

Cannabis and Cannabinoids (PDQ®)

Health Professional Version

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board.

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 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).

Overview

This [cancer](#) information summary provides an overview of the use of [Cannabis](#) and its components as a treatment for people with cancer-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 produce [pharmacologic](#) 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.

Reference citations in some [PDQ](#) cancer information summaries may include links to external websites that are operated by individuals or organizations for the purpose of marketing or advocating the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the websites, or of any treatment or product, by the PDQ Integrative, Alternative, and Complementary Therapies Editorial Board or the [National Cancer Institute](#).

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 compounds found 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.[2] Although few relevant surveys of practice patterns exist, it appears that [physicians](#) caring for cancer patients in the United States who recommend medicinal [Cannabis](#) do so predominantly for [symptom management](#). [3] A growing number of [pediatric](#) patients are seeking symptom relief with [Cannabis](#) or cannabinoid treatment, although studies are limited.[4] The [American Academy of Pediatrics](#) has not endorsed [Cannabis](#) and cannabinoid use because of concerns about brain development.

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-related [side effects](#).

References

1. Adams IB, Martin BR: Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91 (11): 1585-614, 1996. [PubMed: 8972919]
2. Abrams DI: Integrating cannabis into clinical cancer care. *Curr Oncol* 23 (2): S8-S14, 2016. [PMC free article: PMC4791148] [PubMed: 27022315]
3. Doblin RE, Kleiman MA: Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. *J Clin Oncol* 9 (7): 1314-9, 1991. [PubMed: 2045870]
4. Sallan SE, Cronin C, Zelen M, et al.: Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 302 (3): 135-8, 1980. [PubMed: 6985702]

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 in the types of medical conditions for which treatment is allowed.[7]

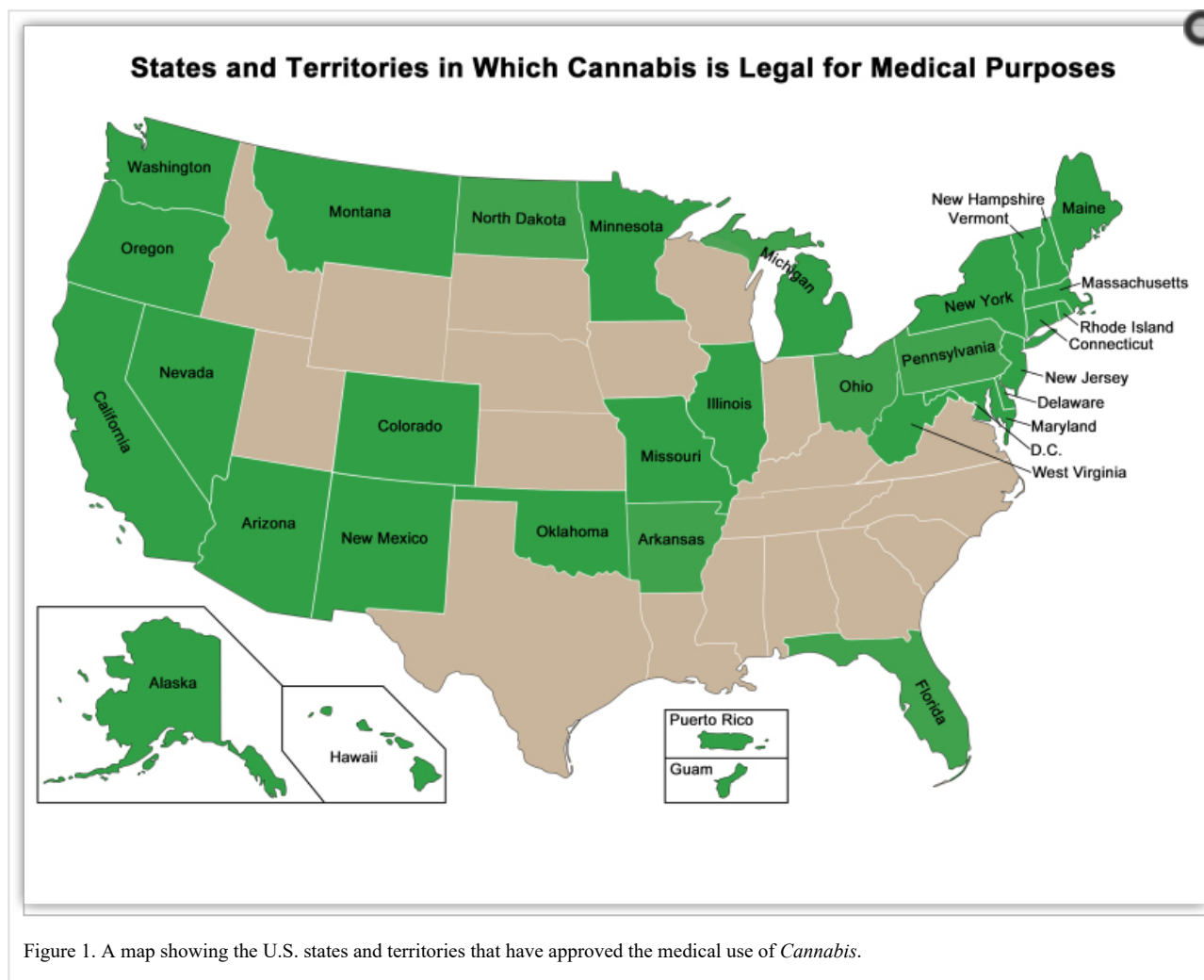


Figure 1. A map showing the U.S. states and territories that have approved the medical use of *Cannabis*.

The main psychoactive constituent of *Cannabis* was identified as delta-9-tetrahydrocannabinol (THC). In 1986, an [isomer](#) of [synthetic](#) delta-9-THC in sesame oil was licensed and approved for the treatment of [chemotherapy](#)-associated [nausea](#) and [vomiting](#) under the [generic](#) name [dronabinol](#). [Clinical trials](#) determined that dronabinol was as effective as or better than other [antiemetic](#) agents available at the time.[8] Dronabinol was also studied for its ability to stimulate weight gain in patients with [AIDS](#) in 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](#).[\[9,10\]](#) Another important [cannabinoid](#) found in *Cannabis* is CBD.[\[11\]](#) This is a nonpsychoactive cannabinoid, which is an [analog](#) of THC.

In recent decades, the neurobiology of cannabinoids has been analyzed.[\[12-15\]](#) 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.[\[16\]](#)

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](#).[\[17\]](#) Canada, New Zealand, and some countries in Europe also approve nabiximols for spasticity of multiple sclerosis, a common symptom that may include muscle stiffness, reduced mobility, and pain, and for which existing therapy is unsatisfactory.

References

1. Abel EL: *Marihuana, The First Twelve Thousand Years*. New York: Plenum Press, 1980. [Also available online](#). Last accessed October 18, 2017.
2. Joy JE, Watson SJ, Benson JA, eds.: *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press, 1999. [Also available online](#). Last accessed October 18, 2017.
3. Mack A, Joy J: *Marijuana As Medicine? The Science Beyond the Controversy*. Washington, DC: National Academy Press, 2001. [Also available online](#). Last accessed October 18, 2017.

4. Booth M: Cannabis: A History. New York, NY: St Martin's Press, 2003.
5. Russo EB, Jiang HE, Li X, et al.: Phytochemical and genetic analyses of ancient cannabis from Central Asia. *J Exp Bot* 59 (15): 4171-82, 2008. [PMC free article: [PMC2639026](#)] [PubMed: [19036842](#)]
6. Schaffer Library of Drug Policy: The Marihuana Tax Act of 1937: Taxation of Marihuana. Washington, DC: House of Representatives, Committee on Ways and Means, 1937. Available online. Last accessed October 18, 2017.
7. National Academies of Sciences, Engineering, and Medicine: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press, 2017.
8. Sallan SE, Zinberg NE, Frei E: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med* 293 (16): 795-7, 1975. [PubMed: [1099449](#)]
9. Gorter R, Seefried M, Volberding P: Dronabinol effects on weight in patients with HIV infection. *AIDS* 6 (1): 127, 1992. [PubMed: [1311935](#)]
10. Beal JE, Olson R, Laubenstein L, et al.: Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 10 (2): 89-97, 1995. [PubMed: [7730690](#)]
11. Adams R, Hunt M, Clark JH: Structure of cannabidiol: a product isolated from the marihuana extract of Minnesota wild hemp. *J Am Chem Soc* 62 (1): 196-200, 1940. Also available online. Last accessed October 18, 2017.
12. Devane WA, Dysarz FA, Johnson MR, et al.: Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 34 (5): 605-13, 1988. [PubMed: [2848184](#)]
13. Devane WA, Hanus L, Breuer A, et al.: Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258 (5090): 1946-9, 1992. [PubMed: [1470919](#)]
14. Pertwee RG, Howlett AC, Abood ME, et al.: International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB₁ and CB₂. *Pharmacol Rev* 62 (4): 588-631, 2010. [PMC free article: [PMC2993256](#)] [PubMed: [21079038](#)]
15. Felder CC, Glass M: Cannabinoid receptors and their endogenous agonists. *Annu Rev Pharmacol Toxicol* 38: 179-200, 1998. [PubMed: [9597153](#)]
16. Pacher P, Bátkai S, Kunos G: The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 58 (3): 389-462, 2006. [PMC free article: [PMC2241751](#)] [PubMed: [16968947](#)]
17. Howard P, Twycross R, Shuster J, et al.: Cannabinoids. *J Pain Symptom Manage* 46 (1): 142-9, 2013. [PubMed: [23707385](#)]

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 have significant 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 of tumors.[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 lung adenocarcinoma 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 in glioma 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 the viability 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 activates autophagy and promotes apoptosis. Other investigations have confirmed that CB1 and CB2 receptors may be potential targets in non-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](#) and [estrogen 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 [experimental](#) system, [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 in tumor cells 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 of [colorectal 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 the [chemotherapy](#) 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] A [meta-analysis](#) of 34 *in vitro* and *in vivo* studies of cannabinoids in glioma reported that all but one study confirmed that cannabinoids selectively kill tumor cells.[34]

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.[35] There also may be direct inhibition of 5-HT3 gated [ion](#) currents through non-CB1 receptor pathways. CB1 receptor antagonists have been shown to elicit [emesis](#) in the least shrew that is reversed by cannabinoid agonists.[36] 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 [synthetic](#) cannabinoid 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.[37,38]

Appetite Stimulation

Many [animal studies](#) have previously demonstrated that delta-9-THC and other cannabinoids have a stimulatory effect on [appetite](#) and increase food intake. It is believed that the endogenous cannabinoid system may serve as a regulator of feeding behavior. The endogenous cannabinoid anandamide potentially enhances appetite in mice.[39] Moreover, CB1 [receptors](#) in the [hypothalamus](#) may be involved in the motivational or reward aspects of eating.[40]

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, and peripheral modes of action, acting on both ascending and descending pain pathways.[41] The CB1 receptor is found in both the [central 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.[42] CB2

receptors, located predominantly in peripheral [tissue](#), 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.[[43,44](#)]

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.[[45-47](#)] 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.[[48](#)]

Cannabinoids have been shown to prevent chemotherapy-induced [neuropathy](#) in animal models exposed to [paclitaxel](#), [vincristine](#), or [cisplatin](#). [[49-51](#)]

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.[[52](#)] Anxiolytic effects of CBD have been shown in several animal models.[[53,54](#)]

The endocannabinoid system has also been shown to play a key role in the modulation of the sleep-waking cycle in rats.[[55,56](#)]

References

1. Adams IB, Martin BR: Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91 (11): 1585-614, 1996. [[PubMed: 8972919](#)]
2. Grotenhermen F, Russo E, eds.: Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential. Binghamton, NY: The Haworth Press, 2002.
3. National Toxicology Program: NTP toxicology and carcinogenesis studies of 1-trans-delta(9)-tetrahydrocannabinol (CAS No. 1972-08-3) in F344 rats and B6C3F1 mice (gavage studies). *Natl Toxicol Program Tech Rep Ser* 446: 1-317, 1996. [[PubMed: 12594529](#)]
4. Bifulco M, Laezza C, Pisanti S, et al.: Cannabinoids and cancer: pros and cons of an antitumour strategy. *Br J Pharmacol* 148 (2): 123-35, 2006. [[PMC free article: PMC1617062](#)] [[PubMed: 16501583](#)]
5. Sánchez C, de Ceballos ML, Gomez del Pulgar T, et al.: Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor. *Cancer Res* 61 (15): 5784-9, 2001. [[PubMed: 11479216](#)]
6. McKallip RJ, Lombard C, Fisher M, et al.: Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. *Blood* 100 (2): 627-34, 2002. [[PubMed: 12091357](#)]
7. Casanova ML, Blázquez C, Martínez-Palacio J, et al.: Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. *J Clin Invest* 111 (1): 43-50, 2003. [[PMC free article: PMC151833](#)] [[PubMed: 12511587](#)]
8. Blázquez C, González-Feria L, Alvarez L, et al.: Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas. *Cancer Res* 64 (16): 5617-23, 2004. [[PubMed: 15313899](#)]
9. Guzmán M: Cannabinoids: potential anticancer agents. *Nat Rev Cancer* 3 (10): 745-55, 2003. [[PubMed: 14570037](#)]
10. Blázquez C, Casanova ML, Planas A, et al.: Inhibition of tumor angiogenesis by cannabinoids. *FASEB J* 17 (3): 529-31, 2003. [[PubMed: 12514108](#)]
11. Vaccani A, Massi P, Colombo A, et al.: Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism. *Br J Pharmacol* 144 (8): 1032-6, 2005. [[PMC free article: PMC1576089](#)] [[PubMed: 15700028](#)]
12. Ramer R, Bublitz K, Freimuth N, et al.: Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1. *FASEB J* 26 (4): 1535-48, 2012. [[PubMed: 22198381](#)]
13. Velasco G, Sánchez C, Guzmán M: Towards the use of cannabinoids as antitumour agents. *Nat Rev Cancer* 12 (6): 436-44, 2012. [[PubMed: 22555283](#)]
14. Cridge BJ, Rosengren RJ: Critical appraisal of the potential use of cannabinoids in cancer management. *Cancer Manag Res* 5: 301-13, 2013. [[PMC free article: PMC3770515](#)] [[PubMed: 24039449](#)]
15. Vara D, Salazar M, Olea-Herrero N, et al.: Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy. *Cell Death Differ* 18 (7): 1099-111, 2011. [[PMC free article: PMC3131949](#)] [[PubMed: 21475304](#)]
16. Preet A, Qamri Z, Nasser MW, et al.: Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis. *Cancer Prev Res (Phila)* 4 (1): 65-75, 2011. [[PMC free article: PMC3025486](#)] [[PubMed: 21097714](#)]
17. Nasser MW, Qamri Z, Deol YS, et al.: Crosstalk between chemokine receptor CXCR4 and cannabinoid receptor CB2 in modulating breast cancer growth and invasion. *PLoS One* 6 (9): e23901, 2011. [[PMC free article: PMC3168464](#)] [[PubMed: 21915267](#)]
18. Shrivastava A, Kuzontkoski PM, Groopman JE, et al.: Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther* 10 (7): 1161-72, 2011. [[PubMed: 21566064](#)]

19. Caffarel MM, Andradas C, Mira E, et al.: Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. *Mol Cancer* 9: 196, 2010. [PMC free article: [PMC2917429](#)] [PubMed: [20649976](#)]
20. McAllister SD, Murase R, Christian RT, et al.: Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Res Treat* 129 (1): 37-47, 2011. [PMC free article: [PMC3410650](#)] [PubMed: [20859676](#)]
21. Aviello G, Romano B, Borrelli F, et al.: Chemopreventive effect of the non-psychoactive phytocannabinoid cannabidiol on experimental colon cancer. *J Mol Med (Berl)* 90 (8): 925-34, 2012. [PubMed: [22231745](#)]
22. Romano B, Borrelli F, Pagano E, et al.: Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. *Phytomedicine* 21 (5): 631-9, 2014. [PubMed: [24373545](#)]
23. Preet A, Ganju RK, Groopman JE: Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. *Oncogene* 27 (3): 339-46, 2008. [PubMed: [17621270](#)]
24. Zhu LX, Sharma S, Stolina M, et al.: Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. *J Immunol* 165 (1): 373-80, 2000. [PubMed: [10861074](#)]
25. McKallip RJ, Nagarkatti M, Nagarkatti PS: Delta-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. *J Immunol* 174 (6): 3281-9, 2005. [PubMed: [15749859](#)]
26. Massa F, Marsicano G, Hermann H, et al.: The endogenous cannabinoid system protects against colonic inflammation. *J Clin Invest* 113 (8): 1202-9, 2004. [PMC free article: [PMC385396](#)] [PubMed: [15085199](#)]
27. Patsos HA, Hicks DJ, Greenhough A, et al.: Cannabinoids and cancer: potential for colorectal cancer therapy. *Biochem Soc Trans* 33 (Pt 4): 712-4, 2005. [PubMed: [16042581](#)]
28. Liu WM, Fowler DW, Dalglish AG: Cannabis-derived substances in cancer therapy--an emerging anti-inflammatory role for the cannabinoids. *Curr Clin Pharmacol* 5 (4): 281-7, 2010. [PubMed: [20925645](#)]
29. Malfitano AM, Ciaglia E, Gangemi G, et al.: Update on the endocannabinoid system as an anticancer target. *Expert Opin Ther Targets* 15 (3): 297-308, 2011. [PubMed: [21244344](#)]
30. Sarfaraz S, Adhami VM, Syed DN, et al.: Cannabinoids for cancer treatment: progress and promise. *Cancer Res* 68 (2): 339-42, 2008. [PubMed: [18199524](#)]
31. Nabissi M, Morelli MB, Santoni M, et al.: Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. *Carcinogenesis* 34 (1): 48-57, 2013. [PubMed: [23079154](#)]
32. Marcu JP, Christian RT, Lau D, et al.: Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Mol Cancer Ther* 9 (1): 180-9, 2010. [PMC free article: [PMC2806496](#)] [PubMed: [20053780](#)]
33. Torres S, Lorente M, Rodríguez-Fornés F, et al.: A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Mol Cancer Ther* 10 (1): 90-103, 2011. [PubMed: [21220494](#)]
34. Rocha FC, Dos Santos Júnior JG, Stefano SC, et al.: Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. *J Neurooncol* 116 (1): 11-24, 2014. [PubMed: [24142199](#)]
35. Pacher P, Bátkai S, Kunos G: The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 58 (3): 389-462, 2006. [PMC free article: [PMC2241751](#)] [PubMed: [16968947](#)]
36. Darmani NA: Delta(9)-tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB(1) receptor antagonist/inverse agonist SR 141716A. *Neuropsychopharmacology* 24 (2): 198-203, 2001. [PubMed: [11120402](#)]
37. Darmani NA: Delta-9-tetrahydrocannabinol differentially suppresses cisplatin-induced emesis and indices of motor function via cannabinoid CB(1) receptors in the least shrew. *Pharmacol Biochem Behav* 69 (1-2): 239-49, 2001 May-Jun. [PubMed: [11420092](#)]
38. Parker LA, Kwiatkowska M, Burton P, et al.: Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). *Psychopharmacology (Berl)* 171 (2): 156-61, 2004. [PubMed: [13680081](#)]
39. Mechoulam R, Berry EM, Avraham Y, et al.: Endocannabinoids, feeding and suckling--from our perspective. *Int J Obes (Lond)* 30 (Suppl 1): S24-8, 2006. [PubMed: [16570101](#)]
40. Fride E, Bregman T, Kirkham TC: Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood. *Exp Biol Med* (Maywood) 230 (4): 225-34, 2005. [PubMed: [15792943](#)]
41. Baker D, Pryce G, Giovannoni G, et al.: The therapeutic potential of cannabis. *Lancet Neurol* 2 (5): 291-8, 2003. [PubMed: [12849183](#)]
42. Walker JM, Hohmann AG, Martin WJ, et al.: The neurobiology of cannabinoid analgesia. *Life Sci* 65 (6-7): 665-73, 1999. [PubMed: [10462067](#)]
43. Meng ID, Manning BH, Martin WJ, et al.: An analgesia circuit activated by cannabinoids. *Nature* 395 (6700): 381-3, 1998. [PubMed: [9759727](#)]
44. Walker JM, Huang SM, Strangman NM, et al.: Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci U S A* 96 (21): 12198-203, 1999. [PMC free article: [PMC18435](#)] [PubMed: [10518599](#)]
45. Facci L, Dal Toso R, Romanello S, et al.: Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. *Proc Natl Acad Sci U S A* 92 (8): 3376-80, 1995. [PMC free article: [PMC42169](#)] [PubMed: [7724569](#)]

46. Ibrahim MM, Porreca F, Lai J, et al.: CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. *Proc Natl Acad Sci U S A* 102 (8): 3093-8, 2005. [PMC free article: PMC549497] [PubMed: 15705714]
47. Richardson JD, Kilo S, Hargreaves KM: Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 75 (1): 111-9, 1998. [PubMed: 9539680]
48. Khasabova IA, Gielissen J, Chandiramani A, et al.: CB1 and CB2 receptor agonists promote analgesia through synergy in a murine model of tumor pain. *Behav Pharmacol* 22 (5-6): 607-16, 2011. [PMC free article: PMC3155626] [PubMed: 21610490]
49. Ward SJ, McAllister SD, Kawamura R, et al.: Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. *Br J Pharmacol* 171 (3): 636-45, 2014. [PMC free article: PMC3969077] [PubMed: 24117398]
50. Rahn EJ, Makriyannis A, Hohmann AG: Activation of cannabinoid CB1 and CB2 receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. *Br J Pharmacol* 152 (5): 765-77, 2007. [PMC free article: PMC2190028] [PubMed: 17572696]
51. Khasabova IA, Khasabov S, Paz J, et al.: Cannabinoid type-1 receptor reduces pain and neurotoxicity produced by chemotherapy. *J Neurosci* 32 (20): 7091-101, 2012. [PMC free article: PMC3366638] [PubMed: 22593077]
52. Campos AC, Guimarães FS: Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology (Berl)* 199 (2): 223-30, 2008. [PubMed: 18446323]
53. Crippa JA, Zuardi AW, Hallak JE: [Therapeutical use of the cannabinoids in psychiatry]. *Rev Bras Psiquiatr* 32 (Suppl 1): S56-66, 2010. [PubMed: 20512271]
54. Guimarães FS, Chiaretti TM, Graeff FG, et al.: Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl)* 100 (4): 558-9, 1990. [PubMed: 1969666]
55. Méndez-Díaz M, Caynas-Rojas S, Arteaga Santacruz V, et al.: Entopeduncular nucleus endocannabinoid system modulates sleep-waking cycle and mood in rats. *Pharmacol Biochem Behav* 107: 29-35, 2013. [PubMed: 23584096]
56. Pava MJ, den Hartog CR, Blanco-Centurion C, et al.: Endocannabinoid modulation of cortical up-states and NREM sleep. *PLoS One* 9 (2): e88672, 2014. [PMC free article: PMC3919802] [PubMed: 24520411]

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 by mouth, 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 drugs concomitant 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 or docetaxel, although the herbal tea route of administration may not reproduce the effects of inhalation or oral ingestion of fat-soluble cannabinoids.

Highly concentrated THC or cannabidiol (CBD) oil extracts are being illegally promoted as potential cancer cures.[5] These oils have not been evaluated in any clinical trials for anticancer activity or safety. Because CBD is a potential inhibitor of certain cytochrome P450 enzymes, highly concentrated CBD oils used concurrently with conventional therapies that are metabolized by these enzymes could potentially increase toxicity or decrease the effectiveness of these therapies.[6,7]

Cancer Risk

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

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*. [8]

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.[9]

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.[10]

A systematic review [assessing](#) 19 studies that evaluated [preinvasive](#) 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.[11] In the review of the published [meta-analyses](#), the National Academies of Sciences, Engineering, and Medicine (NASEM) report concluded that there was moderate evidence of no statistical association between *Cannabis* smoking and the [incidence](#) of lung cancer.[12]

[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 cancer incidence noted in previous studies and suggest that more work needs to be done to understand the potential role of [human papillomavirus infection](#). [13] A systematic review and [meta-analysis](#) of nine case-control studies involving 13,931 participants also concluded that there was insufficient evidence to support or refute a positive or negative association between *Cannabis* smoking and the incidence of [head and neck cancers](#). [14]

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.[15-17] Three population-based case-control studies reported an association between *Cannabis* use and elevated risk of TGCTs, especially [nonseminoma](#) or mixed-histology tumors.[15-17] 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. In a study of 49,343 Swedish men aged 19 to 21 years enrolled in the military between 1969 and 1970, participants were asked once at the time of conscription about their use of *Cannabis* and were followed up for 42 years.[18] This study found no evidence of a significant relation between “ever” *Cannabis* use and the development of [testicular cancer](#), but did find that “heavy” *Cannabis* use (more than 50 times in a lifetime) was associated with a 2.5-fold increased risk. Limitations of the study were that it relied on indirect [assessment](#) of *Cannabis* use; and no information was collected on *Cannabis* use after the conscription-assessment period or on whether the testicular cancers were [seminoma](#) or nonseminoma subtypes. These reports 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).[19]

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 and cancer is still [inconclusive](#). [20]

Patterns of Cannabis Use Among Cancer Patients

A cross-sectional survey of cancer patients seen at the Seattle Cancer Care Alliance was conducted over a 6-week period between 2015 and 2016.[21] In Washington State, *Cannabis* was legalized for medicinal use in 1998 and for recreational use in 2012. Of the 2,737 possible participants, 936 (34%) completed the anonymous questionnaire. Twenty-four percent of patients considered themselves active *Cannabis* users. Similar numbers of patients inhaled (70%) or used edibles (70%), with dual use (40%) being common. Non-mutually exclusive reasons for *Cannabis* use were physical [symptoms](#) (75%), neuropsychiatric symptoms (63%), recreational use/enjoyment (35%), and treatment of cancer (26%). The physical symptoms most commonly cited were pain, [nausea](#), and loss of [appetite](#). The majority of patients (74%) stated that they would prefer to obtain information about *Cannabis* from their cancer team, but less than 15% reported receiving information from their cancer [physician](#) or [nurse](#).

Cancer Treatment

No ongoing clinical trials of *Cannabis* as a treatment for cancer in humans were identified in a PubMed search. The only published trial of any cannabinoid in patients with cancer is a small pilot study of [intratumoral injection](#) of delta-9-THC in patients with [recurrent glioblastoma multiforme](#), which demonstrated no significant clinical benefit.[22,23] In a trial (NCT02255292) conducted in Israel, oral CBD was investigated as a single [salvage](#) agent for recurrent [solid tumors](#). The study was projected to be completed in 2015; however, no results have been published. A small exploratory [phase II](#) study (GWCA1208 Part A [NCT01812603]) was conducted in the United Kingdom that used nabiximols, 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. The study enrolled 21 patients. Final results have not been published.

Another Israeli group postulated that the [anti-inflammatory](#) and [immunosuppressive](#) effects of CBD might make it a valuable [adjunct](#) in the treatment of [acute graft-versus-host disease](#) (GVHD) in patients who have undergone [allogeneic hematopoietic stem cell transplantation](#). The authors investigated CBD 300 mg/d in addition to standard GVHD [prophylaxis](#) in 48 adult patients who had undergone transplantation predominantly for [acute leukemia](#) or [myelodysplastic syndrome](#) (NCT01385124 and NCT01596075).[24] The combination of CBD with standard GVHD prophylaxis was found to be safe. Compared with 101 [historical controls](#) treated with standard prophylaxis, patients who received CBD appeared to have a lower incidence of grade II to grade IV GVHD, suggesting that a [randomized controlled trial](#) (RCT) is warranted.

Clinical data regarding *Cannabis* as an [anticancer agent](#) in [pediatric](#) use is limited to a few [case reports](#).[25,26]

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. [27] Both dronabinol and nabilone have been approved by the [U.S. Food and Drug Administration](#) (FDA) for the treatment of N/V associated with cancer chemotherapy in patients who have failed to [respond](#) 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.[28-31] The National Comprehensive Cancer Network Guidelines recommend cannabinoids as breakthrough treatment for chemotherapy-related N/V.[32] The American Society for Clinical Oncology (ASCO) antiemetic guidelines updated in 2017 recommends that the FDA-approved cannabinoids, dronabinol or nabilone, be used to treat N/V that is resistant to standard antiemetic therapies.[33]

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.[34] Oral nabilone, oral dronabinol, and [intramuscular](#) levonantradol (a synthetic [analog](#) 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 [alzapride](#). 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](#), [sedation](#) or drowsiness, dizziness, dysphoria or [depression](#), [hallucinations](#), [paranoia](#), and [hypotension](#).[34]

Another analysis of 15 [controlled studies](#) compared nabilone with placebo or available antiemetic drugs.[35] Among 600 cancer patients, nabilone was found to be superior to prochlorperazine, domperidone, and alzapride, with nabilone favored for continuous use.

A Cochrane meta-analysis of 23 randomized RCTs reviewed studies conducted between 1975 and 1991 that investigated dronabinol or nabilone, either as [monotherapy](#) or as an adjunct to the [conventional](#) dopamine [antagonists](#) that were the [standard](#) antiemetics at that time.[36] The chemotherapy regimens involved drugs with low, moderate, or high [emetogenic](#) potential. The meta-analysis graded the quality of evidence as low for most outcomes. The review concluded that individuals were more likely to report complete absence of N/V when they received cannabinoids compared with placebo, although they were more likely to withdraw from the study because of an adverse event. Individuals reported a higher preference for cannabinoids than placebo or prochlorperazine. There was no difference in the antiemetic effect of cannabinoids when compared with prochlorperazine. The authors concluded that *Cannabis*-based medications may be useful for treating [refractory](#) chemotherapy-induced N/V; however, they cautioned that their assessment may change with the availability of newer antiemetic regimens.

At least 50% of patients who receive moderately emetogenic chemotherapy may experience delayed chemotherapy-induced N/V. Although selective neurokinin 1 antagonists that inhibit substance P have been approved for delayed N/V, a study was conducted before their availability to assess dronabinol, [ondansetron](#), or their combination in preventing delayed-onset chemotherapy-induced N/V.[37] Ondansetron, a serotonin 5-hydroxytryptamine 3 (5-HT₃) [receptor antagonist](#), is one of the mainstay agents in the current antiemetic armamentarium. In this trial, the primary objective was to assess the response 2 to 5 days after moderately to severely emetogenic chemotherapy. Sixty-one patients were analyzed for efficacy. The total response—a composite endpoint—including nausea intensity, vomiting/retching, and use of rescue medications, was similar with dronabinol (54%), ondansetron (58%), and combination therapy (47%) when compared with placebo (20%). Nausea absence was greater in the active treatment groups (dronabinol 71%, ondansetron 64%, combination therapy 53%) when compared with placebo (15%; $P < .05$ vs. placebo for all). Occurrence rates for nausea intensity and vomiting/retching episodes were the lowest in patients treated with dronabinol, suggesting that dronabinol compares favorably with ondansetron in this situation where a substance P inhibitor would currently be the drug of choice.

(Refer to the *Cannabis* section in the PDQ summary on [Treatment-Related Nausea and Vomiting](#) for more information.)

Cannabis

Three trials have evaluated the efficacy of inhaled *Cannabis* in chemotherapy-induced N/V.[38-41] 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,[38] but in the second trial, a statistically significant superior antiemetic effect of inhaled *Cannabis* versus placebo was found among patients receiving high-dose methotrexate.[39] The third trial was a randomized, double-blind, placebo-controlled, crossover 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.[40]

Newer antiemetics (e.g., 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.[42][Level of evidence: 1c] ASCO antiemetic guidelines updated in 2017 state that evidence remains insufficient to recommend medical marijuana for either the prevention or treatment of N/V in patients with cancer who receive chemotherapy or radiation therapy.[33]

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

Four controlled trials demonstrated that oral THC has variable effects on appetite stimulation and weight loss in patients with advanced malignancies and HIV infection.[35] One study evaluated the efficacy of dronabinol alone or with megestrol acetate compared with that of megestrol acetate alone for managing cancer-associated anorexia.[43] 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 of treatment. 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.[44] Forty-seven patients with advanced lung cancer were randomized to receive nabilone 0.5 mg/d for 2 weeks followed by 1 mg/d for 6 weeks (N = 22) or placebo (N = 25) for 8 weeks (NCT02802540).[45] The study suffered from significant attrition and endpoints were not achieved. The authors reported that at 8 weeks, patients randomized to receive nabilone had increased intake of calories and carbohydrates and better quality of life than the placebo recipients, but appeared to have increased weight loss.

Another clinical trial that involved 139 patients with HIV or AIDS and weight loss found that, compared with placebo, oral dronabinol 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.[46]

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.[47,48]

Despite patients' great interest in oral preparations of *Cannabis* to improve appetite, there is only one trial of *Cannabis* extract used for appetite stimulation. 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.[49]

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.[50][[Level of evidence: 1iC](#)] The CB1 receptor is found in the [central nervous system](#) (CNS) and in peripheral [nerve](#) terminals.[51] 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.[52,53]

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.[54] 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.[55] Higher doses of THC were found to be more sedating 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.[56] 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/d), compared with placebo. Adverse events were dose related, with only the high-dose group (11–16 sprays/d) 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.[57] 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.[58]

An [observational study](#) assessed the effectiveness of nabilone in advanced cancer patients who were experiencing pain and other [symptoms](#) (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.[59]

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.[60] 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 or [taxanes](#). Two RCTs 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.[61,62] Additional trials of inhaled *Cannabis* have also demonstrated the benefit of *Cannabis* over placebo in HIV-associated neuropathic pain.[63]

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.[64]

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.[54][[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.[\[44\]](#)[\[Level of evidence: 1iC\]](#)

Cannabis

Patients often experience mood elevation after exposure to *Cannabis*, depending on their previous experience. In a five-patient [case 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.[\[65\]](#)

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.[\[44\]](#)

Seventy-four patients with newly [diagnosed](#) head and neck cancer self-described as current *Cannabis* users were matched to 74 nonusers in a Canadian study investigating quality of life using the EuroQol-5D and Edmonton Symptom Assessment System instruments.[\[66\]](#) *Cannabis* users had significantly lower scores in the anxiety/depression (difference, 0.74; 95% CI, 0.557–0.930) and pain/discomfort (difference, 0.29; 95% CI, 0.037–1.541) domains. *Cannabis* users were also less tired, had more appetite, and better general well-being.

Clinical Studies of Cannabis and Cannabinoids

Reference	Type of Study	Condition Treated	No. of Patients: Enrolled, Treated, Placebo or No Treatment Control ^b
[133]	RCT	CINV	8, 8, None
[135]	RCT	CINV	15, 15, None
[142]	Phase RCT	CINV	10, 7, 9
[143]	Nonrandomized	Chronic pain	23/10 (topical), 11 (oral)

Table

Table 1. Clinical Studies of *Cannabis*^a.

Reference	Type of Study	Condition Treated	No. of Patients: Enrolled, Treated, Placebo or No Treatment Control ^b	Strategies
[144]	RCT	Cancer-associated anorexia	400; 400; 152; 152; 152, or both 152, none	Marginal increased gain, even patients on dexamethasone

Table

Table 2. Clinical Studies of Cannabinoids^a.

Current Clinical Trials

Use our [advanced clinical trial search](#) to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. [General information](#) about clinical trials is also available.

References

1. Adams IB, Martin BR: Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91 (11): 1585-614, 1996. [\[PubMed: 8972919\]](#)

2. Agurell S, Halldin M, Lindgren JE, et al.: Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev* 38 (1): 21-43, 1986. [\[PubMed: 3012605\]](#)

3. Yamamoto I, Watanabe K, Narimatsu S, et al.: Recent advances in the metabolism of cannabinoids. *Int J Biochem Cell Biol* 27 (8): 741-6, 1995. [\[PubMed: 7584607\]](#)

4. Engels FK, de Jong FA, Sparreboom A, et al.: Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* 12 (3): 291-300, 2007. [\[PubMed: 17405893\]](#)

5. FDA Warns Companies Marketing Unproven Products, Derived From Marijuana, That Claim to Treat or Cure Cancer [News Release]. Silver Spring, Md: Food and Drug Administration, 2017. [Available online](#). Last accessed January 4, 2019.

6. Yamaori S, Okamoto Y, Yamamoto I, et al.: Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metab Dispos* 39 (11): 2049-56, 2011. [\[PubMed: 21821735\]](#)

7. Jiang R, Yamaori S, Okamoto Y, et al.: Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metab Pharmacokinet* 28 (4): 332-8, 2013. [\[PubMed: 23318708\]](#)

8. Berthiller J, Straif K, Boniol M, et al.: Cannabis smoking and risk of lung cancer in men: a pooled analysis of three studies in Maghreb. *J Thorac Oncol* 3 (12): 1398-403, 2008. [\[PubMed: 19057263\]](#)

9. Sidney S, Quesenberry CP, Friedman GD, et al.: Marijuana use and cancer incidence (California, United States). *Cancer Causes Control* 8 (5): 722-8, 1997. [\[PubMed: 9328194\]](#)

10. Hashibe M, Morgenstern H, Cui Y, et al.: Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 15 (10): 1829-34, 2006. [PubMed: 17035389]
11. Mehra R, Moore BA, Crothers K, et al.: The association between marijuana smoking and lung cancer: a systematic review. *Arch Intern Med* 166 (13): 1359-67, 2006. [PubMed: 16832000]
12. National Academies of Sciences, Engineering, and Medicine: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press, 2017.
13. Marks MA, Chaturvedi AK, Kelsey K, et al.: Association of marijuana smoking with oropharyngeal and oral tongue cancers: pooled analysis from the INHANCE consortium. *Cancer Epidemiol Biomarkers Prev* 23 (1): 160-71, 2014. [PMC free article: PMC3947141] [PubMed: 24351902]
14. de Carvalho MF, Dourado MR, Fernandes IB, et al.: Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies. *Arch Oral Biol* 60 (12): 1750-5, 2015. [PubMed: 26433192]
15. Daling JR, Doody DR, Sun X, et al.: Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer* 115 (6): 1215-23, 2009. [PMC free article: PMC2759698] [PubMed: 19204904]
16. Trabert B, Sigurdson AJ, Sweeney AM, et al.: Marijuana use and testicular germ cell tumors. *Cancer* 117 (4): 848-53, 2011. [PMC free article: PMC3017734] [PubMed: 20925043]
17. Lacson JC, Carroll JD, Tuazon E, et al.: Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer* 118 (21): 5374-83, 2012. [PMC free article: PMC3775603] [PubMed: 22965656]
18. Callaghan RC, Allebeck P, Akre O, et al.: Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011. *Cancer Epidemiol Biomarkers Prev* 26 (11): 1644-1652, 2017. [PMC free article: PMC5812006] [PubMed: 29093004]
19. Thomas AA, Wallner LP, Quinn VP, et al.: Association between cannabis use and the risk of bladder cancer: results from the California Men's Health Study. *Urology* 85 (2): 388-92, 2015. [PubMed: 25623697]
20. Health Canada: Marihuana (Marijuana, Cannabis): Dried Plant for Administration by Ingestion or Other Means. Ottawa, Canada: Health Canada, 2010. Available online. Last accessed October 18, 2017.
21. Pergam SA, Woodfield MC, Lee CM, et al.: Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer* 123 (22): 4488-4497, 2017. [PMC free article: PMC5698756] [PubMed: 28944449]
22. Guzmán M, Duarte MJ, Blázquez C, et al.: A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer* 95 (2): 197-203, 2006. [PMC free article: PMC2360617] [PubMed: 16804518]
23. Velasco G, Sánchez C, Guzmán M: Towards the use of cannabinoids as antitumour agents. *Nat Rev Cancer* 12 (6): 436-44, 2012. [PubMed: 22555283]
24. Yeshurun M, Shpilberg O, Herscovici C, et al.: Cannabidiol for the Prevention of Graft-versus-Host-Disease after Allogeneic Hematopoietic Cell Transplantation: Results of a Phase II Study. *Biol Blood Marrow Transplant* 21 (10): 1770-5, 2015. [PubMed: 26033282]
25. Singh Y, Bali C: Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation. *Case Rep Oncol* 6 (3): 585-92, 2013. [PMC free article: PMC3901602] [PubMed: 24474921]
26. Foroughi M, Henderson G, Sargent MA, et al.: Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas--possible role of Cannabis inhalation. *Childs Nerv Syst* 27 (4): 671-9, 2011. [PubMed: 21336992]
27. Sutton IR, Daeninck P: Cannabinoids in the management of intractable chemotherapy-induced nausea and vomiting and cancer-related pain. *J Support Oncol* 4 (10): 531-5, 2006 Nov-Dec. [PubMed: 17136871]
28. Ahmedzai S, Carlyle DL, Calder IT, et al.: Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *Br J Cancer* 48 (5): 657-63, 1983. [PMC free article: PMC2011510] [PubMed: 6315040]
29. Chan HS, Correia JA, MacLeod SM: Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 79 (6): 946-52, 1987. [PubMed: 3035479]
30. Johansson R, Kilku P, Groenroos M: A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. *Cancer Treat Rev* 9 (Suppl B): 25-33, 1982. [PubMed: 6299551]
31. Niiranen A, Mattson K: A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *Am J Clin Oncol* 8 (4): 336-40, 1985. [PubMed: 3002167]
32. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Antiemesis. Version 2.2017. Fort Washington, Pa: National Comprehensive Cancer Network, 2017. Available online with free registration. Last accessed November 14, 2017.
33. Hesketh PJ, Kris MG, Basch E, et al.: Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 35 (28): 3240-3261, 2017. [PubMed: 28759346]
34. Tramèr MR, Carroll D, Campbell FA, et al.: Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ* 323 (7303): 16-21, 2001. [PMC free article: PMC34325] [PubMed: 11440936]
35. Ben Amar M: Cannabinoids in medicine: A review of their therapeutic potential. *J Ethnopharmacol* 105 (1-2): 1-25, 2006. [PubMed: 16540272]

36. Smith LA, Azariah F, Lavender VT, et al.: Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database Syst Rev* (11): CD009464, 2015. [PMC free article: [PMC6931414](#)] [PubMed: [26561338](#)]
37. Meiri E, Jhangiani H, Vredenburg JJ, et al.: Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin* 23 (3): 533-43, 2007. [PubMed: [17355735](#)]
38. Chang AE, Shilling DJ, Stillman RC, et al.: A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 47 (7): 1746-51, 1981. [PubMed: [6261926](#)]
39. Chang AE, Shilling DJ, Stillman RC, et al.: Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med* 91 (6): 819-24, 1979. [PubMed: [293141](#)]
40. Levitt M, Faiman C, Hawks R, et al.: Randomized double blind comparison of delta-9-tetrahydrocannabinol and marijuana as chemotherapy antiemetics. [Abstract] *Proceedings of the American Society of Clinical Oncology* 3: A-C354, 91, 1984.
41. Musty RE, Rossi R: Effects of smoked cannabis and oral delta-9-tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: a review of state clinical trials. *Journal of Cannabis Therapeutics* 1 (1): 29-56, 2001. Also available online. Last accessed October 18, 2017.
42. Duran M, Pérez E, Abanades S, et al.: Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol* 70 (5): 656-63, 2010. [PMC free article: [PMC2997305](#)] [PubMed: [21039759](#)]
43. Jatoi A, Windschitl HE, Loprinzi CL, et al.: Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 20 (2): 567-73, 2002. [PubMed: [11786587](#)]
44. Brisbois TD, de Kock IH, Watanabe SM, et al.: Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol* 22 (9): 2086-93, 2011. [PubMed: [21343383](#)]
45. Turcott JG, Del Rocio Guillen Núñez M, Flores-Estrada D, et al.: The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. *Support Care Cancer* 26 (9): 3029-3038, 2018. [PubMed: [29550881](#)]
46. Beal JE, Olson R, Laubenstein L, et al.: Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 10 (2): 89-97, 1995. [PubMed: [7730690](#)]
47. Foltin RW, Brady JV, Fischman MW: Behavioral analysis of marijuana effects on food intake in humans. *Pharmacol Biochem Behav* 25 (3): 577-82, 1986. [PubMed: [3774823](#)]
48. Foltin RW, Fischman MW, Byrne MF: Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite* 11 (1): 1-14, 1988. [PubMed: [3228283](#)]
49. Strasser F, Luftner D, Possinger K, et al.: Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 24 (21): 3394-400, 2006. [PubMed: [16849753](#)]
50. Aggarwal SK: Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain* 29 (2): 162-71, 2013. [PubMed: [22367503](#)]
51. Walker JM, Hohmann AG, Martin WJ, et al.: The neurobiology of cannabinoid analgesia. *Life Sci* 65 (6-7): 665-73, 1999. [PubMed: [10462067](#)]
52. Calignano A, La Rana G, Giuffrida A, et al.: Control of pain initiation by endogenous cannabinoids. *Nature* 394 (6690): 277-81, 1998. [PubMed: [9685157](#)]
53. Fields HL, Meng ID: Watching the pot boil. *Nat Med* 4 (9): 1008-9, 1998. [PubMed: [9734389](#)]
54. Noyes R, Brunk SF, Baram DA, et al.: Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol* 15 (2-3): 139-43, 1975 Feb-Mar. [PubMed: [1091664](#)]
55. Noyes R, Brunk SF, Avery DA, et al.: The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 18 (1): 84-9, 1975. [PubMed: [50159](#)]
56. Johnson JR, Burnell-Nugent M, Lossignol D, et al.: Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 39 (2): 167-79, 2010. [PubMed: [19896326](#)]
57. Portenoy RK, Ganae-Motan ED, Allende S, et al.: Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain* 13 (5): 438-49, 2012. [PubMed: [22483680](#)]
58. Johnson JR, Lossignol D, Burnell-Nugent M, et al.: An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J Pain Symptom Manage* 46 (2): 207-18, 2013. [PubMed: [23141881](#)]
59. Maida V, Ennis M, Irani S, et al.: Adjunctive nabilone in cancer pain and symptom management: a prospective observational study using propensity scoring. *J Support Oncol* 6 (3): 119-24, 2008. [PubMed: [18402303](#)]
60. Abrams DI, Couey P, Shade SB, et al.: Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther* 90 (6): 844-51, 2011. [PubMed: [22048225](#)]
61. Wilsey B, Marcotte T, Deutsch R, et al.: Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain* 14 (2): 136-48, 2013. [PMC free article: [PMC3566631](#)] [PubMed: [23237736](#)]

62. Wilsey B, Marcotte T, Tsodikov A, et al.: A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 9 (6): 506-21, 2008. [PMC free article: PMC4968043] [PubMed: 18403272]
63. Andrae MH, Carter GM, Shaparin N, et al.: Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. *J Pain* 16 (12): 1221-1232, 2015. [PMC free article: PMC4666747] [PubMed: 26362106]
64. Lynch ME, Cesar-Rittenberg P, Hohmann AG: A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manage* 47 (1): 166-73, 2014. [PubMed: 23742737]
65. Noyes R, Baram DA: Cannabis analgesia. *Compr Psychiatry* 15 (6): 531-5, 1974 Nov-Dec. [PubMed: 4426188]
66. Zhang H, Xie M, Archibald SD, et al.: Association of Marijuana Use With Psychosocial and Quality of Life Outcomes Among Patients With Head and Neck Cancer. *JAMA Otolaryngol Head Neck Surg* 144 (11): 1017-1022, 2018. [PMC free article: PMC6248184] [PubMed: 30073295]

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 [tissues](#) throughout the body, not just in the [central nervous system](#), and [adverse effects](#) include [tachycardia](#), [hypotension](#), [conjunctival](#) injection, 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.

Cannabidiol (CBD) is an inhibitor of cytochrome P450 isoforms *in vitro*. Because many anticancer therapies are metabolized by these [enzymes](#), highly concentrated CBD oils used concurrently could potentially increase the [toxicity](#) or decrease the effectiveness of these therapies.[5,6]

Since *Cannabis* smoke contains many of the same components as [tobacco](#) smoke, there are valid concerns about the adverse [pulmonary](#) effects of [inhaled Cannabis](#). A longitudinal study in a noncancer population evaluated repeated measurements of pulmonary function over 20 years in 5,115 men and women whose smoking histories were known.[7] 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]).

References

1. Adams IB, Martin BR: Cannabis: pharmacology and toxicology in animals and humans. *Addiction* 91 (11): 1585-614, 1996. [PubMed: 8972919]
2. Grotenhermen F, Russo E, eds.: Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential. Binghamton, NY: The Haworth Press, 2002.
3. Sutton IR, Daeninck P: Cannabinoids in the management of intractable chemotherapy-induced nausea and vomiting and cancer-related pain. *J Support Oncol* 4 (10): 531-5, 2006 Nov-Dec. [PubMed: 17136871]
4. Guzmán M: Cannabinoids: potential anticancer agents. *Nat Rev Cancer* 3 (10): 745-55, 2003. [PubMed: 14570037]
5. Yamaori S, Okamoto Y, Yamamoto I, et al.: Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metab Dispos* 39 (11): 2049-56, 2011. [PubMed: 21821735]
6. Jiang R, Yamaori S, Okamoto Y, et al.: Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metab Pharmacokinet* 28 (4): 332-8, 2013. [PubMed: 23318708]
7. Pletcher MJ, Vittinghoff E, Kalhan R, et al.: Association between marijuana exposure and pulmonary function over 20 years. *JAMA* 307 (2): 173-81, 2012. [PMC free article: PMC3840897] [PubMed: 22235088]

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. For an explanation of possible scores and additional information about levels of evidence analysis of Complementary and Alternative Medicine (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](#). Both dronabinol and nabilone are approved by the [U.S. Food and Drug Administration](#) for the [prevention](#) or treatment of chemotherapy-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 and chemotherapy [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.

Changes to This Summary (01/07/2020)

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.

Human/Clinical Studies

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.

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.

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.

Permission to Use This Summary

PDQ is a registered trademark. Although the content of PDQ documents can be used freely as text, it cannot be identified as an NCI PDQ cancer information summary unless it is presented in its entirety and is regularly updated. However, an author would be permitted to write a sentence such as “NCI’s PDQ cancer information summary about breast cancer prevention states the risks succinctly: [include excerpt from the summary].”

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: <https://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq>. Accessed <MM/DD/YYYY>. [PMID: 26389198]

Images in this summary are used with permission of the author(s), artist, and/or publisher for use within the PDQ summaries only. Permission to use images outside the context of PDQ information must be obtained from the owner(s) and cannot be granted by the National Cancer Institute.

Information about using the illustrations in this summary, along with many other cancer-related images, is available in [Visuals Online](#), a collection of over 2,000 scientific images.

Disclaimer

The information in these summaries should not be used as a basis for insurance reimbursement determinations. More information on insurance coverage is available on Cancer.gov on the [Managing Cancer Care](#) page.

Contact Us

More information about contacting us or receiving help with the Cancer.gov website can be found on our [Contact Us for Help](#) page. Questions can also be submitted to Cancer.gov through the website’s [Email Us](#).

Publication Details

Author Information

Authors

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board.

Publication History

Published online: January 7, 2020.

Created: March 16, 2011.

Version History

NBK65755.20	January 7, 2020 (Displayed Version)
NBK65755.19	July 16, 2019
NBK65755.18	June 18, 2019
NBK65755.17	June 6, 2019
NBK65755.16	May 31, 2019
NBK65755.15	January 17, 2019
NBK65755.14	August 16, 2018
NBK65755.13	June 19, 2018
NBK65755.12	November 30, 2017
NBK65755.11	October 20, 2017
NBK65755.10	April 7, 2017
NBK65755.9	March 15, 2017
NBK65755.8	December 8, 2016
NBK65755.7	May 27, 2016
NBK65755.6	April 21, 2016
NBK65755.5	April 8, 2016
NBK65755.4	April 1, 2016
NBK65755.3	January 20, 2016
NBK65755.2	January 7, 2016
NBK65755.1	August 28, 2015

Copyright

Copyright Notice

Publisher

National Cancer Institute (US), Bethesda (MD)

NLM Citation

PDQ Integrative, Alternative, and Complementary Therapies Editorial Board. Cannabis and Cannabinoids (PDQ®): Health Professional Version. 2020 Jan 7. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-.

