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The Management of Cancer Symptoms and Treatment-Induced Side Effects With Cannabis or Cannabinoids

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Abstract

Cannabis and cannabinoids are increasingly being accessed and used by patients with advanced cancer for various symptoms and general quality of life. Specific symptoms of pain, nausea and vomiting, loss of appetite and cachexia, anxiety, sleep disturbance, and medical trauma are among those that have prompted patients with cancer to use cannabis. This conference report from the National Cancer Institute's "Cannabis, Cannabinoid and Cancer Research Symposium" on the topic of "Cancer Symptom/Treatment Side Effect Management" is an expert perspective of cannabis intervention for cancer and cancer treatment-related symptoms. The purpose of the symposium was to identify research gaps, describe the need for high-quality randomized prospective studies of medical cannabis for palliative care in patients with cancer, and evaluate the impact of medical cannabis on cancer survivors' quality of life. Further, education of clinicians and affiliated health-care providers in guiding cancer patients in using cannabis for cancer care would benefit patients. Together, these steps will further aid in refining the use of cannabis and cannabinoids for symptom palliation and improve safety and efficacy for patients.

There is a long history of humans using cannabis for its medicinal, relaxing, calming, and sedative effects, including documented cannabis use across ancient civilizations. In 1922, Felter published a cannabis monograph in his *Materia Medica* (1). This monograph gave specific indications for cannabis use: marked nervous depression, insomnia with brief periods of sleep, sleep disturbed by unpleasant dreams, and spasmodic and painful conditions with depression. The monograph continues, saying, "It produces an agreeable semi-delirium, taking on the character of a sense of well-being and exhilaration, a state highly coveted by its devotees, who called it loftily: "The increaser in pleasure, the laughter mover, the cementer of friendship." Modern research supports that the endocannabinoid system (ECS), a highly conserved mammalian biochemical system, is specifically modulated by the phytocannabinoid delta-9-tetrahydrocannabinol (THC). The ECS has been described as a biochemical system with homeostatic roles, allowing us to relax, eat, sleep, protect, and forget (2).

Cannabis contains more than 400 compounds, with more than 80 from the cannabinoid class, although many are intermediates in the biosynthesis of the primary compounds found at the end of the flowering cycle. THC is the primary active ingredient and psychoactive cannabinoid (3). THC is a highly lipid-soluble, high-affinity, partial agonist at cannabinoid receptor types 1 and 2 (CB_1 and CB_2), mimicking the endogenous cannabinoids anandamide (arachidonoyl-ethanolamine) and 2-ararachidonoyl glycerol and responsible for behavioral effects. At low doses, THC has analgesic, anxiolytic, and antiinflammatory effects, whereas higher doses have opposite effects on anxiety and analgesia (4).

Cannabidiol (CBD) is a low-affinity, nonpsychoactive cannabinoid found in abundance in nondrug-type cannabis, with

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reported inverse agonist or antagonist action at CB_1 and CB_2 receptors or acting as an allosteric modulator (5). Several other pharmacological mechanisms are reported for CBD as a modest agonist at the 5-hydroxytryptamine (or serotonin) 5-HT_{1A} receptor as a potential inhibitor of arachidonoyl-ethanolamine degradation or reuptake and as inducing the heteromerization of a cannabinoid receptor with the 5-HT_{2A} receptor (6-9). CBD also activates the transient receptor potential cation channel 1 and is a cyclooxygenase inhibitor. Although studies supporting analgesic effects of CBD in humans are scant, high doses have anticonvulsant, sedative, anxiolytic, and antiinflammatory activity. CBD may modulate dopamine mechanisms in the ventral tegmental area (related to addiction) (10). THC therapeutic effects are possible with low milligram dosing, but CBD efficacy reportedly begins in the 100s of milligram doses. CBD may attenuate the psychoactive properties of THC as well as reduce drug cravings (11,12).

CB1 is the most widely expressed G protein-coupled receptor in the central nervous system, with the highest densities in the hippocampus, basal ganglia, hypothalamus, basolateral amygdala, and cerebellum. The brainstem has very low density, which may account for the lack of typical drug side effects, such as nausea and respiratory depression, seen with agents that stimulate brainstem receptors.

Both established cannabinoid receptors are G protein-coupled positively to potassium channels and negatively to N-type and P/Q-type calcium channels, activate mitogen active protein kinase (MAPK), and inhibit adenylate cyclase, with CB_1 responsible. CB_1 is distributed widely throughout the peripheral and central nervous systems and is responsible for the psychoactive effects of THC. Activating primary afferent peripheral terminal CB_1 receptors reduces terminal excitability and proinflammatory terminal peptide release (13). CB_2 receptors are located primarily in immune tissues on peripheral monocytes, B and T cells, and mast cells (14). Agonism at CB_2 results in a reduced inflammatory cell mediator release, reduced plasma extravasation of immune cells, and reduced sensitization of afferent terminals (13). Therefore, in the context of pain, peripheral CB_1 and CB_2 receptor agonism results in a combined additive reduction of elevated terminal excitability induced by local injury and inflammation. Cancer patients' pain may arise in multiple sites, with various etiologies and mechanisms, requiring individually tailored strategies for pain control. Additionally, more than 63% of patients report a lack of efficacy of medications for breakthrough cancer pain (15,16).

Through activation of cannabinoid receptors by THC and other pharmacological mechanisms of CBD, cannabis may be beneficial in helping to control some symptoms and side effects related to cancer treatment. Among these are pain, nausea and vomiting, appetite suppression, anxiety, sleep, depression, and poor quality of life. Cancer-related pain is among the most common, most feared, undertreated, and most difficult to treat symptom in cancer patients. The World Health Organization has a 3-level ladder approach (17) that includes opioids, but up to 39% of patients have undertreated pain, are intolerant of opioids, or are aversive to using opioid medications (18,19). Cannabis has been shown preclinically to have opioid-sparing effects, which could help cancer patients minimize their opioid use and avoid opioid-associated side effects of disordered sleep, constipation, fatigue, sedation, dizziness, tolerance, and nausea and vomiting (20).

Nausea, vomiting, and loss of appetite are prevalent symptoms in cancer patients arising from complex and multifactorial etiologies. Cancer-related complications, including gastrointestinal tract obstruction, hypercalcemia, and brain metastasis, can induce nausea and vomiting. Paradoxically, many treatments used in cancer, such as opioids, specific chemotherapy agents, and radiation, are known to induce nausea and vomiting. Although several agents are currently used to prevent and treat these symptoms, control of nausea and vomiting remains an important unmet need in many cancer patients despite enduring recognition of cannabinoids for their antinausea, antiemetic, and appetite-stimulating effects (4,21).

One botanical medicine—cannabis—can potentially address all the cyclic symptomology that patients experience related to pain, tension, nausea and vomiting, the stress and trauma of a cancer diagnosis, and its subsequent treatment. Pain and associated sleep disruptions can exacerbate existing stress and anxiety, leading to more pain, poorer sleep quality, and ultimately to loss of quality of life in a cyclic manner. These symptoms and effects related to chemo- and radiotherapy contribute to adverse psychosocial and psychological functions that reduce patients' quality of life (22). Here, cannabis is addressed for utility for symptom management in patients with cancer, with a discussion of gaps in knowledge and needs to further determine safety and efficacy in the cancer patient and cancer survivor population.

Cannabinoid Signaling in Pain

CB_1 receptors are located in the spinal dorsal horn in lamina I through V and X. Presynaptic CB_1 receptors are partially colocalized with transient receptor potential cation channel 1 receptors. CB_1 agonism reduces N/P/Q-type voltage-sensitive calcium channel influx, acting as a negative feedback loop that reduces neurotransmitter release (23). Postsynaptic CB_1 agonism increases potassium channel conduction, resulting in membrane hyperpolarization and associated reduction in excitability (24). The net result is a decrease in the afferent-evoked excitation of dorsal horn nociceptive neurons. Supraspinal agonism of CB_1 receptors in brain areas associated with pain processing, the basolateral amygdala, periaqueductal gray, and rostroventral medulla activates bulbospinal pathways regulating dorsal horn excitability, resulting in a reduction of afferent-evoked excitation of dorsal horn nociceptive neurons (25).

Analgesic, Opioid-Sparing, and Biphasic Effects of THC

Preclinical evidence of the analgesic properties of THC is quite robust, with positive studies in many pain models, including acute pain ($CB_1 > CB_2$), inflammation (CB_1 and CB_2), nerve injury (CB_1), and visceral pain (CB_1 and CB_2). Although there have been many clinical studies showing a reduction in pain in multiple pain syndromes (HIV neuropathy, neuropathic pain, spinal cord injury, and diabetic neuropathy) (26-29), these studies have limitations: single sites, small samples sizes, difficulty with patient blinding, and attrition due to side effects and short duration of study, precluding the ability to establish analgesic durability.

A meta-analysis included 19 preclinical studies (14 administered THC, 3 administered synthetic CB_1 agonists, 1 used a CB2 agonist) and 3 clinical studies to evaluate the opioid-sparing effect of cannabinoids (30). Preclinically, 90% of the studies demonstrated a statistically significant synergistic analgesic effect on hot plate latency, with 2 showing extended effect duration when THC was coadministered with morphine and codeine (by meta-analysis). The median effective dose of morphine and codeine was 3.6 and 9.5 times lower, respectively, when given in

combination with THC compared with either drug alone. The clinical data reviewed provided insufficient evidence (n = 9 studies, n = 750 patients; 3 were randomized, controlled trials) to establish opioid sparing: some reported worsening pain and higher opioid use, whereas others found opioid and pain reductions (30). To date, there are no well-designed human studies that have mirrored or validated these preclinical opioid-sparing effects in humans (31).

Biphasic effects of cannabinoids have been well documented, preclinically and in human studies, with opposite effects occurring: low doses provided an analgesic benefit, whereas higher doses exacerbated pain (32-35). Plasma THC levels, from a study of inhaled cannabis (29) (400 mg of cannabis containing 1%, 4%, or 7% THC vs placebo) for spontaneous or evoked pain in patients with painful diabetic neuropathy (n = 16), revealed a negative linear association between plasma THC levels and analgesia, where higher THC levels correlated with increased pain compared with baseline (visual analog score) (36) (Figure 1). Modest pain benefit (12%-15% variance) correlated with THC plasma levels falling between 16 and 31 ng/mL. This result emphasizes the importance of precise THC dosing, using guided patient self-titration, starting with a low dose, and going slow on the titration to reach a therapeutic window for analgesia while avoiding pain exacerbation and negative psychoactive effects. Future studies should determine whether optimizing serum levels could be of clinical relevance in patients with cancer pain.

Efficacy of Cannabinoids in Cancer-Related Pain

THC for cancer-related pain was first studied in the 1970s in placebo-controlled crossover studies at doses of 15 mg and 20 mg. These studies reported increased pain relief over placebo but not compared with codeine (37,38). In 2010, a randomized, double-blind, placebo-controlled trial compared nabiximols (THC:CBD in a 1:1 ratio, Sativex) (39) and THC with placebo in cancer patients whose pain was refractory to opioid management (n = 177) (40). Pain scores were reduced from baseline (>30% in difference in numeric rating scale) with THC:CBD compared with placebo (43% and 21% of participants, respectively); however, there was no change in the median opioid dose from baseline (patients were not asked to try to taper opioids). A third report, a randomized, double-blind, placebo-controlled, graded-dose study of nabiximols in cancer patients with pain poorly controlled by opioids (n = 360), found pain benefit at low or medium dose (1-4/6-10 sprays per day; $P = .008$ and $P = .039$, respectively). A 2012 study (n = 360) reported nabiximols provided a greater analgesic effect than placebo at low and medium doses (same doses as the previous study) and suggested nabiximols as a useful add-on analgesic (41).

Two prospective studies, phase 2 and 3 double-blind, randomized, placebo-controlled trials were conducted for advanced cancer pain, where patients refractory to opioids (n = 397; n = 206) were randomly assigned to either self-titrated nabiximols as an add-on analgesic or placebo. Nabiximols (or placebo) was uptitrated over 2 weeks, followed by a 3-week treatment period, and was not found to be superior to placebo on the primary pain outcome when opioid therapy was optimized (42). During the phase 3 trial, researchers found statistically significant improvements in secondary endpoints of sleep disruption ($P = .027$), Subject Global Impression of Change ($P = .0024$, and .0499 at weeks 3 and 5), Patient Satisfaction Questionnaire ($P = .0001$; $P = .0232$ at weeks 3 and 5) and Physician Global Impression of Change ($P = .0314$ at week 5). Nabiximols did not improve average pain scores ($P = .253$) (43). A pooled analysis with companion studies of the same design (42) found that patients enrolled in the United States had improvements in average pain scores and all secondary outcome measures that correlated with lower (>25%) baseline opioid use compared with the rest of the world. Opioid-sparing effects could not be measured because a requirement of the study was for opioid doses to remain stable across the course of the treatment.

Quality Control, Administration, and Dosing

Due to the high lipid solubility of THC, inhalation is the best route of delivery, resulting in higher bioavailability and more consistent early peak plasma levels (44). However, there are obvious health risks associated with inhalation, particularly with smoked or vaporized THC in the form of oil extracts (ie, concentrates found in "vape pens"), and dosing via this method is not recommended (45). There have been many reports of lung damage from vape pens, underlining the possibility that unknown contaminants are introduced by additives or through the extraction processes (45). Inhalation of organically grown plant vapor is the recommended dosing method (46); however, this also carries the risk of unknown contaminants with unregulated cultivation. In 2018, the California Bureau of Cannabis Control instituted a law that requires all cannabis and associated products manufactured on or after January 1, 2018, to undergo quality control (QC) according to Title 16 of the California Code of Regulations. Testing includes cannabinoid content, moisture, residual solvents, pesticides, microbial impurities, mycotoxins, foreign materials, and heavy metals. This QC testing is mandatory in most regulated environments, although the tests required and the testing reliability may vary. The presence of contamination is a potential risk for systemic infection in patients who are immunocompromised (47). Continued improvements in QC, such as the implementation of good manufacturing processes and stricter QC limits on cannabis intended as medicine, would open the door to studying a greater variety of products and, in the interim, allow for patients choosing to use cannabis to access safer products. New and safe methods of rapid delivery via the airway or intranasally could allow for investigations of this administration form in patients with cancer.

Whereas inhalation results in consistent peak plasma THC levels within 5 to 10 minutes with a short duration of effects, ingestion has a more erratic and delayed peak, ranging from 1 to 4 hours across individuals. The erratic nature of ingestion results in challenges with oral dosing of cannabinoids due to individual variations in metabolism. Nonetheless, oral ingestion is the most common method of delivery for medical use (48). Notably, the trials of cannabis for neuropathic pain all used inhalation of cannabis, whereas the cancer trials were all oral delivery.

Given the biphasic effects of THC (49), starting with low milligram doses of THC (0.25-2 mg) and slowly titrating is critical to achieving success with medical cannabis. The ratio of CBD and THC may also be relevant. For most patients, oral preparations of high CBD to THC ratios (20:1 or 30:1, found in many hemp-based products) may allow for less than or equal to 1 mg THC. Administration 3-4 times per day and gradually self-titrating every few days to effect or tolerance seems to allow the most optimized benefit. The field could benefit from further

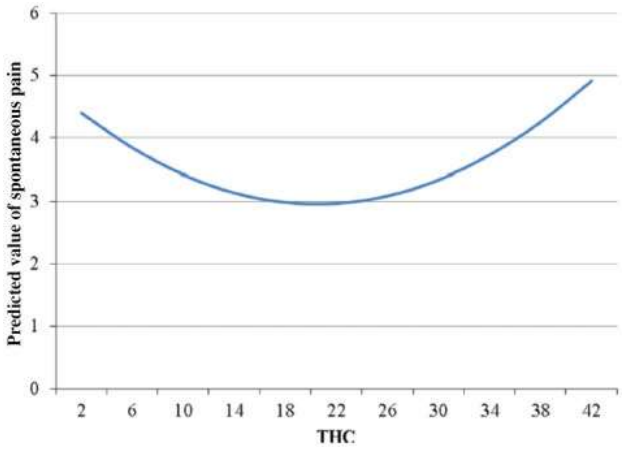

Figure 1. Association of delta-9-tetrahydrocannabinol (THC) plasma levels with pain benefits. Prospective trial of inhaled cannabis for painful diabetic peripheral neuropathy suggests a therapeutic window, between 16 ng/mL and 31 ng/mL, for optimal pain benefit. Low and high THC levels had a negative association (no reduction in pain scores), and THC levels within the window had a positive association (reduction in pain scores).

understanding of neurobiological mechanisms driving cancer pain, the efficacy targeting CB_2 receptors, and studies that would attempt to optimize opioid or cannabinoid ratios or doses for pain management in the cancer setting (50).

Cannabinoids for Cancer-Related Nausea and Vomiting

Exogenous administration of cannabinoids and raising endocannabinoid levels (ie, via inhibition of degradation of anandamide and/or 2-arachidonoylglycerol) hold promise as potential targets for the treatment of nausea and vomiting. Activation of CB_1, widely expressed in the brain, and possibly CB_2, which is expressed in brain tissue in glial cells and more abundantly in peripheral immune tissues or cells, is thought to ameliorate nausea and vomiting by inhibiting the release of excitatory transmitters (ie, serotonin). Others have proposed antiemetic endocannabinoid tone and constitutive cannabinoid receptor activity as potential mechanisms. There is also evidence of cannabinoid activity independent of these 2 receptors and other peripheral effects of cannabinoids, such as their ability to alleviate gastrointestinal cramping, which may also affect these symptoms (51).

Chemotherapy-Induced Nausea and Vomiting (CINV)

Chemotherapy administration is one of the most common culprits for nausea and vomiting in cancer patients. These agents are classified based on their emetogenic potential into high (>90%), moderate (30%-90%), or low risk (<30%) (52). Current guidelines for the prevention or treatment of CINV recommend a combination of 5-HT_3 receptor antagonists (ie, ondansetron), dexamethasone, neurokinin1 receptor antagonist (ie, aprepitant), and olanzapine. CINV may be acute, starting 1 to 2 hours after chemotherapy administration and peaking 4 to 6 hours afterward. There also is delayed nausea and vomiting, which usually occurs within 24 hours after chemotherapy administration. Sometimes, there is anticipatory emesis, a conditioned response in patients who have had nausea and vomiting before with chemotherapy administration.

Clinical Trials of Cannabinoids for CINV

Nabilone (synthetic, racemic analog) and dronabinol (synthetic THC) are orally active cannabinoid compounds with partial agonist activity at CB_1 and CB_2 receptors. These compounds are currently US Food and Drug Administration (FDA)-approved for CINV treatment. Oral THC also has been tested but is not approved for this use. Nabiximols, currently under investigation in the United States for indications other than nausea and vomiting, showed activity in a small phase II trial for delayed CINV (53). Several published studies have tested the efficacy and safety of these cannabinoids for treating cancer-related nausea and vomiting (including CINV), either vs placebo or other antiemetics (54,55). Studies testing cannabinoids against placebo have been plagued by risk of bias, such as patients' ability to identify which drug they received due to adverse effects, selection bias of patients that were regular cannabis users, inclusion of refractory patients, small sample sizes, or inadequate powering (54-56). The studies that looked at cannabinoids vs placebo on nausea, or nausea and vomiting, suggested less vomiting and nausea with cannabinoids, whereas trials that looked at cannabinoids vs placebo on vomiting specifically did not detect statistically significant differences between the interventions (57,58). Regarding patient-reported treatment preferences, most patients favor cannabinoids over a placebo, even though there was a higher rate of mostly psychotropic adverse events with cannabinoids (59,60).

Several small comparative effectiveness studies also have used antiemetics such as prochlorperazine or metoclopramide (61). One caveat of these trials is that the comparators used are currently outdated, thereby limiting the applicability of these studies (62). Some but not all studies found greater benefit with cannabinoids on ameliorating nausea and vomiting. However, there was more participant attrition from these studies due to adverse events with cannabinoids. These adverse events include feeling "high," disorientation, drowsiness, confusion, hallucination, loss of balance, euphoria, fatigue, and dry mouth. Despite these side effects, more patients preferred cannabinoids to these other agents in these studies (63).

One of the few studies comparing cannabinoids with the other agents currently approved for this use looked at the effect of dronabinol vs ondansetron vs placebo, or a combination of ondansetron and dronabinol for delayed CINV (64). The trial, which included 10 to 15 patients per arm, found similar effectiveness in treating CINV between the active treatment arms, and treatments in both active arms were well tolerated. Combination therapy was not more effective than either agent alone. More recently, a multi-center, placebo-controlled, randomized crossover phase 2 trial was published, looking at the efficacy of adding THC and CBD to a combination regimen that included dexamethasone, a 5-HT3 receptor antagonist, and an neurokinin1 receptor antagonist in patients (n = 81) with poorly controlled emesis after the first cycle of chemotherapy. Complete response rates were low in both groups, although the rate was higher in the active drug group (25% vs 14%); two-thirds of patients in the cannabinoid arm required rescue with conventional antiemetics, and one-third still vomited. Nevertheless, most patients preferred cannabinoids over placebo (53). The next phase of this encouraging study is still ongoing.

Clinical Guidelines for Cannabinoids in CINV

Given the paucity of data available, the 2015 American Society of Clinical Oncology and 2017 National Comprehensive Cancer Network guidelines only recommend FDA-approved dronabinol or nabilone to treat nausea and vomiting resistant to standard antiemetic therapies (65). The guidelines also state that the current evidence regarding the use of medical marijuana for chemo- or radiation therapy-related nausea and vomiting prevention, or in place of the FDA-approved cannabinoids, is insufficient. The 2016 Multinational Association for Supportive Care in Cancer and European Society for Medical Oncology guidelines also do not recommend cannabinoids (66).

Knowledge Gaps and Future Directions for Nausea and Vomiting

Dronabinol or nabilone may help treat nausea and vomiting resistant to standard antiemetic therapies. However, current evidence does not support the use of cannabinoids as first-line therapy for these indications. Given the widespread distribution of the ECS, off-target side effects have limited the clinical development of CB_1 agonists. A better understanding of the ECS's role is needed to develop clinical trials that would establish mechanisms by which cannabinoids modulate various pathways and examine the safety and efficacy of these interventions in the context of cancer and cancer therapies.

Loss of Appetite and Palliation in Cancer Care

Cachexia describes a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass that conventional nutritional support cannot fully reverse (67). This loss of muscle leads to progressive functional impairment and ultimately death. However, this definition omits a critical aspect of this syndrome—an absence of appetite coupled with the observation that many patients struggle to eat.

The justification for focusing on loss of appetite goes beyond the need to incorporate it into definitions of cachexia for at least 3 reasons. First, when examining end-of-life symptoms in patients with cancer, loss of appetite is typically found among the top 5 most troubling symptoms, and most patients cite it as problematic (68). Second, a salient aspect of this symptom is its ability to predict early demise. Quinten and colleagues examined patient data from 30 randomized controlled trials, relying on individual data from more than 1500 patients (69). In stratified multivariable analyses, these investigators reported that loss of appetite was associated with an increased risk of death (hazard ratio = 1.05, 95% confidence interval = 1.03 to 1.06, $P < .0001$) (70). Third, the ability to palliate this symptom remains limited. Large, randomized controlled trials have found only 3 drugs effective for appetite palliation: progestational agents, corticosteroids, and more recently anamorelin, an oral ghrelin agonist (71). However, these agents have not provided major, durable palliation. For example, in a 130+-patient, placebo-controlled trial, 70% of patients assigned to the megestrol acetate reported improved appetite with this progestational agent; however, as many as 44% described the same occurrence with the placebo (72). Factoring in the placebo effect, only a small subset of patients appear to be receiving genuine palliation with this agent. Similarly, high patient dropout rates and waning efficacy over time point to short-term palliative benefits. In essence, the troubling nature of this patient-reported symptom, its associated poor outcomes, and the overall limited available options for palliation underscore the importance of continuing to seek better ways to help patients who suffer from loss of appetite in the setting of advanced cancer. In this context, cannabis and cannabinoids merit further study.

Clinical Studies Related to Appetite Stimulation

Abel et al. (73) published a study testing cannabis-spiked marshmallows in a group of healthy young adults concluding that cannabis appeared to stimulate appetite. In 1994, an open-label, single-arm trial tested THC in 18 patients with cancer found that 72% had improved appetite (74). These studies, in conjunction with several others (75,76), suggested a role for the study of cannabis or cannabinoids for appetite stimulation in patients with advanced cancer. Thus, Jatoi and colleagues (77) undertook a multi-site, 469-patient clinical trial that compared dronabinol vs megestrol acetate vs a combination of the 2 for appetite stimulation. In a 3-arm, double-blinded, double-dummy design, patients with advanced cancer and loss of appetite or weight were assigned either dronabinol (2.5 mg twice per day) + placebo, vs megestrol acetate (800 mg, a standard comparative intervention) + placebo, vs dronabinol (2.5 mg twice per day) + megestrol acetate (800 mg twice per day). The study's primary effect of interest was appetite stimulation as assessed by a patient self-report questionnaire. Results showed that the dronabinol intervention was not a statistically significant appetite stimulator. Megestrol acetate-treated patients reported improved appetite and weight compared with dronabinol-treated patients: 75% vs 49%, respectively ($P = .00001$), for appetite and 11% vs 3%, respectively ($P = .02$), for at least 10% baseline weight gain. Combination therapy resulted in no difference in appetite or weight gain compared with megestrol acetate alone.

Four aspects of this study merit discussion. First, this study used a twice-daily dose of dronabinol (2.5 mg) as recommended by the manufacturer. One argument is that dosing 3 times per day may have yielded a more favorable outcome; however, patients could experience more severe adverse effects with more frequent dosing. Second, cancer patients might not derive the same benefit from dronabinol as healthy patients due to distinct pathophysiology of appetite loss. Much of the previous appetite stimulation research with THC or cannabis excluded cancer patients (74). Third, although previous studies have found evidence of appetite stimulation with cannabis or THC, these studies were not placebo controlled (74-76) because the placebo effect is not trivial. Future research could compare botanical THC in the context of the companion chemicals in cannabis (ie, terpenes, flavonoids, other cannabinoids, alkaloids, ketones, fatty acids, etc) (78). However, there are challenges in providing effective placebo controls to ensure double blinding with botanical cannabis or THC.

Finally, Strasser and colleagues (79) conducted a 3-arm, double-blind, placebo-controlled trial in 226 patients with cancer, randomly assigning patients to receive cannabis (THC 2.5 mg + CBD 1 mg twice per day) or a placebo. Researchers found no major appetite stimulation over and above that seen with the placebo; however, the oral dose was well tolerated. These findings suggest that despite the limitations described above, it is possible that cannabis and THC are not as effective for appetite stimulation in cancer patients as in healthy individuals.

Measuring Well-Being Is a Worthwhile Goal for Cancer Research

In the book Dying to Get High: Marijuana as Medicine, Wendy Chapkis documents her research into the "messy terrain of people living and dying with cancer" who are using cannabis to navigate (80). Her patients reported that cannabis provides "a present-tense focus ... [and] may not feel altering so much as enhancing in the context of terminal illness," "it produces a positive shift, and I can go on to something else," "it stops the fear. It stops the worrying," and, "I don't think there is anything wrong with dulling the reality of my situation."

These patient anecdotes describe the cannabis side effect of euphoria not as unwelcome but as a consciousness-altering effect with potential therapeutic value. This effect can include coming back to baseline, experiencing moments of gratitude, providing brief flashes of relaxing into the present moment, and forgetting medical trauma. Psychologist David De Steno (81) has described the experience of gratitude as "allowing us to notice symptoms less, enhance well-being and reduce the stress of chronic illness." Although anecdotes alone are not sufficient to conclude, when coupled with available research evidence they allow for the generation of hypotheses. There is a need for rigorous investigation of how medical cannabis may be affecting patient empowerment, satisfaction, and other patient-reported outcomes (PROs: any report of the patient's health status that comes directly from the patient) (82). For example, anxiety, sleep, mood, medical trauma, and overall well-being are patient outcomes that are particularly relevant in this era where a patient-centered research approach is essential as patients, advocates, researchers, clinicians, and regulators increasingly recognize PROs as worthwhile outcome measures of patient-centered cancer research (83).

Paradoxical and Dose-Dependent Effects of Cannabis on Anxiety

A 2009 systematic review reported that anxiety and panic attacks were the most common side effects of cannabis use (84). Paradoxically, anxiety reduction is a decisive motivating factor for cannabis use. A compilation of 7 cross-sectional human survey results reveals that an average of 52% of these respondents reported antianxiety benefit from cannabis when using cannabis for therapeutic purposes (85-91). To explain this paradox, clinical studies support the biphasic or bidirectional effects of THC; the effect of cannabis on anxiety is dose dependent. Additionally, self-report surveys examining patient substitution of cannabis for prescription drugs find that patients often substitute cannabis for benzodiazepines and other anxiety medications (85,92,93). Respondents reported reasons for using cannabis to substitute for other drugs as "a safer alternative, fewer adverse side effects, better symptom management, and fewer withdrawal symptoms." Despite that cannabis has been reported to induce anxiety, a subset of users report anxiolytic benefits. Anxiolysis or anxiogenesis is attributed to biphasic effects and is context related or associated with individual characteristics such as personality, degree of tolerance, or ECS variations (94).

Anxiety in Cancer Patients

There are no prospective trials investigating cannabis therapeutic benefit for anxiety in cancer patients and, in general, scant evidence of a causal relationship in other patient populations (95,96). A prospective observational study in Israel examined cannabis use for cancer care in patients with medical cannabis licenses for disease-related symptoms or chemotherapy side effects (n = 211) (97). Data were collected at baseline and in a 6- to 8-week follow-up telephone interview after initiating cannabis use. Outcome measures were the Common Terminology Criteria for Adverse Events and the National Comprehensive Cancer Network Distress Thermometer. At 6 to 8 weeks, 50% of patients had continued cannabis use, and by self-report, there were beneficial changes in the degree of cancer treatment-related symptoms over time. Thirty-three percent of those using antianxiety medications and cannabis reported that they had discontinued their use. There were positive changes in the Distress Thermometer scores reported for 34% of the patients. The limitations of this study include the lack of a control group or controlling for the effect of time alone on overall symptom improvement. Although there may be an association of cannabis use with PROs, prospective and rigorous designs, standardization of the cannabis used, and comparative effectiveness studies will further determine the usefulness of cannabis in the setting of cancer-associated anxiety.

Safety and Efficacy in Cancer Patients

Nabiximols were statistically superior to placebo on quality-of-life measures in patients with cancer. For these patients, treatment-emergent adverse effects occurred at an incidence of 5% or less, with nausea and dizziness being the most commonly reported adverse effects (43). Researchers in a prospective analysis of the safety and efficacy of medical cannabis in 2970 cancer patients examined the epidemiology, safety, and efficacy of cannabis therapy (98). Researchers interviewed patients at 1- and 6-month intervals for changes in symptom intensity, physiological and cognitive side effects, quality of life, and a general effect of cannabis using a global assessment of self-rated effect. At the 1-month point, 70% of patients were still using cannabis, and 66% of these reported improvements in overall symptoms whereas 8.3% reported cannabis did not help them. At this time point, the most common side effects were dizziness, coughing (due to smoking), tiredness, nausea, confusion, and disorientation. At the 6-month point (60.6% response rate), 29% reported no need for cannabis, 22.5% reported no therapeutic effect, and 19.3% discontinued use due to side effects. Symptoms with the most improvement included nausea and vomiting, sleep disorders, restlessness, anxiety, depression, pruritis, and headaches. Approximately one-quarter of these respondents reported discontinuing anxiolytic prescriptions. Researchers primarily used high-THC cannabis in this study, with 72% of patients using more than 1 chemotype of cannabis. This study did not determine causality between cannabis therapy and overall improvements in well-being because there was no control group, and they did not account for the impact of changes that can occur over time, such as completion of chemotherapy. Overall, cannabis was relatively well tolerated without serious adverse effects, and future trials should include longitudinal data for long-term safety and efficacy.

Is CBD Effective for Anxiety?

In the United States, hemp-derived CBD products have appeared ubiquitously online and in health food stores, gas stations, and tobacco shops. Their appearance is despite a dearth

of clinical trials supporting CBD, specifically to treat anxiety (a common claim). CBD has been reviewed for efficacy as an anxiolytic, and most of the studies available on behavioral effects are preclinical and primarily attributed to action at the $5HT_{1A}$ receptor (99). Several preclinical studies demonstrated a biphasic (bell-shaped) or dose-response effect of CBD on anxiety (100-102). Anxiolytic effects have been replicated in healthy human patients in various anxiety models where patients were exposed to acute anxiety-provoking stimuli and administered single acute doses from 300 to 800 mg of CBD (84,103). To date, there is 1 study using functional neuroimaging with a single oral dose of 400 mg CBD in patients with social anxiety disorder. This study found a reduction in anxiety, but no studies on cancer-related anxiety currently exist (104). Although the preclinical evidence seems promising, researchers have not examined the efficacy of CBD for treating anxiety in humans.

Further, the consumer-based marketing of CBD as an anxiolytic may be contributing to expectancy or mediating outcomes by promoting the belief of efficacy by the patient (105). Currently, there is insufficient evidence for CBD to treat anxiety in cancer patients, posing the need for prospective trials that evaluate chronic dosing as a therapeutic approach. However, treating anxiety will likely require doses of CBD that may limit the utility of CBD for anxiety in cancer patients due to the potential for drug interactions, the effects on liver enzymes, and other gastrointestinal effects—all of which are relevant for cancer patients (106).

Impact of Cannabis on Sleep Disturbance

Research on the effects of cannabis on sleep began in the 1970s, resulting in mixed findings (107,108). A recent review reported that the varying doses, small sample sizes, lack of validated outcome measures, and failure to control for other variables limited the conclusions available to past research. The 2017 National Academies Press report, The Health Effects of Cannabis and Cannabinoids, found moderate evidence for minor improvements in sleep quality and sleep disturbance across 8 trials (109). CBD administered at 300 mg was shown to affect neither sleep architecture nor other sleep outcomes (110). According to the evidence, CBD is not indicated for sleep because past studies found CBD to be “alerting” at low doses (111).

On the other hand, THC modulates sleep architecture beneficially (112,113). In 1 study for obstructive sleep apnea, patients were given 2.5 mg and 10 mg doses of THC; the 10-mg dose was associated with greater satisfaction in reducing the apnea-hypopnea index and self-reported sleepiness improvement. Given the existing data on the potential benefit of nabiximols on sleep disturbance in patients with cancer, this is a relevant symptom to continue to explore in future studies (43).

Cannabis Effects on Posttraumatic Stress Disorder (PTSD) and Mood

Another indication for cannabis in patients with cancer is for the suppression of adverse memories. PTSD is common in patients with a life-threatening medical diagnosis, with 17% experiencing co-morbid panic disorder. PTSD has been associated with low cannabinoid tone and associated impaired stress resilience (114,115). PTSD can manifest in the cancer patient as high anxiety, hyperarousal, avoidance of cues, intrusive thoughts, and nightmares. CB_1 receptor agonists may suppress these types of adverse memories and the anxiety that coexists (116-118). A recent review of 22 studies suggested that THC, when used in low doses or in combination with CBD, is without adverse effects and may interfere with aversive memory processing to facilitate aversive memory extinction (118).

The Potential Role for Minor Cannabinoids

Researchers have not yet studied the potential mood-altering effects of minor cannabinoids in humans. Still, there are potential mechanisms, such as the cannabinoid cannabigerol (CBG) agonism of the alpha-2 adrenoceptor and as a serotonin $5\text{-}HT_{1A}$ receptor blocker (119). CBG is also known as a partial agonist at CB_1 and CB_2 receptors (120). One study found that CBG inhibits anandamide reuptake (121). Despite the lack of evidence on efficacious dosing or outcomes in humans, the marketing of CBG has already begun. First-in-human dosing for safety and efficacy are needed.

Cannabichromene demonstrated potential as a CB_2 receptor agonist, a novel approach for treating anxiety, mediated via antiinflammatory pathways (122). The first in vivo data on these minor cannabinoids were recently published using the classical tetrad model developed by Martin’s group (123). The researchers added the open field maze as a behavioral model of anxiety-like behavior. Compared with THC, there were less robust effects on anxiety-like behavior by the minor cannabinoids (124). Currently, the evidence base for using minor cannabinoids in a therapeutic setting for cancer patients is lacking.

Botanical Therapy: Terpenes

Terpenoids (or terpenes) are a closely related class of compounds to cannabinoids and the essential oil component of cannabis. They are found across aromatic plants, accounting for approximately 10% of the trichome content by weight, and are widely used in botanical medicine, commonly for aromatherapy. Many of these compounds are “generally recognized as safe” by the FDA as flavoring agents and have greater bioavailability when inhaled or applied topically than when taken orally (125).

This vaporized inhalation of cannabis flower provides rapid onset of effects and direct delivery of both terpenes and cannabinoids to the tissues, largely avoiding the first-pass metabolism. The terpenes synergize functionally with cannabinoids through receptor targets that are not cannabinoid receptors, such as myrcene, which has muscle-relaxant and sedative effects (6,126). Also present is beta-caryophyllene, a terpenoid common to many cannabis chemotypes, which is considered a dietary cannabinoid found in oregano, cinnamon, clove, and black pepper. It is a CB_2 receptor agonist that has been studied for its antiinflammatory action in humans, and an animal study suggested it may have antianxiety effects (127).

Linalool is found primarily in lavender species and is known to potentiate γ-amino butyric acid ($GABA_A$) currents when inhaled. It has produced anxiolytic effects in mice and when taken orally in humans in a preparation that had a 36% linalool component. There were reductions in the participants’ anxiety scores (128-130).

Cannabis chemotypes with “haze” lineage (common vernacular) often have terpinolene. It has sedative effects in mice, has an antihyperalgesic effect, and is proposed to be mediated by the $5\text{-}HT_{2A}$ receptor (131,132). Limonene is a monoterpene with high oral bioavailability. Previous studies found limonene has antidepressive and antistress effects in mice, with potential $GABA_A$ receptor mechanisms or increased serotonin levels

(133,134). Another study in hospitalized human patients demonstrated improvements in depression when limonene was diffused into their hospital room (135).

So-called "whole-plant" preparations may be a misnomer as various extraction processes will fail to extract, will alter, or potentially will lose some compounds. The results from a supercritical CO_2 extraction of cannabis showed the loss of monoterpenes while concentrating cannabinoids and heavier terpenes in 5 different cannabis chemotypes. There was an increase in the potency of the heavier-weight terpenes, with a fourfold increase in the cannabinoid fraction (136). The terpenes can be highly sensitizing for some patients, such as older individuals and those who have had chemotherapy and radiation. Researchers have not examined the safety of ingesting large amounts of essential oils on a chronic basis; it may be neurotoxic or harmful to the kidneys or liver (137).

Using Cannabis in the Clinical Setting

How should cancer patients use cannabis, and does the form of administration matter? A follow-up to the previous studies on cannabis use in cancer patients from Israel describes how patients (n = 108) arbitrarily chose cannabis from 3 available chemotypes. The researchers compared the effectiveness of cannabis use by inhalation or oral administration after 1 month of use. The researchers found that patients using THC-dominant chemotypes were more likely to inhale cannabis, whereas patients using CBD-dominant or mixed chemotypes were more likely to ingest cannabis orally. They measured improvements, regardless of the chemotype or form of administration, using weekly pain intensity and duration and distress at 1 month. They concluded a lack of differential effect regardless of chemotype or form of administration. There was no added benefit or therapeutic value for having more THC, except potentially for sleep duration demonstrated in the group using the high THC-dominant chemotype (138).

Approximately one-half of survey respondents who are using cannabis for therapeutic purposes are reporting anxiolytic benefits (85-89,91) (Figure 2). There has been a long-documented history of using cannabis to treat anxiety showing that THC has dose-dependent effects on anxiety. CBD has some anxiolytic potential but has only been studied in healthy individuals; however, the dose required for this effect may limit cancer patients' use. Minor cannabinoids need more data, especially for first-in-human dosing and for any potential efficacy in humans. Terpenes are bioactive, acting synergistically with cannabinoids, and may be contributing to the overall effects. Cannabis and cannabinoids appear to be pleiotropic and effective tools in cancer patient care. Future studies should evaluate these quality of life (QOL) effects in cancer survivors.

Oncology Patients: Education and Guidance

A survey of 927 oncology patients in Washington State using cannabis for physical and neuropsychiatric symptoms found that 51% of the cannabis users reported major benefits from cannabis use, 39% reported moderate benefits, and 24% were using for palliative purposes. Seventy-four percent of the respondents wanted to receive medical cannabis information from health-care providers, but only 15% did (139). The lingering stigma of the cannabis prohibition era has likely affected how health-care providers approach cannabis in a clinical setting. Health-care providers may not be receiving academic and practical training that provides them with the expertise to guide patients in using medical cannabis safely and effectively.

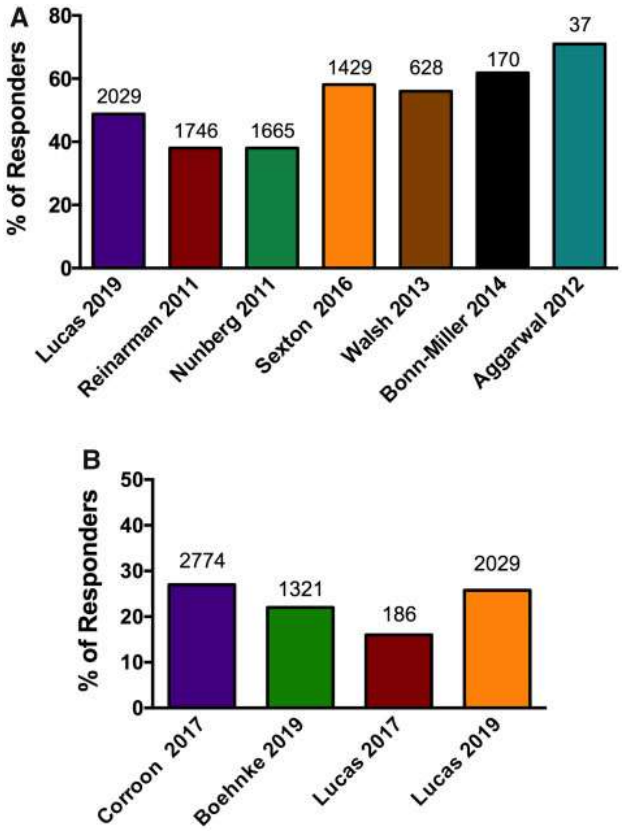

Figure 2. Compilation of studies on cannabis use and anxiety and prescription drug substitution. Ten cross-sectional analyses of cannabis use have been published. This graph displays the reported (**top**) anxiety benefits on behalf of the respondents and (**bottom**) reported substitution of antianxiety medications by cannabis users and respondents across these studies.

Oncologists may be concerned about the development of pulmonary aspergillosis; however, oral administration forms and careful QC (sterilization) of inhaled products could prevent pulmonary issues (140). Another concern is related to the effect of cannabinoids on the metabolism of other drugs; however, this likelihood may be dose dependent and avoided with low-dose titration (141). Among medical doctors surveyed (N = 1544) across 12 specialties in 48 states, oncologists and hematologists had the highest level of support for medical cannabis use (142). In the study mentioned above, a random sample of oncologists self-reported (n = 400) whether they discuss medical cannabis with patients, recommend it clinically, or feel informed enough to do so (143). Only 29% of respondents reported feeling competent, and 56.2% did not consider themselves having sufficient knowledge to make a recommendation to patients. Based on existing scientific evidence, there is a need for educational programs that equip doctors with the necessary knowledge to support patients interested in medical cannabis use.

Social Justice Issues and Medical Cannabis

Social justice issues related to cannabis encompass racial, economic, and access concerns. Racially minoritized and low-income communities are targeted for drug-related law enforcement

actions at considerably higher rates and with more severe legal consequences compared with wealthy White people. In addition, women are the fastest-growing segment of the prison population. Roughly 25% of all incarcerated women in state prisons and 61% in federal prisons were convicted of a drug-related offense (compared with 15% and 50% of incarcerated men, respectively). Although cannabis use occurs at equal rates across the racial spectrum, Black women are twice as likely and Latinas are 1.2 times more likely to be incarcerated for drugs compared with White women (144). Further, more than one-half of all drug arrests in the United States are related to cannabis, with 88% of these arrests being for simple possession of cannabis (145). Health-care providers are ethically obligated to advocate for systemic change in how minoritized populations are treated and to address harmful racist practices when identified. Persistent, systemic racism, such as in drug enforcement policies, harms individuals and communities' mental, physical, and spiritual health.

When considering treatment equity, as of the writing of this text, access to medicinal cannabis in the United States is based mainly on one's geographic location, culturally relevant stigma, and an individual's specific amount of risk involved in cannabis use (146). One opinion is that inequitable access and information may preclude entire populations from using safe, quality-controlled, cannabis-based medicines that may support palliation and support successful completion of and satisfaction with their oncological treatments.

Education for Health-Care Providers

In 2018, the National Council of State Boards of Nursing defined 6 essential education areas for nurses working with medical cannabis patients (147). The 6 essential areas can serve as a universal template for all health-care providers to ensure that cannabis care is adequately addressed and enable providers to be confident and comfortable when educating patients about the safe and effective use of medicinal cannabis. These areas could be included in licensing examinations for various medical certifications to ensure adequate coverage within already crowded curricula. The 6 essentials were adapted here to include all health-care providers:

- The health-care provider shall have a working knowledge of the current state of legalization of medical and recreational cannabis use.
- The health-care provider shall have a working knowledge of the jurisdiction's medical cannabis regulations.
- The health-care provider shall understand the ECS, cannabinoid receptors, cannabinoids, and the interactions among them.
- The health-care provider shall understand cannabis pharmacology and the research associated with the medical use of cannabis.
- The health-care provider shall be able to identify the safety considerations for patient use of cannabis.
- The health-care provider shall approach the patient without judgment regarding the patient's choice of treatment or preferences in managing pain and other distressing symptoms.

Role of the Nursing Health-Care Provider: Educator and Coach

Whole-plant cannabinoid therapeutics are largely used within a self-titration paradigm, one in which the nursing care provider's role could be defined as a "coach" and educator when overseen by a qualified health-care provider. Health-care providers, in general, will benefit from a better understanding of how their patients use cannabis for palliation in oncological care, and patients will benefit from a medical assessment for potential drug interactions. Patients need expert guidance with self-titration of cannabis (along with the standardization of this approach) to find their therapeutic window for dosing and need specific safety information related to their diagnosis (148).

Future Research

In addition to the research priorities defined by the National Academies of Science, Engineering, and Medicine, there is a dearth of qualitative analyses of patients' experiences with using medical cannabis (109). There is a general need for high-quality, well-designed clinical trials; however, the Schedule I status of cannabis, the inability to conduct multi-center trials, low availability of funding, and burdensome and often delaying regulatory hurdles are all barriers to research. There is also almost no access to research-grade cannabis products that match the "real-world" products that patients are accessing and from which patients report benefits. There is an ongoing need for cannabinoid pharmacologic research, clinical efficacy trials, and qualitative research regarding both patient and health-care provider medical cannabis care experiences.

Pain Research

The difference between the inhaled cannabis trials for neuropathic pain and the oral dosing in patients with cancer pain warrants further investigation. Rapid delivery may be a key for analgesia with cannabis for uncontrolled pain, which warrants the development of safe and effective delivery methods for inhaled cannabis vapor or with intra-nasal delivery. Another approach would be to improve on the solubility and bioavailability of ingested forms. Pharmacokinetic studies would shed light on whether cancer patients may require higher serum levels of THC to optimize their pain. Prospective trials that use active opioid tapering using cannabis as a tool, including inhalation for breakthrough pain, might be more likely to provide opioid-sparing effects. For cancer patients, it may be that a higher dose is needed for pain benefit, as found in the 1970s studies, or consideration for combination oral and inhaled cannabis to optimize pain benefit, allow for opioid tapering, and address other symptoms contributing to ongoing pain such as anxiety and sleep disturbance. Future studies should address specific types of cancer pain, specifically on the subset of those with neuropathic and mixed neuropathic and nociceptive pain (approximately 40%) (149). Comparing or combining administration forms and doses are approaches that are untried in this patient population. Mechanistically, ECS and opioidergic crosstalk and modulation of the neuro-immune reflex are areas open to investigation (150).

Nausea and Vomiting Research

Cannabis is known as one of the oldest remedies for nausea and vomiting (151). The relative contributions of CB_1 and CB_2 to nausea and vomiting are not fully understood but are open to investigation (51). Given that CB_2 activation is not psychotropic, agonism at this receptor and a solid understanding of a potential mechanism for benefitting patients may represent an opportunity to treat nausea and vomiting with fewer side effects. The quality of evidence from clinical trials comparing

cannabinoids with a placebo or standard antiemetic therapies is low, and there is a paucity of trials comparing cannabinoids with newer antiemetic combinations that are the current standard of care. Also, selecting a patient population that could benefit from the pleiotropic effects of cannabinoids on other symptoms (eg, pain, appetite, anxiety) and less likely to suffer side effects (younger or older patients) could optimize the risk-benefit ratio of this intervention. Cannabis use for anticipatory nausea in chemotherapy should also be investigated. Mechanistically, synergistic interactions with $5HT_3$ and TRPV1 warrant further investigation.

Appetite Stimulation

Synthetic THC (dronabinol) is FDA approved to manage HIV and AIDS anorexia, and nabilone is FDA approved for CINV. Although these compounds have been investigated for cancer appetite loss and cachexia, other forms of cannabis (inhaled or intranasal for rapid delivery to the brain), different doses, dose titrations, and other cannabinoids have not been tested. Well-designed trials are needed to determine whether researchers can predict patient response and whether cannabis can improve appetite stimulation, improve the enjoyment of food (152), or improve QOL in patients with advanced cancer. Mechanistically, crosstalk of cannabinoids with neuroendocrine effectors such as ghrelin, leptin, and serotonin is warranted (153,154).

Well-Being and QOL

A patient-centered approach requires the prioritization of qualitative research and an increased understanding of PROs. Collecting data on targeted QOL domains and outcomes beyond cancer care would further inform the utility of cannabis in cancer, palliative care, and survivorship. The adverse effects of cannabis are dose related, and individualizing of dose titration to "tolerated doses," rather than prescribed doses, is recommended along with critical selection of QOL tools; insomnia, depression, and anxiety in this patient population appear to be ripe for investigation (41). The incorporation of prospective survivorship care plans that evaluate the role of cannabis beyond cancer treatment is feasible for addressing long-term outcomes. First-in-human dosing for other minor cannabinoids is imperative because patients are already accessing these products and claiming benefits that are unsubstantiated in the existing literature. The terpene class of compounds contributes to the overall effect of cannabis, and trials that use an individual terpene or combined terpenes may yield different results from those using isolated cannabinoid compounds. Using rapid delivery via inhalation, such as with metered dosing, may help study this administration form in new areas such as nausea and vomiting and appetite stimulation (155). Patients accessing cannabis deserve protections in the form of accurate labeling, equality in access to effective and proven products, and affordable products as well as expert guidance in the use of this botanical medicine. A compounding pharmacy model to dispense "medical" cannabis has the potential to benefit both health-care providers and patients.

Physician and Patient Education

Cancer patients are increasingly using cannabis despite the dearth of a solid evidence base (156). There is a need for the medical community to continue building on the existing evidence, such as developing physician and allied health provider education and expert guidelines and recommendations on dosing (148). These steps in education will provide greater consumer safety and satisfaction and enhance the potential for efficacy for the patient. Oncologists may have broad utility for symptom management, and compared with other therapeutic agents, the side effect profile of cannabis is suitable (157,158). To recommend a single treatment that may benefit pain, nausea and vomiting, anorexia, insomnia, and anxiety or overall QOL would be advantageous for patients. Integration of cannabis into cancer care will likely stay as an adjunctive tool for patients living with cancer and the associated side effects of cancer treatment. Patient survivors living with long-term consequences of their diagnosis and treatment also could benefit, and this population warrants further investigation.

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