

Cannabis Use in Palliative Oncology: A Review of the Evidence for Popular Indications

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ABSTRACT: A flowering plant of variegated ingredients and psychoactive qualities, cannabis has long been used for medicinal and recreational purposes. Currently, cannabis is approved in several countries for indications of symptomatic alleviation. However, limited knowledge on the benefits and risks precludes inclusion of cannabis in standard treatment guidelines. This review provides a summary of the available literature on the use of cannabis and cannabinoid-based medicines in palliative oncology. Favorable outcomes are demonstrated for chemotherapy-induced nausea and vomiting and cancer-related pain, with evidence of advantageous neurological interactions. Benefit in the treatment of anorexia, insomnia and anxiety is also suggested. Short- and long-term side effects appear to be manageable and to subside after discontinuation of the drug. Finally, cannabinoids have shown anti-neoplastic effects in preclinical studies in a wide range of cancer cells and some animal models. Further research is needed before cannabis can become a part of evidence-based oncology practice.

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Cannabis has been used as a healing herb and mind-altering drug since ancient times. Explored at the dawn of Chinese medicine close to 5000 years ago, then chronicled as a part of Greek tradition, glorified by Indian folklore and even deliberated in sacred Jewish texts, cannabis has left its mark in history [1]. With the advent of cannabis cultivation in the New World, the burgeoning plant became a prosperous cash crop. It was registered in the American and British Pharmacopeia for nearly a century, until drug enforcement agencies designated it an illegal drug in 1971. In recent years, cannabis and cannabinoid-based medicines (CBMs) have gained approval across a broad range of indications in many countries, with emerging literature espousing symptomatic amelioration in chronic disease. In 2015, the Israel Ministry of Health updated its criteria for oncological patients to obtain a cannabis license

Cannabis is used in palliative oncology for amelioration of chemotherapy-induced nausea and vomiting and cancer-related pain

and included cancer-related pain in advanced disease and chemotherapy-induced symptoms [2].

Much information is yet to be elucidated concerning the benefits and risks of this controversial drug, since high quality clinical trials are too few and hardly standardized. This review aims to provide a thorough investigation of the therapeutic use of cannabis in palliative oncology. We first summarize its potential mechanisms of action and list currently approved CBMs. We then explore its utility in five palliative indications, namely chemotherapy-induced nausea and vomiting (CINV), cancer-related pain, anorexia, insomnia, and depression, and describe the main adverse effects. We conclude with the anti-cancer potential of cannabis.

CANNABIS

Cannabis is a genus of flowering plant that includes species *sativa*, *indica* and *ruderalis*. Indigenous to Central Asia and India and cultivated in tropical and equatorial regions, cannabis comes in the form of marijuana (dried flower buds) and hashish (blocks of resin). Unique qualities of each cannabis strain derive from three bioactive molecules: flavonoids, terpenoids, and cannabinoids. Relative proportions of the nearly 100 different cannabinoids determine the psychoactive potency of the cannabis plant, the two most well-known of these being delta-9-tetrahydrocannabinol (Δ^9 -THC) and cannabidiol (CBD) [2].

Cannabinoids exert mental and physical effects by binding to G protein-coupled cannabinoid receptors 1 and 2 (CB1 and CB2), stimulating the endogenous cannabinoid system and altering levels of endocannabinoids (eCBs). These receptors are widely distributed throughout the body, with the highest concentration of CB1 and CB2 found in the central nervous system and immune cells respectively. Derived from arachidonic acid, eCBs are neuroactive lipid messengers that contribute to physiological processes such as reward, motivation, memory, learning, and pain processing [2].

Cannabinoids may be extracted naturally from the plant and taken in herbal form or manufactured synthetically. They can be mixed with food or tea, inhaled, smoked or injected. Nabiximols (Sativex[®], GW Pharmaceuticals LTD., UK) oromucosal spray, a

1:1 mixture of Δ^9 -THC and CBD isolated directly from *Cannabis sativa*, is listed for management of cancer pain. Synthetic forms of cannabis include dronabinol (Marinol[®], Banner Pharmacaps, Inc., USA) capsules and nabilone (Cesamet[®], Valeant Pharmaceuticals International, Canada), generic Δ^9 -THC in oral or inhaled solutions, approved for treatment of CINV [3].

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Endocannabinoid receptors are interspersed within emetic reflex pathways, making them a promising target for managing CINV. Central regulation of emesis occurs via the dorsal vagal complex (DVC), which includes the area postrema, the nucleus of the solitary tract (nTS), and the dorsal motor nucleus of the vagus. Located just outside the blood-brain barrier in the fourth ventricle of the brain, the area postrema provides direct communication between blood-borne signals such as chemotherapy and the autonomic neurons that elicit emesis. All three regions of the DVC, as well as its vagal outputs in the gastrointestinal tract are populated with CB-1 receptors, which have shown anti-emetic effects when activated by Δ^9 -THC [4]. Neurotransmitters involved in emesis include dopamine, histamine, acetylcholine, serotonin (5-HT₃) and substance P, serving as targets for anti-emetic medicines. Δ^9 -THC has shown opposite effects on the nTS compared to nausea-inducing 5-HT₃ agonists [5].

In a meta-analysis by Machado et al. [6] investigating synthetic Δ^9 -THC in cancer patients receiving chemotherapy, dronabinol demonstrated superior anti-emetic activity to neuroleptics, while other CBMs had a clinical but not statistical advantage. Moreover, Lane et al. [7] showed a synergistic effect for dronabinol and prochlorperazine. Meiri et al. [8] undertook a blinded, placebo-controlled comparison between CBMs and 5-HT₃ antagonists and established non-inferiority for dronabinol, although synergism with ondansetron was not achieved. CBMs have also shown greater activity in suppressing anticipatory nausea than 5-HT₃ antagonists. Smoked marijuana has been proposed to be a more effective anti-emetic than oral Δ^9 -THC, but no controlled studies have validated this possibility [9]. Cannabis is not currently listed in CINV guidelines. The dearth of data comparing cannabis to first-line anti-emesis regimens hampers recognition of its therapeutic potential and limits its clinical use.

CANCER-ASSOCIATED PAIN

Cannabis has long been used for its analgesic properties. CB-1Rs densely populate the hippocampus and association cortices, the cerebellum, and the basal ganglia, with remarkably similar neuroanatomic, neurochemical and pharmacological characteristics to receptors of the opioid system. They are thought to modulate nociceptive processing in the brain, independently and in synergism with exogenous opioids.

CB-2Rs located in areas of intense nociceptive integration, such as dorsal root ganglion sensory neurons and the spinal cord, may also have a role; they stimulate release of analgesic beta-endorphins and reduce C-fiber activity in neuropathic pain models. Peripheral cannabinoid receptors have been implicated in anti-nociception by activating noradrenergic pathways [10].

Research suggests that cannabis is a potent therapeutic adjunct, with a penchant for relieving neuropathic pain. Noyes and colleagues [11] demonstrated that high doses of Δ^9 -THC were significantly superior to placebo in pain reduction and comparable to codeine, albeit associated with considerable sedation. Several trials have examined the analgesic effects of Δ^9 -THC/CBD preparations in subjects with opioid refractory cancer pain. Portenoy et al. [12] found a higher proportion of patients reporting analgesia with low and medium dose nabiximols than placebo, while poor drug tolerability was noted in the high dose group. Johnson and team [13] observed superior pain relief in patients treated with Δ^9 -THC/CBD as compared to Δ^9 -THC alone or placebo, which was sustained for as long

Preclinical studies show cannabinoid-induced anti-neoplastic effects in a wide range of cancer cells

as 2 years without the need for raising opioid dosages. Similarly, Bar-Sela et al. [14] performed an observational study evaluating patient-reported cancer-related symptoms while on CBMs and found not only pain lessening but also reduction in opioid dose in close to half the subjects. Despite positive results, standardization is difficult due to differing cannabis preparations and dosages and, therefore, larger trials are needed to delineate a more accurate picture.

ANOREXIA AND CACHEXIA SYNDROME

Early reports of increased appetite and weight stability in HIV/AIDS patients using dronabinol [15] sparked a wave of research in oncology. Anorexia and cachexia in cancer patients refer to a spectrum of metabolic changes that begins with reduced caloric intake and variable degrees of inflammation, and progresses to a refractory, pro-catabolic state linked to low performance and short survival. Jatoti and group [16] compared dronabinol and megastrol acetate for cancer-associated anorexia, with significant findings in favor of megastrol. A large phase III trial comparing Δ^9 -THC to Δ^9 -THC+CBD to placebo found no significant improvements in survival, weight, or other nutritional variables [17]. However, cannabis has been associated with improved taste, smell and food enjoyment [18].

INSOMNIA

A large meta-analysis by Whiting et al. [19] reviewed 19 studies that evaluated sleep as an outcome as well as two trials specifically investigating sleep problems and found a positive association between cannabinoids and improved sleep quality. The study cohort included patients with chronic pain and

multiple sclerosis, thus implications for cancer patients are not certain [19].

DEPRESSION AND ANXIETY

In the aforementioned meta-analysis, no trials evaluating depression fulfilled inclusion criteria. In the five trials of non-cancer patients where depression was reported as an outcome measure, no difference was found compared to placebo, with the exception of a negative effect for high dose nabiximols in one. Positive results were found, however, in individuals with social anxiety disorder, as well as in anxiety outcomes in patients with chronic pain [19].

ADVERSE EFFECTS

Adverse effects of cannabis are mostly short term and include somnolence, dizziness, dry mouth and disorientation, as well as euphoria, anxiety and hallucination. Memory and cognition problems, addiction, and exacerbation or provocation of nascent psychiatric illness, such as depression and anxiety disorders, have also been associated with cannabis use. Events are mostly attributed to $\Delta 9$ -THC, while the opposing cannabinoid CBD is thought to alleviate its effects, and rather facilitates learning, prevents psychosis and eases anxiety. Street cannabis notoriously contains high levels of $\Delta 9$ -THC and negligible CBD, while CBMs supplied for research or patient use have dramatically different potencies and cannabinoid proportions. Most long-term effects of cannabis have been shown to subside within 6 weeks of abstinence from cannabis use [20].

CANNABIS AS AN ANTI-NEOPLASTIC AGENT

The anti-cancer potential of cannabis has been explored in preclinical research, with evidence of a connection to cancer cell signaling pathways. It has been shown to induce apoptosis and inhibit tumor proliferation, vascularization and metastasis. In non-small cell lung carcinoma, administration of $\Delta 9$ -THC inhibited endothelial growth factor-induced migration in vitro, as well as tumor and metastasis growth in mice models. In murine gliomas, CBD had anti-proliferative effects, and selective CB2 agonists caused tumor regression. Activation of CB1 in mice with colon carcinoma reduced tumor growth. Treatment with cannabinoids has also been associated with reduced tumor growth in models of breast cancer, hepatocellular carcinoma, and multiple hematological malignancies [21].

Research on cannabis as an anti-neoplastic medication is lacking. In a phase I trial where intracranial $\Delta 9$ -THC was used in nine patients with refractory glioblastoma multiforme (GBM), drug delivery was safe, and in two patients was associated with decreased proliferative biomarker expression [21]. There are currently five ongoing or recently completed clinical trials according to the National Institutes of Health database [22]. Two

phase I trials are testing dexamabinol, a synthetic cannabinoid derivative, in patients with advanced solid tumors and brain cancer, respectively. Two phase II trials are evaluating nabiximols as an adjunct to temozolomide in recurrent GBM, the larger of the two being placebo controlled. Finally, pure CBD is being investigated as single-agent therapy for solid tumors. The studies primarily analyze safety measures, with survival outcomes and tumor indices assessed secondarily.

CONCLUSIONS

Cohort studies have added support to the growing body of knowledge on cannabis use in palliative oncology. However, these studies have many limitations. Promising data on pain, nausea and vomiting relief, as well as a relatively favorable safety profile and potential anti-cancer properties, will allow for more focused research in the future. Meanwhile, basic clinical trials are needed to find the right constellation of drug composition, dose and means of administration, to tailor specific cannabis-based medicine per indication and per patient. With evolving legislation, improved education and training, and increasing availability, medical cannabis is back in the limelight and gradually integrating into standard, evidence-based oncology practice.

Further clinical trials are needed to tailor specific cannabis-based medicine per indication and per patient

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