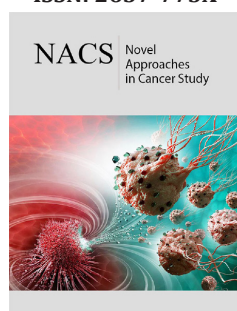


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Use of Medicinal Cannabis in the Treatment of Symptoms in Cancer Patients

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Abstract

Cannabinoids, the active constituents of *Cannabis sativa*, replicate the effects of endogenous cannabinoids by engaging specific cannabinoid receptors, notably the CB1 receptor predominantly located in the central nervous system and the CB2 receptor primarily associated with immune function. Delta-9-tetrahydrocannabinol, the principal bioactive cannabinoid in this plant has been approved as a prescription medication for managing chemotherapy-induced nausea and vomiting as well as anorexia. Furthermore, cannabinoids may provide relief in cancer-related pain due to a potential synergistic effect with opioid analgesics. They have also demonstrated efficacy in alleviating peripheral neuropathy resulting from chemotherapy. While cannabinoids possess a favorable safety profile, their therapeutic application is often constrained by their psychoactive properties and limited bioavailability. This review aimed to explore the application of medicinal cannabis in alleviating symptoms experienced by cancer patients.

Keywords: Cannabinoids; Cannabis sativa; Cancer-related symptoms; Cancer patient care

Introduction

Cannabis has been used in medicine for thousands of years before it became an illegal substance. In fact, the use of cannabis as a medicine dates back almost 3000 years. Having been widely used in the Indian subcontinent, cannabis was introduced to Western medicine in the 1840s by W.B. O'Shaughnessy, a surgeon who gained firsthand knowledge of its therapeutic advantages during his tenure with the British East Indies Company. It was then that its analgesic, sedative, anti-inflammatory, antispasmodic and anticonvulsant properties were first reported. Later, cannabis was said to have been the treatment of choice for Queen Victoria's dysmenorrhea. In the early 1900s, drugs that were indicated for each of the supposed medicinal properties of cannabis were introduced into Western arsenals, making its use less widespread. Physicians in the United States were the main opponents of cannabis use. The Marijuana Tax Act of the U.S. Treasury Department in 1937, devised by Harry Anslinger, director of the Federal Bureau of Narcotics, who testified to Congress that "marijuana is the most dangerous and violent drug in the history of mankind." The legislation established a tax of one dollar per ounce for medicinal purposes and a prohibitive fee of one hundred dollars per ounce for recreational use, which was considered exorbitant in 1937. This law was opposed only by the American Medical Association, which felt that there was a lack of objective evidence of the dangers of cannabis. In 1942, cannabis was excluded from the United States Pharmacopeia. In 1970, with the commencement of the Controlled Substances Act, marijuana was classified as a Schedule I drug. Both Schedule I and II drugs have a high potential for abuse. Schedule I drugs are distinguished by having no accepted medical use. This includes heroin, LSD, mescaline, methylqualone and gamma-hydroxybutyrate (GHB) [1].

Delta-9-tetrahydrocannabinol (Delta-9-THC) is one of approximately 100 cannabinoids found in the cannabis plant and is considered to be the primary psychoactive component. In total, the plant contains approximately 400 compounds derived from its secondary metabolism, many of which may contribute to its pharmacological activity [2]. The synthetic Delta-9-THC in sesame oil (dronabinol) was first licensed and approved in 1986 for the treatment of chemotherapy-induced nausea and vomiting. Clinical trials conducted at the time demonstrated that dronabinol was as effective, if not more effective, than available antiemetic agents [3]. Nabilone is one more synthetic Delta-9-THC that is too obtainable by prescription. Cannabinoids likely have natural roles in pain regulation, movement control and memory. The natural role of cannabinoids in the immune system is likely multifaceted and remains unclear [2].

Although long recognized for its medicinal values and widely used by millions of patients worldwide, cannabis has received little attention in the formal literature due to its status as a controlled substance and its classification in the United States as a Schedule I substance with a high potential for abuse and no known medical use. Data on the potential efficacy of medicinal cannabis are difficult to come by due to the limited number of clinical trials conducted to date. Furthermore, as a plant cannabis shares the difficulties encountered in studying plants grown in different climates and environments from different genetic strains and harvested under variable conditions [1].

The purpose of this review was to investigate the use of medicinal cannabis in the treatment of symptoms in patients with cancer. A literature search was conducted in the Google Scholar and Pubmed databases. The search was carried out without chronological restriction and using the terms: "cannabis", "medicinal cannabis", "cancer", "cancer patients", "symptoms", "management".

Cannabinoid chemistry and biological effects

Cannabinoids are a group of 21 carbonoterpenephenolic compounds produced uniquely by the species *Cannabis sativa* and *Cannabis indica* [2]. With the discovery of endogenous cannabinoids and their distinction from pharmaceutical compounds, plant compounds can also be referred to as phytocannabinoids. Although delta-9-THC is the primary active ingredient in cannabis, there are many non-THC cannabinoids and non-cannabinoid compounds that also have biological activity. Cannabidiol (CBD), cannabinol, cannabichromene, cannabigerol, tetrahydrocannabivirine and delta-8-THC are just a few of the additional cannabinoids that have been identified. It is hypothesized that secondary compounds may enhance the beneficial effects of delta-9-THC, for example by modulating THC-induced anxiolytic, anticholinergic, or immunosuppressive effects, and may reduce the adverse effects of delta-9-THC, for example by attenuating seizures, psychosis, or incoordination. In addition, terpenoids and flavonoids associated with cannabis may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity [2,4].

The neurobiology of cannabinoids has been elucidated over the past 25 years. In the mid-1980s, researchers developed a potent cannabinoid agonist. In 1986, it was discovered that cannabinoids inhibit the accumulation of 3'-5' cyclic adenosine monophosphate (cAMP), suggesting the presence of a receptor-mediated mechanism. In 1988, the first cannabinoid receptor, CB1 was pharmacologically identified in the brain through the attachment of a radiolabel to the synthetic cannabinoid. The CB1 receptor is coupled to Gi proteins, and its binding inhibits adenylyl cyclase and voltage-gated calcium channels, and stimulates rectifying potassium conductance's and mitogen-activated protein kinase. By 1990, researchers had cloned the CB1 receptor, identified its DNA, and mapped its location in the brain, with the highest expression being in the basal ganglia, cerebellum, hippocampus, and cerebral cortex. Today, the CB1 receptor is known to be a ubiquitous protein found in virtually all tissues of the body [5].

CB1 receptors mediate most of the central nervous system effects attributed to the phytocannabinoid delta-9-THC. CB1 receptors are regulatory receptors coupled to guanine nucleotide-binding proteins that primarily activate Gi/o proteins, resulting in inhibition of adenylyl cyclase. CB1 receptors are expressed primarily on the membranes of presynaptic terminals. The effects of CB1 receptor activation are to inhibit the release of a variety of neurotransmitters. Upon activation, CB1 receptors experience inactivation and internalization. These receptors are distributed across the central nervous system, with a noted low density in the medullary nucleus. In 1993, a second cannabinoid receptor, CB2, was identified outside the brain. Initially detected in macrophages and the marginal zone of the spleen, the highest abundance of CB2 receptors is found on B lymphocytes and natural killer cells, suggesting a role in immunity. The CB2 receptor was previously referred to as the peripheral cannabinoid receptor. This designation stemmed from its identification and significant presence in the immune system, along with its previously noted absence in the central nervous system. It is now accepted that CB2 receptors are also expressed in the central nervous system. CB2 receptors have been shown to be expressed in brain microglia during neuronal inflammation. Dorsal root ganglia upregulation of CB2 receptors plays an important role in perceptual effects [6,7].

The presence of cannabinoid receptors has been confirmed in additional animal species, including invertebrates. In 1992, a compound in the brain that interacts with cannabinoids in sensory nerves was discovered. It was named anandamide, after the Sanskrit word for bliss, and was the first endocannabinoid discovered. 2-arachidonoylglycerol (2-AG) was later discovered as part of the body's endogenous cannabinoid system. These endocannabinoids act as neuromodulators. As ligands for the 7-transmembrane domain are found in presynaptic nerve terminals, binding of the endocannabinoid leads to G protein activation and a cascade of events ensues resulting in the opening of potassium channels that reduce cell firing and the closing of calcium channels that reduce neurotransmitter release [8-10].

Cannabis pharmacology

Cannabis, when taken orally, has a low (6-20%) and variable bioavailability. 10 Peak plasma concentrations occur after 1-6 hours and remain high, with a terminal half-life of 20-30 hours. Upon oral ingestion, delta-9-THC is first processed in the liver into 11-OH-THC, a metabolite that possesses significant psychoactive properties. On the other hand, when inhaled, cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2-10 minutes, which decreases rapidly over the next 30 minutes. With inhalation, a higher peak concentration is thus achieved with a shorter duration of action. Less of the psychoactive metabolite 11-OH-THC is formed. When nabilone is taken orally, there do not appear to be any pharmacokinetic interactions between its two main cannabinoid components, THC and CBD, and the pharmacokinetic properties of THC present in nabilone are similar to those of oral THC [11].

Cannabinoids can interact with the hepatic cytochrome P450 enzyme system [2]. CBD, for example, can inactivate CYP3A4. After repeated doses, some of the cannabinoids can induce P450 isoforms. The effects are mainly related to the CYP1A2, CYP2C and CYP3A isoforms. The potential for cannabinoids to interact with cytochrome P450 and therefore, possibly metabolize pharmaceutical agents has led to a small body of data on the potential for herbal drug interactions. For instance, in one of the first studies, twenty-four cancer patients received treatment with intravenous irinotecan (600mg, n = 12) or docetaxel (180mg, n = 12), followed by a concurrent administration of the same drugs along with medicinal cannabis (an herbal tea consumed for 15 consecutive days, beginning 12 days prior to the second treatment). Pharmacokinetic evaluations indicated that the use of cannabis in tea form did not have a significant impact on the exposure and clearance rates of either irinotecan or docetaxel [12,13]. The medicinal cannabis products available are dronabinol, nabilone, cannabidiol, and nabiximols.

Cannabinoids and cancer symptom management

Nausea and vomiting

The strongest clinical evidence for the use of cannabinoids is related to a therapeutic benefit in adult patients with chemotherapy-induced nausea and vomiting. Oral cannabinoids are effective antiemetics [14,15]. Several research studies have been investigating the Delta-9-THC pharmaceuticals, nabilone and dronabinol. Analyses concluded that these cannabinoids were more effective than placebo and as effective as commonly available antiemetics [16,17]. Also, a later Cochrane review of 23 randomized controlled trials concluded that cannabis-based medicines may also be useful in treating chemotherapy-induced nausea and vomiting [18]. In three recent systematic reviews, the authors appeared to be less enthusiastic about recommending cannabinoids, citing increased side effects compared with standard treatments, a lack of comparison with more trials with current antiemetic drugs, and an overall low methodological quality of the published results [19-21].

The American Society of Clinical Oncology (ASCO) concluded in 2020 that the evidence remains insufficient to recommend medical marijuana for the prevention of nausea and vomiting in cancer patients receiving chemotherapy or radiation therapy [22]. Where is the evidence that cannabis has antiemetic effects, one wonders? One reason for the lack of evidence for the herbal medicine itself is the significant barriers to studying the potential therapeutic benefits of cannabis [14,23]. In the United States, still classified as a Schedule I substance with a high potential for abuse and no accepted medical use, cannabis is only legal for research studies by the National Institute on Drug Abuse (NIDA). NIDA is mandated by Congress to study "substances of abuse" as substances of abuse, not as therapeutic agents. As a result, there are very few clinical trials of cannabis's usefulness in chemotherapy-induced nausea [16,17]. In two of these clinical trials, cannabis was only available after THC had failed, so it is unlikely to be successful. Another study compared cannabis with dronabinol in twenty cancer patients and most had no preference. A Phase II trial of the whole plant extract nabiximols administered as an oromucosal spray to 16 patients showed that 4.8 sprays of nabiximols were more effective than placebo in further reducing chemotherapy-induced nausea and vomiting in patients receiving standard antiemetics [24]. A larger multicenter randomized, placebo-controlled trial of an oral cannabis extract THC: CBD was conducted in 81 cancer patients receiving emetogenic intravenous chemotherapy with persistent nausea and vomiting despite standard antiemetics. Patients were randomized to receive THC and CBD capsules, 2.5mg 3 times daily, or identical placebo capsules. Complete response was improved from 14% to 25% with the THC: CBD capsule ($P=0.041$). Despite moderate to severe adverse events reported in 31% of patients receiving THC: CBD compared with 7% receiving placebo ($P = 0.002$), 83% of patients preferred cannabis to placebo [25]. Anecdotal reports from patients suggest that smoking cannabis alleviated chemotherapy-induced nausea and vomiting, prompting oncologists to begin investigating the antiemetic effects of cannabis. Indeed, nabilone (THC in a capsule) is an FDA-approved treatment for chemotherapy-induced nausea and vomiting in humans [26].

Dronabinol or nabilone may be helpful in treating chemotherapy-resistant nausea and vomiting. However, current evidence does not endorse the use of cannabinoids as a primary treatment for these conditions. Given the widespread distribution of endogenous cannabinoids in the body, off-target side effects have limited the clinical development of CB1 receptor agonists. A better understanding of the endogenous cannabinoid system will help develop clinical trials that demonstrate mechanisms by which cannabinoids regulate various pathways and examine the safety and efficacy of these interventions in the context of cancer therapies [27].

Anorexia

Patients who have taken cannabis report a stimulating effect on their appetite. It showed potential in improving appetite and reducing weight loss in cancer patients, although the results are variable across studies [28].

In 1994, a study evaluated the effects of THC on 18 cancer patients, revealing that 72% experienced an enhancement in appetite [29]. Research has indicated that cannabis or cannabinoids may play a role in enhancing appetite among patients suffering from advanced cancer [27]. In a multisite clinical trial conducted by Jatoi et al. [30], 469 patients were evaluated to compare the effects of dronabinol, megestrol acetate, and a combination of both on appetite stimulation. The study involved patients suffering from advanced cancer who experienced appetite or weight loss. Participants were administered either dronabinol (2.5mg twice daily) alongside a placebo, megestrol acetate (800mg, serving as the standard comparator) with a placebo, or a combination of dronabinol (2.5mg twice daily) and megestrol acetate (800mg twice daily). The primary measure of outcome was appetite stimulation, which was determined through a self-report questionnaire completed by the patients. The findings indicated that dronabinol did not demonstrate statistically significant effects as an appetite stimulant. In contrast, patients treated with megestrol acetate reported notable improvements in both appetite and weight compared to those receiving dronabinol: 75% versus 49% for appetite ($P < 0.0001$) and 11% versus 3% for achieving at least a 10% weight gain ($P < 0.02$). Furthermore, the combination therapy did not yield any significant differences in appetite or weight gain when compared to megestrol acetate alone [30]. This study presents four key points for consideration. Firstly, it administered dronabinol at a twice-daily dosage of 2.5mg, as per the manufacturer's guidelines. There is a perspective that a thrice-daily regimen might yield better outcomes; however, this could also lead to an increased risk of significant adverse effects for patients. Secondly, cancer patients may not experience the same level of benefit from dronabinol as healthy individuals, owing to the distinct pathophysiological factors contributing to appetite loss in this population. Thirdly, while earlier research has indicated that cannabis or THC can stimulate appetite, it is important to note that these studies lacked a placebo control [31-33]. Future studies may examine THC alongside the various compounds present in cannabis, such as terpenes, flavonoids, other cannabinoids, alkaloids, ketones, and fatty acids [34]. Nonetheless, there are difficulties in implementing effective placebo controls to guarantee double-blinding when using herbal cannabis or THC [27].

Also, Strasser et al. [35] performed a double-blind, placebo-controlled study involving 226 cancer patients, who were randomly assigned to receive either cannabis (THC 2.5mg and CBD 1mg administered twice daily) or a placebo. The results indicated no significant increase in appetite beyond what was observed with the placebo. Nevertheless, the oral dosage was well tolerated. These results imply that, despite the aforementioned limitations, cannabis and THC may not be as effective in enhancing appetite in cancer patients compared to healthy individuals [35].

Pain

There is a growing interest in the use of cannabinoid-based medications among patients with chronic pain worldwide. The use of THC for cancer-related pain was first studied in the 1970s

in placebo-controlled trials at doses of 15mg and 20mg. These studies reported increased pain relief compared to placebo but not compared to codeine. The evidence regarding effectiveness in managing cancer-related pain was mixed. Some studies reported modest benefits, while others found no significant difference compared to placebo [28,36].

In 2010, a randomized, double-blind, placebo-controlled trial compared nabiximols (THC: CBD in a 1:1 ratio, brand name Sativex) and THC with placebo in cancer patients whose pain was refractory to opioid therapy ($n=177$). Pain scores were reduced from baseline ($>30\%$ difference on the numeric rating scale) with THC: CBD compared with placebo (43% and 21% of participants, respectively). However, there was no change in opioid dose and patients were not asked to try to reduce opioids [37,38]. Another randomized, double-blind, placebo-controlled, dose-escalation trial of nabiximols in patients with cancer and pain receiving opioids ($n=360$) found a benefit for pain with low or moderate doses of nabiximols (1-4/6-10 sprays per day, $P < 0.008$ and $P < 0.039$, respectively). A study conducted in 2012 with 360 participants indicated that nabiximols demonstrated superior analgesic effectiveness compared to a placebo at both low and medium doses, which were consistent with those used in the prior study, and proposed it as a beneficial adjunct analgesic [39]. Two prospective studies, specifically phase 2 and 3 double-blind, randomized, placebo-controlled trials, were carried out involving patients suffering from advanced cancer and pain. These patients were resistant to opioids and were randomly assigned to receive either self-titrated nabiximols as an additional analgesic or a placebo. The administration of nabiximols or placebo was titrated over a period of 2 weeks, followed by a 3-week treatment phase. Ultimately, it was determined that nabiximols did not demonstrate superiority over the placebo regarding the initial pain outcomes when opioid therapy was optimized [40]. Elevated levels of the CB1 receptor are found in brain regions that regulate pain processing [41]. While it was initially believed that opioids and cannabinoids functioned through the same pathways, they actually interact with distinct receptors and the pain-relieving properties of cannabinoids remain unaffected by opioid antagonists. Furthermore, agonists of the CB1 and CB2 receptors exhibit analgesic effects both peripherally and centrally. Both cannabinoids and terpenoids may possess anti-inflammatory properties that contribute to their analgesic effects. Reports indicate that some of the most compelling evidence supporting the therapeutic benefits of cannabis lies in its ability to alleviate pain [14].

Peripheral neuropathy

There is preclinical evidence to support the development of cannabinoid-based pharmacotherapies for the treatment of chemotherapy-induced peripheral neuropathy and associated pain. However, clinicians should scale up clinical trials to investigate which cannabinoid is most effective [26].

The medicinal benefits of cannabis in treating peripheral neuropathy have been evidenced in cases related to diabetes and HIV, showing a reduction in daily pain by as much as 34%

following cannabis use [42-44]. Furthermore, studies have been carried out to investigate the impact of cannabis on relieving chemotherapy-induced peripheral neuropathy in laboratory mice. Both CBD and THC individually reduced mechanical allodynia in mice administered with paclitaxel [45]. Additional preclinical studies have demonstrated effectiveness in preventing the onset of chemotherapy-induced peripheral neuropathy [46]. Waissengrin et al. [47] conducted a review of medical records for 768 consecutive patients who received treatment with oxaliplatin in conjunction with a 5-fluorouracil-based regimen, evaluating the extent of chemotherapy-induced peripheral neuropathy, the cumulative dose of oxaliplatin and the duration of neuropathy-free survival. Patients were categorized based on their cannabis usage: those who used cannabis prior to oxaliplatin treatment (cannabis first), those who began cannabis use after starting oxaliplatin (oxaliplatin first), and those with no cannabis exposure (control group). Out of the total, 513 patients qualified for inclusion, with 248 receiving cannabis and 265 serving as controls. The cannabis-first group comprised 116 patients (46.7%), while the oxaliplatin-first group included 132 patients (53.3%). A notable difference was observed in the incidence of chemotherapy-induced peripheral neuropathy grades 2-3 between the cannabis-exposed patients and the control group (15.3% versus 27.9%, respectively, $p < 0.001$). The protective effect of cannabis was significantly greater in patients who were treated with cannabis prior to oxaliplatin compared to those who received oxaliplatin first (75% versus 46.2%, respectively, $p < 0.001$). In summary, the incidence of neuropathy was lower in patients treated with both cannabis and oxaliplatin, with a more pronounced reduction in those who received cannabis before oxaliplatin treatment, indicating a potential protective effect [47].

Anxiety

There are few prospective trials investigating medical cannabis for anxiety in cancer patients and overall, there is little evidence of a causal relationship in other patient populations. In a recent meta-analysis by Crichton et al. [48] the use of medicinal cannabis did not demonstrate any impact on emotional functioning, mood alterations, confusion, disorientation or quality of life. The reliability of these findings was compromised due to several studies exhibiting a high or ambiguous risk of bias and imprecise aggregated estimates. There is a lack of sufficient evidence to assess the effectiveness and safety of medicinal cannabis as a treatment for depression, anxiety or stress in individuals with active cancer [48,49].

A prospective observational study conducted in Israel investigated the use of cannabis for alleviating anxiety in cancer patients who held a medical cannabis license for managing symptoms associated with their illness or the side effects of chemotherapy ($n=211$). Data collection occurred at baseline and during a follow-up telephone interview conducted 6 to 8 weeks after the commencement of cannabis use. The outcome measures included the Common Terminology Criteria for Adverse Events and the National Comprehensive Cancer Network Distress Thermometer. At the 6-to-8-week mark, 50% of the patients

continued their cannabis use, and there were notable improvements in the severity of symptoms related to cancer treatment over time. Additionally, 33% of patients using both anxiolytic medications and cannabis reported that they had ceased their medication use. Furthermore, 34% of patients indicated positive changes in their Distress Thermometer scores [50].

While cannabis is known to induce anxiety in some individuals, others experience its anxiolytic properties. The dual effects of cannabis, which can either alleviate or exacerbate anxiety, are linked to various factors including the user's context, personal traits such as personality, tolerance levels, and differences in the endogenous cannabinoid system [51]. In the United States, CBD products sourced from cannabis have become ubiquitous both online and in retail outlets. Although there is a scarcity of clinical trials validating the use of CBD for anxiety relief, its popularity continues to grow. Research has assessed CBD's potential effectiveness as an anxiolytic, with the majority of existing studies on behavioral impacts being preclinical and largely linked to its interaction with the 5HT1A receptor [52]. The anxiolytic effects of CBD have been observed in both healthy individuals and those with medical conditions across different anxiety models, where participants were subjected to acute stress-inducing stimuli and administered single doses ranging from 300 to 800mg [53]. A single study utilized functional neuroimaging to assess the effects of 400mg of CBD administered orally to individuals diagnosed with social anxiety disorder. This research indicated a decrease in anxiety levels; however, there is presently no research available regarding anxiety in patients with cancer [54]. The application of CBD for alleviating anxiety in cancer patients necessitates additional and thorough research considering the possibility of drug interactions, impacts on liver and gastrointestinal enzymes as well as the distinct biological characteristics of cancer [55].

Sleep disorders

Investigations into the impact of cannabis on sleep commenced in the 1970s, yielding varied results [56]. A review highlighted that the differing dosages of cannabinoids used limited sample sizes, absence of validated outcomes and the inability to account for other variables hinder the establishment of strong and widely applicable conclusions. In 2017, a National Academies Press report on the health effects of cannabis and cannabinoids reported moderate evidence for improvements in sleep quality and sleep disorders [57]. CBD administered at 300mg was shown to have no effect on sleep architecture or other sleep outcomes [58]. On the other hand, THC beneficially modulates sleep architecture [59]. Given the existing data on the potential benefit of nabiximols in sleep disturbance in cancer patients, this is a relevant symptom that should be further investigated in future studies [60].

Post-traumatic stress disorder

Another indication for the use of cannabis in cancer patients is for the suppression of unpleasant memories. Post-traumatic stress disorder (PTSD) is common in patients with a life-threatening medical diagnosis, with 17% presenting with comorbid panic

disorder. PTSD can manifest in the cancer patient with high anxiety, hyperarousal, intrusive thoughts and nightmares. CB1 receptor agonists may suppress these symptoms and the unpleasant memories and anxiety that accompany them. A recent review of 22 studies found that THC, when used at low doses or in combination with CBD is safe and without side effects and may affect the processing of aversive memory to facilitate the aversion of the memory [61]. However, studies in cancer patients are lacking and this issue needs to be investigated [27].

Safety and side effects

Cannabinoids have an extremely favorable drug safety profile [1,2,10]. Unlike opioid receptors, cannabinoid receptors are not located in brainstem regions that control breathing, so fatal overdoses due to respiratory depression do not occur. Administration of cannabinoids to experimental animals and humans results in psychoactive effects. In humans, central nervous system effects are both stimulant and depressant and are mainly divided into four groups: emotional (euphoria and easy laughter), sensory (temporal and spatial perceptual changes and disorientation), physical (somnolence, dizziness and motor incoordination) and cognitive effects (confusion, memory lapses and difficulty concentrating). Since cannabinoid receptors are not only found in the central nervous system but are present in tissues throughout the body, additional side effects include tachycardia and hypotension, conjunctival irritation, bronchodilation, muscle relaxation and decreased gastrointestinal motility. The effects of cannabis appear to develop rapidly in experimental animals and humans. This is thought to be due to a reduction in the number of total and functionally coupled cannabinoid receptors on the cell surface with a possible small contribution from increased biotransformation and excretion of cannabinoids with repeated exposure [62].

Although cannabinoids are considered by some to be addictive drugs, their addictive potential is significantly lower than other prescription agents or substances of abuse. The brain develops tolerance to cannabinoids and animal research suggests a potential for dependence. It is reported that 9% of cannabis users develop dependence according to DSM-IV criteria [63].

In the USA, 46% of the population has used cannabis, with 9% becoming dependent on it, and the risk is much lower than that of nicotine, heroin, cocaine, alcohol and is equivalent to the rate of dependence on anxiolytics. Withdrawal symptoms include irritability, insomnia with sleep EEG abnormalities, restlessness, hot flashes, and rarely nausea or cramps. These symptoms are usually milder than those associated with opiate or benzodiazepine withdrawal and usually resolve within 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 THC intake is not associated with a rapid decrease in plasma concentration that would precipitate withdrawal symptoms or intense drug seeking [64,65].

Also noteworthy is the synergy between opioids and

cannabinoids that has been hypothesized and subsequently accepted in various animal models [66]. The perceptual effects of morphine are mediated primarily by μ -opioid receptors, but may be enhanced by delta-9-THC activation of kappa and delta-opioid receptors. It has further been suggested that cannabinoid–opioid interaction may occur at the level of their signal transduction mechanisms. The receptors for both classes of drugs are linked to similar intracellular signalling mechanisms that lead to a decrease in cAMP production through activation of the Gi protein. There has also been some evidence that cannabinoids may increase the synthesis or release of endogenous opioids or both. A study by Abrams et al. [67] examined the pharmacokinetic interaction to investigate the effect of concomitant cannabis on the kinetic disposition of opioid analgesics. Ten patients with chronic pain on a stable dose of sustained-release morphine and 11 on sustained-release oxycodone were assessed for their opioid concentration-time curves before and after 4 days of cannabis vapor exposure. Adverse effects of the combination of cannabinoids and opioids were observed during the in-hospital evaluation. There were no significant changes in the area under the curves for opioids after the addition of cannabis vapor. Although the study was not powered for pain as an endpoint, evidence of a potential synergistic effect in pain relief was assessed. If cannabinoids and opioids were shown to be synergistic in a larger controlled clinical trial, it is possible that lower doses of opioids would be effective for longer periods of time with fewer side effects, with a clear benefit for the patient with pain [67].

Discussion

Cancer patients experience a multitude of symptoms and side effects from both the disease itself and the anticancer treatments administered. Nausea, vomiting, loss of appetite, pain, peripheral neuropathy, anxiety, depression and insomnia are some of them. Despite the availability of pharmaceutical treatments for all of these symptoms, other herbal therapies such as cannabis and cannabinoids have also been used. Medicinal cannabis, when used with the consent and will of the patient and the awareness of the oncology team can have beneficial effects in relieving symptoms.

The conundrums surrounding medicinal cannabis complicate clinical care and the conduct of research on medicinal cannabis. As a result, in part, the risks and benefits of medicinal cannabis have not been well delineated in the cancer patient. Particularly with regard to the medicinal benefits of cannabis, much of the research has focused on individual cannabinoids (e.g., synthetic THC derivatives) rather than the entire spectrum of herbal medicine. The scientific evidence is characterized as incomplete or equivocal, but medicinal cannabis may be a useful adjunct to standard therapy in alleviating the side effects of cancer and treatments. However, further research is needed to produce convincing evidence. Although preclinical findings are promising, there is little support in the medical literature to date for the actions of cannabis or cannabinoids. More research and education of health professionals are also needed to better understand how this versatile plant and its derived compounds may benefit cancer patients [68].

It should be noted here that long-term cannabis use can cause symptoms such as cannabis hyperemesis syndrome, characterized by cyclic nausea and vomiting that tends to be worse in the morning. Its pathophysiological mechanisms remain unclear. Symptoms can be improved by stopping cannabis use, taking a warm bath, or applying topical capsaicin. There have also been recent reports of an increased risk of serious lung disease associated with cannabis vaping products, called electronic lung injury, which has been linked to unlicensed cannabis products. Although not directly related to the cancer patient, all of these are likely to occur [69,70]. Cannabis products also impair driving ability, and this may put patients at risk, even when traveling to and from the oncology clinic [71].

Another important issue is the legal implications, as in some regions and countries, cannabis is illegal at the state level. Therefore, patients should only take approved medicinal cannabis products to avoid legal penalties. In addition, cancer care remains a significant financial burden for patients. As cannabis is more widely legalized, its use is increasing both recreationally and medically [72,73]. In almost all US states that have legalized medical cannabis, its use requires a prescription or certification from a licensed provider, while in European Union countries, policies vary between countries. The use of medical cannabis usually begins at the suggestion of a healthcare professional or at the request of the patient [73].

Then, there is limited or no coverage for complementary medicines, such as cannabis products, and this can lead to financial challenges. The cost of cannabis can vary greatly depending on availability. The exorbitant cost of medicinal cannabis can lead patients to illegal purchases [74]. Therefore, given the extensive accessibility of medicinal cannabis and its derivatives, it is imperative to comprehend its safety, the consequences of its application, and its possible efficacy for medical purposes in cancer treatment [75].

Medicinal cannabis has potential for therapeutic applications in oncology, but the available evidence and legal status are challenging. Cannabis and cannabinoids are useful in the management of symptoms associated with cancer and anticancer therapies. Preclinical evidence suggests that cannabinoids are not only effective in the treatment but also in the prevention of symptoms such as chemotherapy-induced nausea and vomiting, anorexia, peripheral neuropathy and pain. Cannabinoids could be synergistic with opioids in pain relief. Some patients report subjective benefits from cannabis for nausea, appetite, sleep, and anxiety, but the level of evidence remains low. Cannabis' safety profile is acceptable, with side effects that are generally tolerable and short-lived. Clinical data on the effects of cannabis products on cancer are not yet available. Oncologists could find cannabis and cannabinoids to be effective tools in the care of patients living with and beyond cancer [76,77].

It is known that different people experience different effects from cannabis and its products. Therefore, it can be expected that the optimal cannabis treatment will vary between patients. However, developing an effective, standardized regimen can be a difficult task when the cannabis-derived products available on the market are so diverse. A unified strategy for regulating cannabis products (e.g.,

one based on THC and/or CBD content and THC:CBD ratio) would greatly improve their utility in the medical setting. Regulation would allow for a more standardized treatment plan and make it easier for providers to balance any potential interactions between different treatments. However, it is also important to consider the ultimate goal: if the goal is simply to relieve symptoms and patients report success with minimal side effects, then the specifics of the dosing strategy really matter as long as a satisfactory outcome is achieved [78].

Closing the discussion, the most recent updated guidelines from the American Society of Clinical Oncology (ASCO) were published to assist clinicians, cancer patients, caregivers and researchers in understanding the medical use of cannabis and cannabinoids in adult cancer care. While cannabis and cannabinoids should not replace standard cancer treatments, they may be considered in clinical trials as adjuncts. For symptom management, particularly chemotherapy-induced nausea and vomiting that is unresponsive to standard therapy, products like dronabinol, nabilone, or a controlled 1:1 THC: CBD extract can be considered. However, high-dose CBD ($\geq 300\text{mg/day}$) is discouraged outside of trials due to safety concerns and lack of proven benefit. There is insufficient evidence to recommend cannabinoids for other symptoms, such as pain, outside of clinical research settings. The guideline also outlines safety risks, including cognitive side effects, psychiatric disorders, driving impairment, and the potential for cannabis use disorder. Barriers such as regulatory challenges, inconsistent product quality and limited research funding hinder progress, highlighting the need for further studies to evaluate efficacy, safety and therapeutic potential in oncology [79].

Conclusion

Cannabis has been used since ancient times for a range of medical indications, in addition to recreational, religious and spiritual purposes. In the United States, since 1970, marijuana has been classified at the federal level as a Schedule I substance under the Controlled Substances Act, defined as a drug with no currently accepted medical use and a high potential for abuse. Based on current knowledge of the mechanism of action of cannabinoids, the therapeutic effect of these THC-rich preparations in the treatment of classic cancer symptoms is due to THC-induced activation of cannabinoid CB1 receptors located at precise anatomical locations. This encompasses, for instance, the suppression of nausea and vomiting, the enhancement of appetite, the alleviation of cachexia and the mitigation of pain, all of which are also influenced by cannabinoid CB2 receptors. Similarly, the engagement of CB1 receptors located in specific brain regions probably causes the typical adverse effects described by cannabis such as dizziness, drowsiness, confusion and disorientation. Beyond THC, it is increasingly accepted that CBD, in addition to exerting its own therapeutic activity, modulates the psychoactive risk of cannabis. Thus, well-produced and standardized THC: CBD balanced formulations could be considered a therapeutically safer option than dronabinol or nabilone, whose therapeutic windows are usually very narrow. Other cannabis constituents, particularly terpenes

(e.g. myrcene, α -pinene and β -caryophyllene) have been suggested to exert synergistic therapeutic effects with phytocannabinoids. However, evidence for this potential mechanism and therapeutic effect is lacking.

Additional rigorous clinical studies are needed to confirm the scattered anecdotal and preclinical evidence and to integrate it into clinical practice. Today, for practical reasons, the interpretation of the empirical evidence on the use of medical cannabis, combined with a rational application of our current understanding of the mechanism of action of cannabinoids, may be the only way to delineate which cannabis preparations can best adapt (in terms of efficacy and tolerability) to the specific needs of each patient at each stage of the disease.

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