

Review

Medical Marijuana Use in Oncology

A Review

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IMPORTANCE Medicinal marijuana use is currently legal in 23 states and the District of Columbia. As more states approve marijuana use for medical indications, physicians will be asked by their patients for more information regarding the risks and benefits of use. This article reviews the history, adverse effects, and proposed mechanisms of action of marijuana and summarizes the available literature regarding symptom relief and therapeutic value in patients with cancer.

OBSERVATIONS Marijuana in oncology may have potential for use as an antiemetic, for refractory cancer pain, and as an antitumor agent. However, much of the data are based on animal data, small trials, or are outdated.

CONCLUSIONS AND RELEVANCE More research is needed in all areas related to the therapeutic use of marijuana in oncology.

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Medical marijuana use is controversial in American society. While states move to legalize marijuana for medical and/or recreational use, research is needed to elucidate the adverse effects and potential therapeutic benefits of cannabis therapy. This literature review focuses on the history of marijuana use, potential mechanisms of action, the therapeutic use of marijuana in oncology, and its adverse effects.

History and Legal Status

Cannabis has a history of both medicinal and recreational use dating back centuries. Tradition holds that Chinese Emperor Shen Nung touted the benefits of cannabis in the 28th century BC.¹ Cannabis was believed to have healing powers for ailments including rheumatism, gout, malaria, and "absent-mindedness."² In 1611, the Jamestown settlers brought marijuana (commonly known as hemp) to North America, and throughout the colonial period hemp fiber was an important export.² Cannabis was first introduced to Western medicine by surgeon W.B. O'Shaughnessy in the 1840s. While working for the British East India company, he reportedly found it to have good analgesic, anti-inflammatory, antispasmodic, and anticonvulsant properties. During this same time, a French psychiatrist, Jacques-Joseph Moreau, conducted studies that found that marijuana use suppressed headaches, increased appetite, and aided sleep. Marijuana was introduced into the US Pharmacopeia in 1850 and was prescribed for conditions such as labor pain, nausea, and rheumatism.² The passage of the Harrison Act of 1914 defined the use of marijuana as a crime, which led individual states such as California and Texas to pass laws prohibiting marijuana use for nonmedical purposes.³ The US Congress then passed the Marijuana Tax Act, criminalizing the drug in 1937.^{3(pp971-1203)} It was removed from the US

Pharmacopeia in 1941 because it was no longer recognized to have medicinal use.² The Boggs Act and Narcotics Control Act of 1951 increased marijuana possession and distribution penalties and led to the enforcement of mandatory prison sentences.^{3(pp971-1203)} In 1970, marijuana became a Schedule I drug,⁴ a classification given by the US Drug Enforcement Administration to drugs with no currently accepted medical use with a high potential for abuse.⁵ In 1986, the Anti-Drug Abuse Act was passed, reinstating mandatory minimum penalties and increasing federal penalties for both possession and distribution of marijuana.^{6(pp189-190)} It was not until 1996 that California became the first state to relegalize marijuana for use by people with AIDS, cancer, and other serious illnesses.^{6(p321)} In 2010, California rejected proposition 19, which would have legalized marijuana use for recreational purposes.^{7(pp159-215)} In November of 2012, the passage of Colorado's Amendment 64 and Washington's Initiative 502 made them the first US states to pass recreational use laws.⁸ Currently, 23 states and the District of Columbia have laws legalizing marijuana use in some form, with 4 states and the District of Columbia legalizing marijuana for recreational use (Table).⁸

The current state of cannabis use for both medical and recreational purposes in the United States is highly debated. While it is still classified as an illegal substance federally, many states have moved to decriminalize and/or legalize marijuana for medical and/or recreational use.⁹ Despite limited research on the effects of smoked cannabis, states appear to be motivated to legalize marijuana use for financial gain. In 2010, it was predicted that legalizing marijuana use would generate \$8.7 billion in annual federal and state tax revenues while saving billions of dollars that were previously spent for regulating marijuana use.^{10(pp1-62)} The state of Washington generated \$70 million in tax revenue from marijuana sales in the first year of marijuana legalization.¹¹ In addition, many states' residents support marijuana legalization.¹¹

With access to medical marijuana increasing, physicians may be asked for prescriptions and information about this substance. Physicians have mixed attitudes about the legalization of medical marijuana use. In 2005, Charuvastra et al¹² sampled 960 physicians for their opinions about the legal prescription of marijuana as medical therapy. Their results showed that 36% of physicians believe marijuana use should be legal, while 26% were neutral to the proposition. In 2013, Adler and Colber¹³ completed a poll of 1446 physicians and found that 76% approved of using marijuana for a medical purpose. Most physicians in this study cited their "responsibility as caregivers to alleviate suffering" as their reason for support. The American Medical Association has stated that it would support marijuana rescheduling if it facilitated research and the development of cannabinoid-based medicine.¹⁴

Mechanism of Action

The exact mechanism of action of cannabis remains unclear. Cannabis is composed of 3 different bioactive molecules called flavonoids, terpenoids, and cannabinoids. The most well-studied cannabinoid is Δ^9 -tetrahydrocannabinol (THC), the most active constituent of the plant. Small alterations in the structure of cannabinoids, such as THC, can dramatically change their potency.¹⁵ Cannabis exerts its actions by binding to specific receptors called cannabinoid receptors, making up the endogenous cannabinoid system. Devane et al¹⁶ characterized the cannabinoid receptor, whereas Compton et al¹⁷ showed a strong correlation between the binding affinity for the receptor site and the corresponding potency of a large number of cannabinoid analogs. These receptors, called cannabinoid receptors 1 and 2 (CB1 and CB2), work via their action as G-protein coupled receptors, where they inhibit both adenylate cyclase and calcium channels and activate inwardly rectifying potassium channels.¹⁸

The distribution of these receptors accounts for many of the observed effects associated with cannabis use. Cannabinoid 1 receptors appear to be ubiquitously located throughout the body, with the highest concentration of receptors found in the central nervous system. Cannabinoid 1 receptors are well studied given their connection to the observed psychoactive effects of THC.¹⁹ Cannabinoid 2 receptor expression is found mainly in the immune system, with the highest expression seen in B-lymphocytes, involved in immune suppression and cell migration induction.²⁰

In addition to THC, cannabis has high concentrations of cannabidiol (CBD), a nonpsychotropic constituent of the plant.²¹ Cannabidiol's mechanism of action is not clearly understood, but it is thought to modify the metabolism and effects of THC and act as an antagonist of CB1 and CB2 receptors given its low binding affinity.²¹⁻²³ Cannabidiol is also a potent anti-inflammatory agent.²⁴

The role of the endogenous cannabinoid system in both normal functioning and disease is still under investigation. Whereas THC is better researched, less is understood about the other cannabinoids and their exact mechanisms of action, including how synthetic cannabinoids and THC analogs may interact with receptors and produce effects differently. Cannabis has been studied for its use as a treatment in a number of symptoms related to cancer. This review focuses on the research examining cannabis use in chemotherapy-induced nausea and vomiting (CINV), cancer-associated pain, and cannabis as an antitumor agent.

Table. Twenty-Three States and District of Columbia With Legal Marijuana Use^a

State	Year Passed	Personal Marijuana Possession Limit and Home Cultivation Limit
Alaska	1998	1 oz; 6 plants (3 mature, 3 immature)
Arizona	2010	2.5 oz; 12 plants
California	1996	8 oz; 6 mature or 12 immature plants
Colorado	2000	2 oz; 6 plants (3 mature, 3 immature)
Connecticut	2012	1-mo supply (exact amount to be determined)
Delaware	2011	6 oz
Hawaii	2000	4 oz; 7 plants
Illinois	2013	2.5 oz during a period of 14 d
Maine	1999	2.5 oz; 6 plants
Maryland	2014	30-d supply, amount to be determined
Massachusetts	2012	60-d supply for personal medical use
Michigan	2008	2.5 oz; 12 plants
Minnesota	2014	30-d supply of nonsmokable marijuana
Montana	2004	1 oz; 4 plants mature; 12 seedlings
Nevada	2000	1 oz; 7 plants (4 mature, 4 immature)
New Hampshire	2013	2 oz during a 10-d period
New Jersey	2010	2 oz
New Mexico	2007	6 oz; 16 plants (4 mature, 12 immature)
New York	2014	30-d supply nonsmokable marijuana
Oregon	1998	2.5 oz; 24 plants (6 mature, 18 immature)
Rhode Island	2006	2.5 oz; 12 plants
Vermont	2004	2 oz; 9 plants (2 mature, 7 immature)
Washington	1998	24 oz; 15 plants
Washington, DC	2010	2 oz dried; limits on other forms to be determined

^a Voters in Alaska, Colorado, Oregon, Washington, and Washington, DC, approved legalizing recreational marijuana use in November 2014.

Chemotherapy-Induced Nausea and Vomiting

Cannabis is known for its antiemetic properties, which makes it an appealing treatment for CINV. It has been proposed that THC may treat nausea via emetic reflex pathways by acting at receptors located in the nucleus tractus solitarius at the level of the area postrema.²⁵ It has also been shown that THC reverses the effects of 5-HT₃ receptor agonists, which normally induce vomiting.²⁵

Cannabis has anecdotally been effective in suppressing anticipatory nausea. Parker et al²⁶ completed experiments in which house musk shrews (*Suncus murinus*) were repeatedly exposed to contextual cues, which were then paired with the emetic effects of lithium chloride (LiCl) injections. They then confirmed that the shrews had developed a conditioned retching response to the cue even in the absence of LiCl. They then found that pretreatment of the shrews with principal cannabinoids 1 and 2 completely suppressed the retching reaction, while pretreatment with ondansetron did not suppress this reaction. They concluded that marijuana may suppress the expression of anticipatory nausea better than 5-HT₃ receptor antagonists.

There have been numerous studies comparing the antiemetic properties of cannabis and its derivatives to those of other medications used in CINV. Dronabinol, a synthetic THC, and nabilone, a synthetic analog of THC, both oral medications, are well-studied antiemetics, whereas data on smoked cannabis are more limited. With

the availability of effective options such as corticosteroids, serotonin 5-HT₃ receptor antagonists, and neurokinin-1 (NK1) receptor antagonists for the prevention of CINV, cannabinoids are only used for patients intolerant of or refractory to first-line antiemetics.²⁷ There are also no current data comparing smoked cannabis, THC, or its derivatives to current first-line CINV treatment regimens. Marijuana is, therefore, not recommended for the management of CINV, and it is not part of the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for antiemesis.²⁸

There are 2 systematic reviews available for the comparison of THC-derived drugs to older antiemetics. Tramèr et al²⁹ completed a systematic review of 30 randomized comparisons of cannabinoids with placebo or other antiemetics. Three different cannabinoids (oral nabilone, oral dronabinol, and intramuscular levonantadol hydrochloride) were tested as first-line antiemetic agents in 1366 patients to evaluate the complete absence of nausea and vomiting in the first 24 hours of chemotherapy. When comparing all trials, they found that cannabinoids were significantly more effective antiemetics than prochlorperazine, metoclopramide hydrochloride, chlorpromazine, haloperidol, domperidone, or alizapride in patients receiving medium emetogenic regimens (consisting of cyclophosphamide, methotrexate, or fluorouracil) but not highly emetogenic regimens (consisting of high-dose methotrexate, cisplatin, or doxorubicin and cyclophosphamide). Toxic adverse effects were observed. Beneficial nontherapeutic effects were a "high" sensation, sedation, drowsiness, and euphoria, and less desirable adverse effects included dizziness, dysphoria, depression, hallucinations, paranoia, and hypotension. In 18 studies crossover was allowed and 38% to 90% of patients reported preferring cannabinoid therapy for future chemotherapy cycles. Limitations of this review include the potential inconsistent administration times of medications in relation to chemotherapy administration, the overall small sample size of each of the trials compared (range, 8-139 patients), and the heterogeneity of study participants included. Some included patients had refractory CINV or previously used cannabis prior to treatment, which may have influenced their drug response.

Ben Amar³⁰ summarized 15 randomized clinical trials consisting of 600 patients that compared either nabilone to placebo or other available antiemetic drugs as first-line agents. He found nabilone to be superior to prochlorperazine, domperidone, and alizapride, with patients favoring nabilone for continuous use. In the same meta-analysis, he reported that in 14 studies of dronabinol involving 681 patients, the cannabinoid antiemetic effect was significantly greater than that of chlorpromazine and equivalent to metoclopramide, thiethylperazine, and haloperidol. This review does not highlight the timing of drug administration in relation to cytotoxic exposure, the emetogenic nature of the chemotherapeutic regimen used in each study, or the definitions used to assess nausea and vomiting in all trials. The variability within each trial included in the review affects the generalizability of this research to specific populations. Because neither review included trials using current highly effective antiemetic drugs, clinical practice is not affected.

Numerous studies have shown that the combination of THC derivatives with other antiemetics works best for nausea. Plasse et al³¹ reported that combinations of THC and prochlorperazine resulted in enhanced efficacy as assessed by duration and severity of nausea and vomiting. Lane et al³² showed that the combination

of dronabinol and prochlorperazine was significantly more effective than either single agent in controlling CINV.

This potential synergistic effect was not seen when dronabinol was given with ondansetron. Meiri et al³³ compared the administration of dronabinol in combination with ondansetron to ondansetron alone for the treatment of delayed CINV. Patients who were receiving either moderately or highly emetogenic chemotherapy were given dexamethasone, ondansetron, and either placebo or dronabinol before chemotherapy on day 1. The primary outcomes were occurrence and intensity of nausea, vomiting, and retching episodes, and total response defined as nausea intensity less than 5 mm on a 100-mm visual analog scale, no vomiting or retching, and no use of rescue antiemetics. They found total response to be similar in all treated groups in comparison with placebo. Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. In conclusion, dronabinol and ondansetron had similar effectiveness for CINV, but combination therapy was not more effective than either agent alone.

Case reports of cannabinoid-induced hyperemesis syndrome have increased as access to marijuana increases across the country. Cannabinoid hyperemesis syndrome is characterized by long-term cannabis use, cyclic episodes of nausea and vomiting, and frequent hot bathing. It occurs via an unknown mechanism.³⁴ Patients using cannabis on a long-term basis while undergoing chemotherapy could develop cannabinoid hyperemesis syndrome, although to date no cases have been reported.³⁵

There are currently no clinical trials comparing smoked cannabis to current first-line antiemetic therapies. Given the lack of data with regard to smoked cannabis as a form of treatment, it is not recommended as a first-line antiemetic. More research examining the mechanism by which cannabinoids may function and clinical trials using current antiemetic regimens as comparison to cannabis in moderate to highly emetogenic chemotherapies are needed.

Cancer-Associated Pain

Cannabinoids have been studied for their analgesic potential in cancer-associated pain, specifically neuropathic pain.³⁶ Cannabinoid 1 receptors, in the central nervous system, are found in high concentrations in areas of the brain that modulate nociceptive processing, with a similar distribution to opioid receptors.³⁷ Cannabinoids may also act on mast cell receptors, inhibiting the release of inflammatory substances and enhancing the release of analgesic opioids to combat inflammation.^{38,39} Cannabinoids may be effective in treating neuropathic pain by inhibiting the acute pain response in C-fibers and the windup phenomenon that contributes to the development of hyperalgesia.³⁶ Cannabinoids are also believed to have a synergistic analgesic effect with opioids via unknown mechanisms.⁴⁰ Cannabinoids may function to suppress spinal and thalamic nociceptive neurons.⁴¹

Several clinical trials examining the use of cannabinoid receptor agonists to relieve chronic cancer pain have been published. Noyes et al⁴² examined 10 patients with various cancer diagnoses in a double-blind placebo-controlled trial. They found that the analgesic effect of THC at higher doses of 15 and 20 mg was significantly superior to placebo, but with patients reporting substantial sedation at those doses. Noyes et al⁴³ also completed another study of 36 patients comparing placebo to THC at both 10 and 20 mg and to codeine at 60 and

120 mg. They reported that 10 mg of THC produced analgesic effects over a 7-hour observation period comparable to 60 mg of codeine, and 20 mg of THC induced similar effects to 120 mg of codeine. The study again reported that higher doses of THC were more sedating than codeine. Both studies' results are limited by the small sample size and the fact that all patients also received their usual analgesic regimen concurrently with either THC or placebo. They also report that patients became sedated at higher THC doses so reports of pain level might not have been accurate. Whereas their results support that THC may have analgesic effects, sedation may limit its use.

Nabiximols, a novel cannabinoid oromucosal spray, is a 1:1 combination of THC and CBD. Portenoy et al⁴⁴ completed a randomized, double-blind, placebo-controlled, graded-dose study of 360 randomized patients with advanced cancer and opioid-refractory pain. Patients received placebo or nabiximols at a low dose (1-4 sprays/d), medium dose (6-10 sprays/d), or high dose (11-16 sprays/d). They found that low and medium doses of nabiximols had improved analgesia over placebo after 5 weeks of treatment. Higher doses were not more effective than lower doses. However, this study was limited by the investigators' decision to discourage changes in concurrent opioid dosing as study participants who dropped out may have experienced adverse effects that could have been controlled by altering opioid dose. Johnson et al⁴⁵ then examined the effects of cannabis extract preparations containing THC and CBD in 177 patients with advanced cancer and uncontrolled cancer pain despite long-term opioid use. The study had 3 arms with THC:CBD extract (n = 60), THC extract (n = 58), and placebo (n = 59). The results showed that pain relief was superior in the THC:CBD group, with twice as many patients experiencing a 30% reduction in pain when compared with placebo. The THC-alone group performed similarly to the placebo group. On the basis of these 2 limited studies, there may be a role for THC and CBD therapy in patients with cancer who have opioid-refractory pain.

Because each study used different preparations of cannabis or THC, there is insufficient evidence to recommend cannabis or THC for the first-line management of cancer-associated pain, but the results suggest a benefit as an add-on medication. More clinical trials examining the effects of smoked cannabis, THC, CBD, and its other derivatives are needed.

Cannabis as an Antitumor Agent

There is evidence that suggests that cannabis may be used as a potential chemotherapeutic treatment. Endocannabinoid signaling is increased in some human tissue malignant neoplasms when compared with noncancerous tissue, especially in highly invasive cancers, suggesting that endocannabinoids may play a role in tumor growth.⁴⁶ In vivo and in vitro research propose that cannabinoids can inhibit tumor growth via various mechanisms including increasing cellular apoptosis and suppressing cell proliferation.^{47,48} Conflictingly, McKallip et al⁴⁹ showed that THC may increase tumor growth due to reduced immune function. Cannabinoid receptors are widespread throughout the body and regulate a variety of physiological functions, including neuronal development and energy metabolism. Activation of CB1 and CB2 receptors leads to a cascade of cellular activity affecting ion channels, production of cyclic adenosine monophosphate, and regulation of mitogen-activated protein kinase families involved with cellular signaling, proliferation, inva-

sion, and adhesion.⁵⁰ Cannabinoids may work to induce cancer cell death through cellular signaling pathways leading to apoptosis.⁴⁰

Munson et al⁵¹ published the first study examining the effects of THC on tumor growth. Mice with lung adenocarcinoma given oral THC showed slowed tumor growth. Animals that were treated for 10 days demonstrated a dose-dependent retardation of tumor growth. This initial study prompted further investigation of the antitumor actions of THC.

Massi et al⁵² evaluated the in vitro antiproliferative ability of CBD on human glioma cell lines. They found that adding CBD to cell lines led to significant decreases in mitochondrial metabolism and glioma cell viability. They also showed that the antiproliferative effect of CBD was correlated with the induction of apoptosis, which was then reversed by cannabinoid antagonists. Cannabidiol injected into mice also inhibited the growth of implanted human glioma cells, suggesting the application of CBD as a potential anti-neoplastic agent.

Sánchez et al⁵³ examined the effects of CB2 receptor modulation in cancer and demonstrated that local administration of selective CB2 agonists in mice induced a considerable regression of malignant tumors generated by inoculation of C6 glioma cells. This study supports that the entire cannabinoid system may have implications on the treatment of cancer as opposed to just CB1 receptors.

Cannabinoids may play a role in preventing cancer metastasis. Qamri et al⁵⁴ showed that the CB2 agonist JWH-133 and the CB1 and CB2 agonist WIN-55,212-2 inhibited cell proliferation and migration under in vitro conditions, with replication of these results in mice studies. Mice treated with JWH-133 or WIN-55,212-2 showed a 40% to 50% reduction in tumor growth and a 65% to 80% reduction in lung metastases. This suggests that CB1 and CB2 receptors may be involved in the metastatic process.

Finally, there has only been 1 clinical trial examining the effects of THC on cancer. Guzmán et al⁵⁵ studied intracranial administration of THC to 9 patients with recurrent glioblastoma multiforme whose surgery and radiotherapy had failed. Treatment with THC decreased tumor growth and tumor progression, as assessed by magnetic resonance imaging and biomarker expression, in at least 2 of the 9 patients studied. The study is limited by the small sample size, lack of control group, and the study design's inability to comment on the effects of THC on survival time.

The majority of data examining cannabis as a chemotherapeutic agent are based on animal models, which support endocannabinoid system involvement in cancer growth. Extension of this research to human subjects is needed to see whether these results can be duplicated. There are 2 ongoing clinical studies aimed at evaluating the antitumoral activity of cannabinoid use. The first is a safety study comparing nabiximols with placebo (both with dose-intense temozolomide) in patients with recurrent glioblastoma (NCT01812616) and the other is a study of pure CBD as a single-agent therapy for solid tumors (NCT02255292). Currently, there is insufficient evidence that cannabis or THC should be used for its antitumor properties outside of a clinical trial.

Safety Profile of Cannabis

Cannabinoids have a favorable safety profile when compared with other analgesic medications.^{56(pp137-180)57} In the aforementioned studies, THC was seen to be more sedating than codeine but unlike opi-

oids was not associated with respiratory depression.⁴³ The extrapolated estimated lethal dose of cannabinoids from animal studies is approximately 680 kg smoked in 15 minutes, making overdose unlikely.³⁶ The central nervous system adverse and nontherapeutic effects include euphoria, disorientation, drowsiness, dizziness, motor incoordination, and poor concentration. The peripheral adverse effects include tachycardia, hypotension, conjunctival injection, bronchodilation, muscle relaxation, and decreased gastrointestinal motility.³⁶

There is concern regarding the addictive potential of cannabis. The risk of dependence on cannabis is reported to be 9% in long-term users,⁵⁸ significantly less than the addiction rates of heroin, cocaine, alcohol, and prescribed anxiolytics.^{56(pp92-100)}

Conclusions

Cannabis in oncology may have potential in its use for anticipatory and refractory CINV, refractory cancer pain, and as an antitumor agent; however, much of the data are based on animal studies and small clinical trials. In addition, many published studies are outdated. More research is needed in all areas related to the therapeutic use of cannabis, THC, and/or other cannabinoids. Currently, cannabis is not a primary means of treatment for any cancer or treatment-related adverse effect. However, as marijuana legalization, access, and research increases, this may change.

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