed Alzheimer disease.[115]

Cannabinoids as Antineoplastic Agents

Cannabinoid receptors have been found on cancer cells,[116] and cannabinoids have shown evidence of antitumoral effects in vivo and in vitro in preclinical studies[116] in glioma,[117] hepatocellular carcinoma,[118] prostate cancer,[119] lung cancer,[120] cholangiocarcinoma,[121] breast cancer,[122] and melanoma.[123] Clinical trials, however, have been limited. A small phase 1 study in patients with glioma demonstrated that THC could be administered safely intratumorally.[124] Another study found that a cannabis tea did not affect the pharmacokinetics of the chemotherapy agents docetaxel or irinotecan.[125] Studies of cannabinoids in the treatment of patients with glioma are currently ongoing.[126,127]

Potential Harms of Marijuana

Cancer

Because smoked marijuana contains carcinogens, it does have the potential to cause cancer. Few studies, however, have examined this. Most of the studies that have looked for a link between marijuana smoking and cancer have been case-control studies in which individuals with cancer were compared with those without the disease. In these studies, tobacco smoking was found to be an important confounder. In addition, the retrospective nature of these studies leads to a potential of recall bias.

Although one case-control study did show a link between marijuana smoking and incidence of head and neck cancer,[128] many others did not.[129-132]

For lung cancer, a case-control study found no link to marijuana smoking (even for those smoking more than one

marijuana cigarette per day for 30 years) after adjustment for confounders such as cigarette smoking.[132] Another case-control study, set in Tunisia, Morocco, and Algeria, found a higher risk of lung cancer in marijuana smokers; however, the results are difficult to interpret because all of those who smoked marijuana in the study also smoked tobacco.[133] A recent cohort study of military conscripts indicated a higher risk of lung cancer in individuals who indicated that they had smoked marijuana more than 50 times at the time of their baseline examination. The elevated risk persisted after adjustment for baseline smoking status (among factors). However, this study only collected information at a single time point.[134]

In terms of other cancers, 2 case-control studies found an increased risk of testicular cancer among users of marijuana,[135,136] and a hospital-based case-control study found a link between habitual marijuana use and transitional cell carcinomas.[137] Again, however, both the patients with cancer and the controls had high rates of tobacco use (greater than 90%).

There are no published studies of oral marijuana ingestion and cancer risk, nor are there any studies of vaporized marijuana and cancer risk.

Lung Problems

Marijuana smoking can cause injury to the large airways and an increase in the symptoms of chronic bronchitis. However, these effects subside after discontinuation of use, and there is no clear link between smoking marijuana and the development of chronic obstructive pulmonary disease.[138]

Neuropsychiatric

Studies have found acute effects of marijuana that include a reduction in performance at tests measuring memory, attention, reaction time, tracking, and motor function, which are THC dose-dependent. These effects are highest during the first hour for smoked marijuana, and at 1 to 2 hours after oral intake. The effects dissipate to the point of becoming undetectable after 3 to 4 hours. However, differences in cognitive effects are noted with differences in the frequency and chronicity of marijuana use. For example, daily smokers showed greater impairment than those who smoked on average once a month on tests of attentional and executive functions after a minimum of 19 hours of abstinence. In addition, current heavy users can show cognitive impairment for up to 7 days after last use. Studies have indicated that heavy users, while achieving higher THC levels from an equivalent amount of marijuana, demonstrate less impairment in some tests, indicating the development of tolerance for some of the cognitive effects of marijuana intoxication.[139-141]

Although marijuana intoxication often leads to a feeling of euphoria, some individuals experience feelings of anxiety and/or paranoia, with hallucinations and other psychotic symptoms also being described. Generally, these symptoms resolve within minutes or hours, but in some subjects have lasted for days.[142] Although schizophrenic patients report using marijuana to "self-medicate," controlled studies of THC in patients with schizophrenia demonstrated that it can exacerbate schizophrenic symptoms.[143] Studies have also linked cannabis use with an earlier age of onset and an increased incidence of schizophrenia and other psychoses.[143] Some studies have found a potential genetic basis for this.[143] In fact, a recent study found a link between a genetic predisposition toward schizophrenia and an increased use of cannabis in healthy individuals.[144]

Other

Similar to other intoxicants, marijuana can impair driving skills and increase the risk of motor vehicle accidents.[145] Marijuana can also worsen impairment from alcohol,[146] including impairment of driving tasks.[147,148]

In one study, women who used marijuana during pregnancy were more likely to have a stillbirth.[149,152] The use of marijuana during pregnancy has also been linked to adverse neurobehavioral effects in the offspring.[150]

Long-term recreational cannabis use has been linked to a rare condition known as cannabinoid hyperemesis syndrome. The risk of relapse is high unless the patient stops using cannabis.[151]

Summary

Both cannabis and cannabinoid pharmaceuticals can be helpful for a number of problems, including many affecting patients with cancer. There have been fewer studies of marijuana than cannabinoid pharmaceuticals, perhaps in part due to regulatory restrictions, and what studies of marijuana have been conducted to date had a tendency to enroll small numbers of patients. Gaps in the available evidence likely adversely influence the quality of decisions by patients and clinicians. Additional high-quality studies of marijuana and cannabinoid pharmaceuticals in the treatment of a number of medical conditions would better elucidate the clinical effects of the various strains of marijuana and the bioactive compounds found within it. Such studies could also assess how best to administer marijuana and its bioactive components. The differences in pharmacokinetics between oral ingestion and inhalation may mean differences in clinical effect for different indications. For example, given the limitations inherent in using oral medications to treat nausea and vomiting, inhalation of marijuana or a cannabinoid may be better than oral ingestion in treating this condition. However, because marijuana smoke contains toxins and carcinogens, vaporization may be preferable as a way to inhale because it has

less potential for harm. There is also a need for high-quality studies of the long-term effects of marijuana and its cannabinoids. Given the problems with confounding and potential recall bias in case-control studies examining cancer outcomes, these outcomes may be better examined through prospective cohort studies. ■

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