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PDQ Cancer Information Summaries [Internet].

Cannabis and Cannabinoids (PDQ®)

Health Professional Version

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board.

Published online: May 27, 2016.

Created: March 16, 2011.

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of Cannabis and cannabinoids in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

This summary is reviewed regularly and updated as necessary by the PDQ Integrative, Alternative, and Complementary TherapiesEditorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

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Overview

This cancer information summary provides an overview of the use of *Cannabis* and its components as a treatment for people withcancer-related symptoms caused by the disease itself or its treatment.

This summary contains the following key information:

- *Cannabis* has been used for medicinal purposes for thousands of years.
- By federal law, the possession of *Cannabis* is illegal in the United States, except within approved research settings; however, a growing number of states, territories, and the District of Columbia have enacted laws to legalize its medical use.
- The U.S. Food and Drug Administration has not approved *Cannabis* as a treatment for cancer or any other medical condition.
- Chemical components of *Cannabis*, called cannabinoids, activate specific receptors throughout the body to producepharmacologic effects, particularly in the central nervous system and the immune system.
- Commercially available cannabinoids, such as dronabinol and nabilone, are approved drugs for the treatment of cancer-related side effects.

- Cannabinoids may have benefits in the treatment of cancer-related side effects.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

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General Information

Cannabis, also known as marijuana, originated in Central Asia but is grown worldwide today. In the United States, it is a controlled substance and is classified as a Schedule I agent (a drug with a high potential for abuse, and no currently accepted medical use). The *Cannabis* plant produces a resin containing psychoactive compounds called cannabinoids, in addition to other compoundsfound in plants, such as terpenes and flavonoids. The highest concentration of cannabinoids is found in the female flowers of the plant.[1] Clinical trials conducted on medicinal *Cannabis* are limited. The U.S. Food and Drug Administration (FDA) has not approved the use of *Cannabis* as a treatment for any medical condition. To conduct clinical drug research with *Cannabis* in the United States, researchers must file an Investigational New Drug (IND) application with the FDA, obtain a Schedule I license from the U.S. Drug Enforcement Administration, and obtain approval from the National Institute on Drug Abuse.

The potential benefits of medicinal *Cannabis* for people living with cancer include antiemetic effects, appetite stimulation, pain relief, and improved sleep. Although few relevant surveys of practice patterns exist, it appears that physicians caring for cancerpatients in the United States who recommend medicinal *Cannabis* do so predominantly for symptom management.[2] A growing number of pediatric patients are seeking symptom relief with *Cannabis* or cannabinoid treatment, although studies are limited.[3] The American Academy of Pediatrics has not endorsed *Cannabis* and cannabinoid use because of concerns about braindevelopment.

Cannabinoids are a group of terpenophenolic compounds found in *Cannabis* species (e.g., *Cannabis sativa* L.). This summary will review the role of *Cannabis* and the cannabinoids in the treatment of people with cancer and disease-related or treatment-relatedside effects.

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History

Cannabis use for medicinal purposes dates back at least 3,000 years.[1-5] It was introduced into Western medicine in 1839 by W.B. O'Shaughnessy, a surgeon who learned of its medicinal properties while working in India for the British East India Company. Its use was promoted for reported analgesic, sedative, anti-inflammatory, antispasmodic, and anticonvulsant effects.

In 1937, the U.S. Treasury Department introduced the Marihuana Tax Act. This Act imposed a levy of $1 per ounce for medicinal use of *Cannabis* and $100 per ounce for nonmedical use. Physicians in the United States were the principal opponents of the Act. The American Medical Association (AMA) opposed the Act because physicians were required to pay a special tax for prescribing*Cannabis*, use special order forms to procure it, and keep special records concerning its professional use. In addition, the AMA believed that objective evidence that *Cannabis* was harmful was lacking and that passage of the Act would impede further research into its medicinal worth.[6] In 1942, *Cannabis* was removed from the U.S. Pharmacopoeia because of persistent concerns about its potential to cause harm.[2,3]

In 1951, Congress passed the Boggs Act, which for the first time included *Cannabis* with narcotic drugs. In 1970, with the passage of the Controlled Substances Act, marijuana was classified by Congress as a Schedule I drug. Drugs in Schedule I are distinguished as having no currently accepted medicinal use in the United States. Other Schedule I substances include heroin, LSD, mescaline, and methaqualone.

Despite its designation as having no medicinal use, *Cannabis* was distributed by the U.S. government to patients on a case-by-case basis under the Compassionate Use Investigational New Drug program established in 1978. Distribution of *Cannabis* through this program was closed to new patients in 1992.[1-4] Although federal law prohibits the use of *Cannabis*, figure 1 below shows the states and territories that have legalized *Cannabis* use for medical purposes. Additional states have legalized only one ingredient in *Cannabis*, such as cannabidiol (CBD), and are not included in the map. Some medical marijuana laws are broader than others, and there is state-to-state variation as to the types of medical conditions for which treatment is allowed.

Figure

Figure 1. *Cannabis* map.

The main psychoactive constituent of *Cannabis* was identified as delta-9-tetrahydrocannabinol (THC). In 1986, an isomer ofsynthetic delta-9-THC in sesame oil was licensed and approved for the treatment of chemotherapy-associated nausea andvomiting under the generic name dronabinol. Clinical trials determined that dronabinol was as effective as or better than otherantiemetic agents available at the time.[7] Dronabinol was also studied for its ability to stimulate weight gain in patients with AIDSin the late 1980s. Thus, the indications were expanded to include treatment of anorexia associated with human immunodeficiency virus infection in 1992. Clinical trial results showed no statistically significant weight gain, although patients reported an improvement in appetite.[8,9] Another important cannabinoid found in *Cannabis* is CBD.[10] This is a nonpsychoactive cannabinoid, which is an analog of THC.

In recent decades, the neurobiology of cannabinoids has been analyzed.[11-14] The first cannabinoid receptor, CB1, was identified in the brain in 1988. A second cannabinoid receptor, CB2, was identified in 1993. The highest expression of CB2 receptors is located on B lymphocytes and natural killer cells, suggesting a possible role in immunity. Endogenous cannabinoids (endocannabinoids) have been identified and appear to have a role in pain modulation, control of movement, feeding behavior, mood, bone growth, inflammation, neuroprotection, and memory.[15]

Nabiximols (Sativex), a *Cannabis* extract with a 1:1 ratio of THC:CBD, is approved in Canada (under the Notice of Compliance with Conditions) for symptomatic relief of pain in advanced cancer and multiple sclerosis.[16] Canada, New Zealand, and some countries in Europe also approve nabiximols for spasticity of multiple sclerosis, a common symptom that may include musclestiffness, reduced mobility, and pain, and for which existing therapy is unsatisfactory.

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Laboratory/Animal/Preclinical Studies

Cannabinoids are a group of 21-carbon–containing terpenophenolic compounds produced uniquely by *Cannabis* species (e.g.,*Cannabis sativa* L.).[1,2] These plant-derived compounds may be referred to as phytocannabinoids. Although delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient, other known compounds with biologic activity are cannabinol, cannabidiol (CBD), cannabichromene, cannabigerol, tetrahydrocannabivarin, and delta-8-THC. CBD, in particular, is thought to havesignificant analgesic, anti-inflammatory, and anxiolytic activity without the psychoactive effect (high) of delta-9-THC.

Antitumor Effects

One study in mice and rats suggested that cannabinoids may have a protective effect against the development of certain types oftumors.[3] During this 2-year study, groups of mice and rats were given various doses of THC by gavage. A dose-related decrease in the incidence of hepatic adenoma tumors and hepatocellular carcinoma (HCC) was observed in the mice. Decreased incidences of benign tumors (polyps and adenomas) in other organs (mammary gland, uterus, pituitary, testis, and pancreas) were also noted in the rats. In another study, delta-9-THC, delta-8-THC, and cannabinol were found to inhibit the growth of Lewis lungadenocarcinoma cells *in vitro* and *in vivo*.[4] In addition, other tumors have been shown to be sensitive to cannabinoid-induced growth inhibition.[5-8]

Cannabinoids may cause antitumor effects by various mechanisms, including induction of cell death, inhibition of cell growth, and inhibition of tumor angiogenesis invasion and metastasis.[9-12] Two reviews summarize the molecular mechanisms of action of cannabinoids as antitumor agents.[13,14] Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts and may even protect them from cell death. For example, these compounds have been shown to induce apoptosis inglioma cells in culture and induce regression of glioma tumors in mice and rats, while they protect normal glial cells of astroglial and oligodendroglial lineages from apoptosis mediated by the CB1 receptor.[9]

The effects of delta-9-THC and a synthetic agonist of the CB2 receptor were investigated in HCC.[15] Both agents reduced theviability of HCC cells *in vitro* and demonstrated antitumor effects in HCC subcutaneous xenografts in nude mice. The investigations documented that the anti-HCC effects are mediated by way of the CB2 receptor. Similar to findings in glioma cells, the cannabinoids were shown to trigger cell death through stimulation of an endoplasmic reticulum stress pathway that activatesautophagy and promotes apoptosis. Other investigations have confirmed that CB1 and CB2 receptors may be potential targets innon-small cell lung carcinoma [16] and breast cancer.[17]

An *in vitro* study of the effect of CBD on programmed cell death in breast cancer cell lines found that CBD induced programmed cell death, independent of the CB1, CB2, or vanilloid receptors. CBD inhibited the survival of both estrogen receptor–positive andestrogen receptor–negative breast cancer cell lines, inducing apoptosis in a concentration-dependent manner while having little effect on

nontumorigenic mammary cells.[18] Other studies have also shown the antitumor effect of cannabinoids (i.e., CBD and THC) in preclinical models of breast cancer.[19,20]

CBD has also been demonstrated to exert a chemopreventive effect in a mouse model of colon cancer.[21] In this experimentalsystem, azoxymethane increased premalignant and malignant lesions in the mouse colon. Animals treated with azoxymethane and CBD concurrently were protected from developing premalignant and malignant lesions. In *in vitro* experiments involving colorectal cancer cell lines, the investigators found that CBD protected DNA from oxidative damage, increased endocannabinoid levels, and reduced cell proliferation. In a subsequent study, the investigators found that the antiproliferative effect of CBD was counteracted by selective CB1 but not CB2 receptor antagonists, suggesting an involvement of CB1 receptors.[22]

Another investigation into the antitumor effects of CBD examined the role of intercellular adhesion molecule-1 (ICAM-1).[12] ICAM-1 expression has been reported to be negatively correlated with cancer metastasis. In lung cancer cell lines, CBD upregulated ICAM-1, leading to decreased cancer cell invasiveness.

In an *in vivo* model using severe combined immunodeficient mice, subcutaneous tumors were generated by inoculating the animals with cells from human non-small cell lung carcinoma cell lines.[23] Tumor growth was inhibited by 60% in THC-treated mice compared with vehicle-treated control mice. Tumor specimens revealed that THC had antiangiogenic and antiproliferative effects. However, research with immunocompetent murine tumor models has demonstrated immunosuppression and enhanced tumor growth in mice treated with THC.[24,25]

In addition, both plant-derived and endogenous cannabinoids have been studied for anti-inflammatory effects. A mouse study demonstrated that endogenous cannabinoid system signaling is likely to provide intrinsic protection against colonic inflammation.[26] As a result, a hypothesis that phytocannabinoids and endocannabinoids may be useful in the risk reduction and treatment ofcolorectal cancer has been developed.[27-30]

CBD may also enhance uptake of cytotoxic drugs into malignant cells. Activation of the transient receptor potential vanilloid type 2 (TRPV2) has been shown to inhibit proliferation of human glioblastoma multiforme cells and overcome resistance to thechemotherapy agent carmustine.[31] One study showed that coadministration of THC and CBD over single-agent usage had greater antiproliferative activity in an *in vitro* study with multiple human glioblastoma multiforme cell lines.[32] In an *in vitro* model, CBD increased TRPV2 activation and increased uptake of cytotoxic drugs, leading to apoptosis of glioma cells without affecting normal human astrocytes. This suggests that coadministration of CBD with cytotoxic agents may increase drug uptake and potentiate cell death in human glioma cells. Also, CBD together with THC may enhance the antitumor activity of classic chemotherapeutic drugs such as temozolomide in some mouse models of cancer.[13,33]

Antiemetic Effects

Preclinical research suggests that emetic circuitry is tonically controlled by endocannabinoids. The antiemetic action of cannabinoids is believed to be mediated via interaction with the 5-hydroxytryptamine 3 (5-HT3) receptor. CB1 receptors and 5-HT3 receptors are colocalized on gamma-aminobutyric acid (GABA)-ergic neurons, where they have opposite effects on GABA release.[34] There also may be direct inhibition of 5-HT3 gated ion currents through non–CB1 receptor pathways. CB1 receptor antagonistshave been shown to elicit emesis in the least shrew that is reversed by cannabinoid agonists.[35] The involvement of CB1 receptor in emesis prevention has been shown by the ability of CB1

antagonists to reverse the effects of THC and other syntheticcannabinoid CB1 agonists in suppressing vomiting caused by cisplatin in the house musk shrew and lithium chloride in the least shrew. In the latter model, CBD was also shown to be efficacious.[36,37]

Appetite Stimulation

Many animal studies have previously demonstrated that delta-9-THC and other cannabinoids have a stimulatory effect on appetiteand increase food intake. It is believed that the endogenous cannabinoid system may serve as a regulator of feeding behavior. The endogenous cannabinoid anandamide potently enhances appetite in mice.[38] Moreover, CB1 receptors in the hypothalamus may be involved in the motivational or reward aspects of eating.[39]

Analgesia

Understanding the mechanism of cannabinoid-induced analgesia has been increased through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists. Cannabinoids produce analgesia through supraspinal, spinal, andperipheral modes of action, acting on both ascending and descending pain pathways.[40]The CB1 receptor is found in both thecentral nervous system (CNS) and in peripheral nerve terminals. Similar to opioid receptors, increased levels of the CB1 receptor are found in regions of the brain that regulate nociceptive processing.[41] CB2 receptors, located predominantly in peripheraltissue, exist at very low levels in the CNS. With the development of receptor-specific antagonists, additional information about the roles of the receptors and endogenous cannabinoids in the modulation of pain has been obtained.[42,43]

Cannabinoids may also contribute to pain modulation through an anti-inflammatory mechanism; a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents, such as histamine and serotonin, and on keratinocytes to enhance the release of analgesic opioids has been described.[44-46] One study reported that the efficacy of synthetic CB1- and CB2-receptor agonists were comparable with the efficacy of morphine in a murine model of tumor pain.[47]

Cannabinoids have been shown to prevent chemotherapy-induced neuropathy in animal models exposed to paclitaxel, vincristine, or cisplatin.[48-50]

Anxiety and Sleep

The endocannabinoid system is believed to be centrally involved in the regulation of mood and the extinction of aversive memories. Animal studies have shown CBD to have anxiolytic properties. It was shown in rats that these anxiolytic properties are mediated through unknown mechanisms.[51] Anxiolytic effects of CBD have been shown in several animal models.[52,53]

The endocannabinoid system has also been shown to play a key role in the modulation of the sleep-waking cycle in rats.[54,55]

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Go to:

Human/Clinical Studies

Cannabis Pharmacology

When oral *Cannabis* is ingested, there is a low (6%–20%) and variable oral bioavailability.[1,2]
Peak plasma concentrations of delta-9-tetrahydrocannabinol (THC) occur after 1 to 6 hours and remain

elevated with a terminal half-life of 20 to 30 hours. Taken bymouth, delta-9-THC is initially metabolized in the liver to 11-OH-THC, a potent psychoactive metabolite. Inhaled cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2 to 10 minutes, declining rapidly for a period of 30 minutes and with less generation of the psychoactive 11-OH metabolite.

Cannabinoids are known to interact with the hepatic cytochrome P450 enzyme system.[3,4] In one study, 24 cancer patients were treated with intravenous irinotecan (600 mg, n = 12) or docetaxel (180 mg, n = 12), followed 3 weeks later by the same drugsconcomitant with medicinal *Cannabis* taken in the form of an herbal tea for 15 consecutive days, starting 12 days before the second treatment.[4]
The administration of *Cannabis* did not significantly influence exposure to and clearance of irinotecan ordocetaxel, although the herbal tea route of administration may not reproduce the effects of inhalation or oral ingestion of fat-solublecannabinoids.

Cancer Risk

A number of studies have yielded conflicting evidence regarding the risks of various cancers associated with *Cannabis* use.

A pooled analysis of three case-cohort studies of men in northwestern Africa (430 cases and 778 controls) showed a significantly increased risk of lung cancer among tobacco smokers who also inhaled *Cannabis*.[5]

A large, retrospective cohort study of 64,855 men aged 15 to 49 years from the United States found that *Cannabis* use was not associated with tobacco-related cancers and a number of other common malignancies. However, the study did find that, among nonsmokers of tobacco, ever having used *Cannabis* was associated with an increased risk of prostate cancer.[6]

A population-based case-control study of 611 lung cancer patients revealed that chronic low *Cannabis* exposure was not associated with an increased risk of lung cancer or other upper aerodigestive tract cancers and found no positive associations with any cancer type (oral, pharyngeal, laryngeal, lung, or esophagus) when adjusting for several confounders, including cigarette smoking.[7]

A systematic review assessing 19 studies that evaluated premalignant or malignant lung lesions in persons 18 years or older who inhaled *Cannabis* concluded that observational studies failed to demonstrate statistically significant associations between*Cannabis* inhalation and lung cancer after adjusting for tobacco use.[8]

Epidemiologic studies examining one association of *Cannabis* use with head and neck squamous cell carcinomas have also been inconsistent in their findings. A pooled analysis of nine case-control studies from the U.S./Latin American International Head and Neck Cancer Epidemiology (INHANCE) Consortium included information from 1,921 oropharyngeal cases, 356 tongue cases, and 7,639 controls. Compared with those who never smoked *Cannabis*, *Cannabis* smokers had an elevated risk of oropharyngeal cancers and a reduced risk of tongue cancer. These study results both reflect the inconsistent effects of cannabinoids on cancerincidence noted in previous studies and suggest that more work needs to be done to understand the potential role of human papillomavirus infection.[9]

With a hypothesis that chronic marijuana use produces adverse effects on the human endocrine and reproductive systems, the association between *Cannabis* use and incidence of testicular germ cell tumors (TGCTs) has been examined.[10-12] Three population-based case-control studies reported an association between *Cannabis* use and elevated risk of TGCTs,

especiallynonseminoma or mixed-histology tumors.[10-12] However, the sample sizes in these studies were inadequate to address *Cannabis*dose by addressing associations with respect to recency, frequency, and duration of use. These early reports of *Cannabis* use and TGCTs established the need for larger, well-powered, prospective studies, especially studies evaluating the role of endocannabinoid signaling and cannabinoid receptors in TGCTs.

An analysis of 84,170 participants in the California Men's Health Study was performed to investigate the association between*Cannabis* use and the incidence of bladder cancer. During 16 years of follow-up, 89 *Cannabis* users (0.3%) developed bladder cancer compared with 190 (0.4%) of the men who did not report *Cannabis* use ($P < .001$). After adjusting for age, race, ethnicity, and body mass index, *Cannabis* use was associated with a 45% reduction in bladder cancer incidence (hazard ratio, 0.55; 95% confidence interval, 0.33–1.00).[13]

A comprehensive Health Canada monograph on marijuana concluded that while there are many cellular and molecular studies that provide strong evidence that inhaled marijuana is carcinogenic, the epidemiologic evidence of a link between marijuana use andcancer is still inconclusive.[14]

Cancer Treatment

Clinical data in pediatric use is limited to a few case reports.[15,16] No clinical trials of *Cannabis* as a treatment for cancer in humans were identified in a PubMed search; however, a single, small study of intratumoral injection of delta-9-THC in patients withrecurrent glioblastoma multiforme reported potential antitumoral activity.[17,18] In a trial that is now closed, controlled human studies investigated oral cannabidiol (CBD) as a single agent for solid tumors, using a 1:1 ratio of THC:CBD in a *Cannabis*-based medicinal extract oromucosal spray in conjunction with temozolomide in treating patients with recurrent glioblastoma multiforme (GWCA1208 Part A [NCT01812603]) and CBD as a treatment for acute graft-versus-host disease in patients who have undergoneallogeneic hematopoietic stem cell transplantation (NCT01596075).

Antiemetic Effect

Cannabinoids

Despite advances in pharmacologic and nonpharmacologic management, nausea and vomiting (N/V) remain distressing side effects for cancer patients and their families. Dronabinol, a synthetically produced delta-9-THC, was approved in the United States in 1986 as an antiemetic to be used in cancer chemotherapy. Nabilone, a synthetic derivative of delta-9-THC, was first approved in Canada in 1982 and is now also available in the United States.[19] Both dronabinol and nabilone have been approved by the U.S. Food and Drug Administration for the treatment of N/V associated with cancer chemotherapy in patients who have failed torespond to conventional antiemetic therapy. Numerous clinical trials and meta-analyses have shown that dronabinol and nabilone are effective in the treatment of N/V induced by chemotherapy.[20-23] The National Comprehensive Cancer Network Guidelinesrecommend cannabinoids as breakthrough treatment for chemotherapy-related N/V.

One systematic review studied 30 randomized comparisons of delta-9-THC preparations with placebo or other antiemetics from which data on efficacy and harm were available.[24] Oral nabilone, oral dronabinol, and intramuscular levonantradol (a syntheticanalog of dronabinol) were tested. Inhaled *Cannabis* trials were not included. Among all 1,366 patients included in the review, cannabinoids were found to be more effective than the conventional

antiemetics prochlorperazine, metoclopramide,chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride. Cannabinoids, however, were not more effective for patients receiving very low or very high emetogenic chemotherapy. Side effects included a feeling of being high, euphoria, sedationor drowsiness, dizziness, dysphoria or depression, hallucinations, paranoia, and hypotension.[24]

Another analysis of 15 controlled studies compared nabilone with placebo or available antiemetic drugs.[25] Among 600 cancerpatients, nabilone was found to be superior to prochlorperazine, domperidone, and alizapride, with nabilone favored for continuous use.

(Refer to the *Cannabis* section in the PDQ summary on Nausea and Vomiting for more information.)

Cannabis

Ten trials have evaluated the efficacy of inhaled *Cannabis* in chemotherapy-induced N/V.[26-29] In two of the studies, inhaled*Cannabis* was made available only after dronabinol failure. In the first trial, no antiemetic effect was achieved with marijuana in patients receiving cyclophosphamide or doxorubicin,[26] but in the second trial, a statistically significant superior antiemetic effect of inhaled *Cannabis* versus placebo was found among patients receiving high-dose methotrexate.[27] The third trial was a randomized, double-blind, placebo-controlled, cross-over trial involving 20 adults in which both inhaled marijuana and oral THC were evaluated. One-quarter of the patients reported a favorable antiemetic response to the cannabinoid therapies. This latter study was reported in abstract form in 1984. A full report, detailing the methods and outcomes apparently has not been published, which limits a thorough interpretation of the significance of these findings.[28]

Newer antiemetics (e.g., 5-hydroxytryptamine 3 [5-HT3] receptor antagonists) have not been directly compared with *Cannabis* or cannabinoids in cancer patients. However, the *Cannabis*-extract oromucosal spray, nabiximols, formulated with 1:1 THC:CBD was shown in a small pilot randomized, placebo-controlled, double-blinded clinical trial in Spain to treat chemotherapy-related N/V.[30][Level of evidence: 1iC]

Appetite Stimulation

Anorexia, early satiety, weight loss, and cachexia are problems experienced by cancer patients. Such patients are faced not only with the disfigurement associated with wasting but also with an inability to engage in the social interaction of meals.

Cannabinoids

Three controlled trials demonstrated that oral THC has variable effects on appetite stimulation and weight loss in patients with advanced malignancies and human immunodeficiency virus (HIV) infection.[25] One study evaluated the efficacy of dronabinolalone or with megestrol acetate compared with that of megestrol acetate alone for managing cancer-associated anorexia.[31] In this randomized, double-blind study of 469 adults with advanced cancer and weight loss, patients received 2.5 mg of oral THC twice daily, 800 mg of oral megestrol daily, or both. Appetite increased by 75% in the megestrol group and weight increased by 11%, compared with a 49% increase in appetite and a 3% increase in weight in the oral THC group after 8 to 11 weeks oftreatment. These two differences were statistically significant. Furthermore, the combined therapy did not offer additional benefits beyond those provided by megestrol acetate alone. The authors concluded that dronabinol did little to promote appetite or weight gain in advanced cancer patients compared with megestrol acetate. However, a smaller, placebo-controlled trial

of dronabinol in cancer patients demonstrated improved and enhanced chemosensory perception in the cannabinoid group—food tasted better, appetite increased, and the proportion of calories consumed as protein was greater than in the placebo recipients.[32]

In a randomized clinical trial, researchers compared the safety and effectiveness of orally administered *Cannabis* extract (2.5 mg THC and 1 mg CBD), THC (2.5 mg), or placebo for the treatment of cancer-related anorexia-cachexia in 243 patients with advanced cancer who received treatment twice daily for 6 weeks. Results demonstrated that although these agents were well tolerated by these patients, no differences were observed in patient appetite or quality of life among the three groups at this dose level and duration of intervention.[33]

Another clinical trial that involved 139 patients with HIV or AIDS and weight loss found that, compared with placebo, oraldronabinol was associated with a statistically significant increase in appetite after 4 to 6 weeks of treatment. Patients receiving dronabinol tended to have weight stabilization, whereas patients receiving placebo continued to lose weight.[34]

Cannabis

In trials conducted in the 1980s that involved healthy control subjects, inhaling *Cannabis* led to an increase in caloric intake, mainly in the form of between-meal snacks, with increased intakes of fatty and sweet foods.[35,36]

No published studies have explored the effect of inhaled *Cannabis* on appetite in cancer patients.

Analgesia

Cannabinoids

Pain management improves a patient's quality of life throughout all stages of cancer. Through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists, the mechanisms of cannabinoid-induced analgesia have been analyzed.[37][Level of evidence:1iC] The CB1 receptor is found in the central nervous system (CNS) and in peripheral nerveterminals.[38] CB2 receptors are located mainly in peripheral tissue and are expressed in only low amounts in the CNS. Whereas only CB1 agonists exert analgesic activity in the CNS, both CB1 and CB2 agonists have analgesic activity in peripheral tissue.[39,40]

Cancer pain results from inflammation, invasion of bone or other pain-sensitive structures, or nerve injury. When cancer pain is severe and persistent, it is often resistant to treatment with opioids.

Two studies examined the effects of oral delta-9-THC on cancer pain. The first, a double-blind placebo-controlled study involving ten patients, measured both pain intensity and pain relief.[41] It was reported that 15 mg and 20 mg doses of the cannabinoid delta-9-THC were associated with substantial analgesic effects, with antiemetic effects and appetite stimulation.

In a follow-up, single-dose study involving 36 patients, it was reported that 10 mg doses of delta-9-THC produced analgesic effects during a 7-hour observation period that were comparable to 60 mg doses of codeine, and 20 mg doses of delta-9-THC induced effects equivalent to 120 mg doses of codeine.[42] Higher doses of THC were found to be more sedative than codeine.

Another study examined the effects of a plant extract with controlled cannabinoid content in an oromucosal spray. In a multicenter, double-blind, placebo-controlled study, the THC:CBD nabiximols extract and THC extract alone were compared in the analgesic management of patients with advanced cancer and with moderate-to-severe cancer-related pain. Patients were assigned to one of three treatment groups: THC:CBD extract, THC extract, or placebo. The researchers concluded that the THC:CBD extract was efficacious for pain relief in advanced cancer patients whose pain was not fully relieved by strong opioids.[43] In a randomized, placebo-controlled, graded-dose trial, opioid-treated cancer patients with poorly controlled chronic pain demonstrated significantly better control of pain and sleep disruption with THC:CBD oromucosal spray at lower doses (1–4 and 6–10 sprays/day), compared with placebo. Adverse events were dose related, with only the high-dose group (11–16 sprays/day) comparing unfavorably with the placebo arm. These studies provide promising evidence of an “adjuvant analgesic” effect of THC:CBD in this opioid-refractory patient population and may provide an opportunity to address this significant clinical challenge.[44] An open-label extension study of 43 patients who had participated in the randomized trial found that some patients continued to obtain relief of their cancer-related pain with long-term use of the THC:CBD oromucosal spray without increasing their dose of the spray or the dose of their other analgesics.[45]

A randomized, placebo-controlled, crossover pilot study of nabiximols in 16 patients with chemotherapy-induced neuropathic pain showed no significant difference between the treatment and placebo groups. A responder analysis, however, demonstrated that five patients reported a reduction in their pain of at least 2 points on an 11-point scale, suggesting that a larger follow-up study may be warranted.[46]

An observational study assessed the effectiveness of nabilone in advanced cancer patients who were experiencing pain and othersymptoms (anorexia, depression, and anxiety). The researchers reported that patients who used nabilone experienced improved management of pain, nausea, anxiety, and distress when compared with untreated patients. Nabilone was also associated with a decreased use of opioids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, gabapentin, dexamethasone,metoclopramide, and ondansetron.[47]

Cannabis

Animal studies have suggested a synergistic analgesic effect when cannabinoids are combined with opioids. The results from one pharmacokinetic interaction study have been reported. In this study, 21 patients with chronic pain were administered vaporized*Cannabis* along with sustained-release morphine or oxycodone for 5 days.[48] The patients who received vaporized *Cannabis* and sustained-release morphine had a statistically significant decrease in their mean pain score over the 5-day period; those who received vaporized *Cannabis* and oxycodone did not. These findings should be verified by further studies before recommendations favoring such an approach are warranted in general clinical practice.

Neuropathic pain is a symptom cancer patients may experience, especially if treated with platinum-based chemotherapy ortaxanes. Two randomized controlled trials of inhaled *Cannabis* in patients with peripheral neuropathy or neuropathic pain of various etiologies found that pain was reduced in patients who received inhaled *Cannabis*, compared with those who received placebo.[49,50] Two additional trials of inhaled *Cannabis* have also demonstrated the benefit of *Cannabis* over placebo in HIV-associated neuropathic pain.[51,52]

Anxiety and Sleep

Cannabinoids

In a small pilot study of analgesia involving ten patients with cancer pain, secondary measures showed that 15 mg and 20 mg doses of the cannabinoid delta-9-THC were associated with anxiolytic effects.[41][Level of evidence: 1iC]

A small placebo-controlled study of dronabinol in cancer patients with altered chemosensory perception also noted increased quality of sleep and relaxation in THC-treated patients.[32][Level of evidence: 1iC]

Cannabis

Patients often experience mood elevation after exposure to *Cannabis*, depending on their previous experience. In a five-patientcase series of inhaled *Cannabis* that examined analgesic effects in chronic pain, it was reported that patients who self-administered *Cannabis* had improved mood, improved sense of well-being, and less anxiety.[53]

Another common effect of *Cannabis* is sleepiness. A small placebo-controlled study of dronabinol in cancer patients with altered chemosensory perception also noted increased quality of sleep and relaxation in THC-treated patients.[32]

Clinical Studies of *Cannabis* and Cannabinoids

Table 1. Clinical Studies of *Cannabis*[a]

Reference Citation	Type of Study	Condition Treated	No. of Patients: Enrolled; Treated; Control[b]	Strongest Benefit Reported[c]	Concurrent Therapy Used (Yes/No/Unknown)[d]	Level of Evidence Score[e]
[26]	RCT	CINV	8; 8; None	None	Unknown	1iC
[27]	RCT	CINV	15; 15; None	Decreased N/V	Unknown	1iiC
[30]	Pilot RCT	CINV	16; 7; 9	Decreased/delayed N/V	5-HT3 receptor antagonists	1iC

CINV = chemotherapy-induced nausea and vomiting; HIV = human immunodeficiency virus; RCT = randomized controlled trial; N/V = nausea and vomiting.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

[b]Number of patients treated plus number of patient controls may not equal number of patients enrolled; number of patients enrolled equals number of patients initially recruited/considered by the researchers who conducted a

study; number of patients treated equals number of enrolled patients who were given thetreatment being studied AND for whom results were reported.

[c]Strongest evidence reported that the treatment under study has activity or otherwise improves the well-being of cancer patients.

[d]Concurrent therapy for symptoms treated (not cancer).

[e]For information about levels of evidence analysis and an explanation of the level of evidence scores, refer to Levels of Evidence for Human Studies of Integrative, Alternative, and Complementary Therapies.

Table 2. Clinical Studies of Cannabinoids[a]

Reference Citation	Type of Study	Condition Treated	No. of Patients: Enrolled; Treated; Control[b]	Strongest Benefit Reported[c]	Concurrent Therapy Used (Yes/No/ Unknown)[d]	Level of Evidence Score[e]
[31]	RCT	Cancer-associated anorexia	469; dronabinol152, megestrolacetate 159, or both 158; none	Megestrol acetate provided superioranorexia palliation among advancedcancer patients compared withdronabinol alone	Unknown	1iC
[32]	Pilot RCT	Appetite	21; 11; 10	THC, compared with placebo, improved and enhanced chemosensory perception	Unknown	1iC
[33]	RCT	Cancer-relatedanorexia-cachexia syndrome	243; *Cannabis*extract 95, THC 100; 48	No differences in patients' appetite or QoL were found	Unknown	1iC
[34]	RCT	Appetite	139; 72; 67	Increase in appetite	Unknown	1iC
[37]	Survey ofRCTs	Pain		Decreased pain	Unknown	1iC
[41]	RCT	Pain	10; none; none	Pain relief	Unknown	1iC

Reference Citation	Type of Study	Condition Treated	No. of Patients: Enrolled; Treated; Control[b]	Strongest Benefit Reported[c]	Concurrent Therapy Used (Yes/No/ Unknown)[d]	Level of Evidence Score[e]
[47]	Observational study	Pain	112; 47; 65	Decreased pain		

No. = number; QoL = quality of life; RCT = randomized controlled trial; THC = delta-9-tetrahydrocannabinol.

[a]Refer to text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

[b]Number of patients treated plus number of patient controls may not equal number of patients enrolled; number of patients enrolled equals number of patients initially recruited/considered by the researchers who conducted a study; number of patients treated equals number of enrolled patients who were given thetreatment being studied AND for whom results were reported.

[c]Strongest evidence reported that the treatment under study has activity or otherwise improves the well-being of cancer patients.

[d]Concurrent therapy for symptoms treated (not cancer).

[e]For information about levels of evidence analysis and an explanation of the level of evidence scores, refer to Levels of Evidence for Human Studies of Integrative, Alternative, and Complementary Therapies.

Current Clinical Trials

Check the list of NCI-supported cancer clinical trials for integrative, alternative, and complementary therapies clinical trials ondronabinol, marijuana, nabiximols, nabilone and cannabidiol that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

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Adverse Effects

Cannabis and Cannabinoids

Because cannabinoid receptors, unlike opioid receptors, are not located in the brainstem areas controlling respiration, lethal overdoses from *Cannabis* and cannabinoids do not occur.[1-4] However, cannabinoid receptors are present in other tissuesthroughout the body, not just in the central nervous system, and adverse effects include tachycardia, hypotension, conjunctivalinjection, bronchodilation, muscle relaxation, and decreased gastrointestinal motility.

Although cannabinoids are considered by some to be addictive drugs, their addictive potential is considerably lower than that of other prescribed agents or substances of abuse.[2,4] The brain develops a tolerance to cannabinoids.

Withdrawal symptoms such as irritability, insomnia with sleep electroencephalogram disturbance, restlessness, hot flashes, and, rarely, nausea and cramping have been observed. However, these symptoms appear to be mild compared with withdrawal symptoms associated with opiates or benzodiazepines, and the symptoms usually dissipate after a few days.

Unlike other commonly used drugs, cannabinoids are stored in adipose tissue and excreted at a low rate (half-life 1–3 days), so even abrupt cessation of cannabinoid intake is not associated with rapid declines in plasma concentrations that would precipitate severe or abrupt withdrawal symptoms or drug cravings.

Since *Cannabis* smoke contains many of the same components as tobacco smoke, there are valid concerns about the adversepulmonary effects of inhaled *Cannabis*. A longitudinal study in a noncancer population evaluated repeated measurements ofpulmonary function over 20 years in 5,115 men and women whose smoking histories were known.[5] While tobacco exposure was associated with decreased pulmonary function, the investigators concluded that occasional and low-cumulative *Cannabis* use was not associated with adverse effects on pulmonary function (forced expiratory volume in the first second of expiration [FEV1] and forced vital capacity [FVC]).

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Summary of the Evidence for Cannabis and Cannabinoids

To assist readers in evaluating the results of human studies of integrative, alternative, and complementary therapies for people with cancer, the strength of the evidence (i.e., the levels of evidence) associated with each type of treatment is provided whenever possible. To qualify for a level of evidence analysis, a study must:

- Be published in a peer-reviewed scientific journal.
- Report on therapeutic outcome or outcomes, such as tumor response, improvement in survival, or measured improvement in quality of life.
- Describe clinical findings in sufficient detail for a meaningful evaluation to be made.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. An overall level of evidence score cannot be assigned to cannabinoids because there has been insufficient clinical research to date. For an explanation of possible scores and additional information about levels of evidence analysis of CAM treatments for people with cancer, refer to Levels of Evidence for Human Studies of Integrative, Alternative, and Complementary Therapies.

Cannabinoids

- Several controlled clinical trials have been performed, and meta-analyses of these support a beneficial effect of cannabinoids (dronabinol and nabilone) on chemotherapy-induced nausea and vomiting (N/V) compared with placebo. Bothdronabinol and nabilone are approved by the U.S. Food and Drug Administration for the prevention or treatment ofchemotherapy-induced N/V in cancer patients but not for other symptom management.

Cannabis

- There have been ten clinical trials on the use of inhaled *Cannabis* in cancer patients that can be divided into two groups. In one group, four small studies assessed antiemetic activity but each explored a different patient population andchemotherapy regimen. One study demonstrated no effect, the second study showed a positive effect versus placebo, the report of the third study did not provide enough information to characterize the overall outcome as positive or neutral. Consequently, there are insufficient data to provide an overall level of evidence assessment for the use of *Cannabis* for chemotherapy-induced N/V. Apparently, there are no published controlled clinical trials on the use of inhaled *Cannabis* for other cancer-related or cancer treatment–related symptoms.
- An increasing number of trials are evaluating the oromucosal administration of *Cannabis* plant extract with fixed concentrations of cannabinoid components, with national drug regulatory agencies in Canada and in some European countries that issue approval for cancer pain.
- At present, there is insufficient evidence to recommend inhaling *Cannabis* as a treatment for cancer-related symptoms or cancer treatment–related symptoms or cancer treatment-related side effects; however, additional research is needed.

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Changes to This Summary (05/27/2016)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

This summary is written and maintained by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of NCI. The summary reflects an independent

review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® - NCI's Comprehensive Cancer Database pages.

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About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of Cannabis and cannabinoids in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Cannabis and Cannabinoids are:

- Donald I. Abrams, MD (UCSF Osher Center for Integrative Medicine)
- Nagi B. Kumar, PhD, RD, FADA (Fellow of the American Dietetic Association)

Any comments or questions about the summary content should be submitted to Cancer.gov through the NCI website's Email Us. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Integrative, Alternative, and Complementary Therapies Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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The preferred citation for this PDQ summary is:

PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ Cannabis and Cannabinoids. Bethesda, MD: National Cancer Institute. Updated <MM/DD/YYYY>. Available at: http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq. Accessed <MM/DD/YYYY>. [PMID: 26389198]

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