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

Ilit Turgeman MD and Gil Bar-Sela MD

1Division of Oncology, Rambam Health Care Campus, Haifa, Israel
2Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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.

KEY WORDS: cannabis, cancer, palliative care, nausea and vomiting, pain

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 anticancer 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 (Δ9-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 Δ9-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 Δ9-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 Δ9-THC [4].

In a meta-analysis by Machado et al. [6] investigating synthetic Δ9-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 Δ9-THC, but no controlled studies have validated this possibility [9].

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 Δ9-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 Δ9-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 Δ9-THC/CBD as compared to Δ9-THC alone or placebo, which was sustained for as long 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. Jatoi 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 Δ9-THC to Δ9-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 Δ9-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 Δ9-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].

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

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 Δ9-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 Δ9-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 dexanabinol, 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.

Correspondence
Dr. G. Bar-Sela
Director, Palliative Care Unit, Division of Oncology, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096, Israel
Phone: (972-4) 777-6409
Fax: (972-4) 777-6427
e-mail: g_barsela@rambam.health.gov.il

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### Capsule

**Neuron development in human embryos**

Mammalian fertility depends on the secretion of gonadotropin-releasing hormone (GnRH) from a population of specialized neurons residing in the hypothalamus. During embryogenesis, these neurons develop at the olfactory placodes, and they subsequently migrate to the brain. Very little is known about the process in humans, however. Casoni et al. studied this in depth by using donated human embryonic tissue. They tracked the differentiation and migration of GnRH neurons through the first trimester of gestation by examining samples at different developmental stages and identified important differences between humans and rodents. Unexpectedly, they also found that some of these neurons migrate to extra-hypothalamic regions of the brain, suggesting that they play roles in other processes not linked to fertility. *Development* 2016; 10.1242/dev.139444

Eitan Israeli

### Capsule

**Increased activity of TNAP compensates for reduced adenosine production and promotes ectopic calcification in the genetic disease ACDC**

ACDC (arterial calcification due to deficiency of CD73) is an autosomal recessive disease resulting from loss-of-function mutations in NT5E, which encodes CD73, a 5’-ectonucleotidase that converts extracellular adenosine monophosphate to adenosine. ACDC patients display progressive calcification of lower extremity arteries, causing limb ischemia. Tissue non-specific alkaline phosphatase (TNAP), which converts pyrophosphate (PPI) to inorganic phosphate (Pi), and extracellular purine metabolism play important roles in other inherited forms of vascular calcification. Jin et al. showed that compared to cells from healthy subjects, induced pluripotent stem cell-derived mesenchymal stromal cells (iMSCs) from ACDC patients displayed accelerated calcification and increased TNAP activity when cultured under conditions that promote osteogenesis. TNAP activity generated adenosine in iMSCs derived from ACDC patients but not in iMSCs from control subjects, which have CD73. In response to osteogenic stimulation, ACDC patient-derived iMSCs had decreased amounts of the TNAP substrate PPI, an inhibitor of extracellular matrix calcification, and exhibited increased activation of AKT, mechanistic target of rapamycin (mTOR), and the 70 kDa ribosomal protein S6 kinase (p70S6K), a pathway that promotes calcification. In vivo, teratomas derived from ACDC patient cells showed extensive calcification and increased TNAP activity. Treating mice bearing these teratomas with an A2b adenosine receptor agonist, the mTOR inhibitor rapamycin, or the bisphosphonate etidronate reduced calcification. These results show that an increase of TNAP activity in ACDC contributes to ectopic calcification by disrupting the extracellular balance of PPI and Pi and identify potential therapeutic targets for ACDC. *Sci Signal* 2016; 9: ra121

Eitan Israeli