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Monograph

MONOGRAPH

Cannabinoids and Cancer Chemotherapy-Associated Adverse Effects

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Abstract

The use of cannabis is not unfamiliar to many cancer patients, as there is a long history of its use for cancer pain and/or pain, nausea, and cachexia induced by cancer treatment. To date, the US Food and Drug Administration has approved 2 cannabis-based pharmacotherapies for the treatment of cancer chemotherapy-associated adverse effects: dronabinol and nabilone. Over the proceeding decades, both research investigating and societal attitudes toward the potential utility of cannabinoids for a range of indications have progressed dramatically. The following monograph highlights recent preclinical research focusing on promising cannabinoid-based approaches for the treatment of the 2 most common adverse effects of cancer chemotherapy: chemotherapy-induced peripheral neuropathy and chemotherapy-induced nausea and vomiting. Both plant-derived and synthetic approaches are discussed, as is the potential relative safety and effectiveness of these approaches in relation to current treatment options, including opioid analgesics.

The use of cannabis is not unfamiliar to many cancer patients, as there is a long history of its use for cancer pain and/or pain, nausea, and cachexia induced by cancer treatment. To date, there are 2 US Food and Drug Administration (FDA)–approved clinically available synthetic cannabis-based medications for cancer patients—dronabinol and nabilone—for the treatment of nausea and vomiting associated with chemotherapy. Several factors have limited the use of these prescription medications, however, the climate has been changing regarding knowledge, perceptions, and legal access to cannabinoids, making this an exciting time for cannabis-based research for chemotoxicities.

Chemotherapy-induced peripheral neuropathy (CIPN) is a progressive, enduring, and often irreversible condition characterized by pain, numbness, tingling, paresthesia, and sensitivity to cold in the hands and feet that sometimes progresses to the arms and legs. It is estimated that 30% to 40% of patients undergoing chemotherapy will be afflicted by CIPN (1). Chemotherapeutic agents associated with CIPN include the vinca alkaloids vincristine and vinblastine; the taxanes paclitaxel and docetaxel; proteasome inhibitors, such as bortezomib; epithilones, such as ixabepilone; the platinum-based drugs cisplatin, oxaliplatin, and carboplatin; and immunomodulatory drugs, such as thalidomide (2). Three key mechanisms believed to be involved in the development of CIPN are mitochondrial dysfunction, loss of Ca^{++} homeostasis, and oxidative stress (3).

Management of CIPN is particularly vexing because it is a serious dose-limiting side effect that can, in the most serious cases, force change or termination of cancer treatment. In most cases, CIPN is only partially reversible with the cessation of treatment, and in the worst cases, damage can be permanent (4). To date, no one drug or drug class is considered to be safe and effective for the treatment of CIPN. The 2 major classes of compounds most often used for the treatment of neuropathic pain are tricyclic antidepressants (TCAs) and anticonvulsant and/or anti-epileptic drugs (AEDs). The TCA amitriptyline and

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AED gabapentin have roughly equivalent clinical success rates (ie, number needed to treat); however, gabapentin is generally prescribed more often because of a better side effect profile compared with amitriptyline (5,6). A recent meta-analysis of clinical trial data suggested TCAs and the gabapentinoids pregabalin and gabapentin or duloxetine (a serotonin and norepinephrine reuptake inhibitor) as first-line treatments (7). The TCAs are associated with significant side effects, including sedation and cardiovascular complications, as well as only marginal efficacy (8). The AEDs, despite their efficacy in animal models of CIPN, are only partially effective in the majority of patients suffering from CIPN (9).

Besides suffering from pain and loss of function, patients with CIPN are at particular risk of another medical problem—the inappropriate use of opioid medications. Upward of 97% of CIPN patients reported using prescription opioids for pain management, even though there is only weak evidence that long-term continuation of opioids provides clinically significant pain relief in these patients. This mostly inappropriate use of opioids continues for many of these patients; in 1 study of cancer patients exposed to neurotoxic agents, those with CIPN surviving more than 5 years continued to have substantial impairments and were twice as likely to be prescribed opioids on an ongoing basis than those without CIPN (4).

It is therefore necessary to identify novel therapies to prevent or treat CIPN that target 1 or several of the putative underlying mechanisms. It has been proposed that derivatives of the compounds from the *Cannabis sativa* L. plant may be helpful in this regard. The pain-alleviating properties of the chemical constituents of the *C. sativa* plant have been appreciated since ancient times but are now supported in diverse animal models of a variety of pain states, from nociceptive to inflammatory to neuropathic pain. Rodent models of CIPN have been developed using mice and rats and are sensitive to many of the sensory, electrophysiological, and histological changes observed in humans exposed to an array of chemotherapeutic regimens (10). A range of cannabinoids has been tested to determine whether they can either prevent the development of or reverse the effects of CIPN, with promising results that occur from interactions with the endocannabinoid system and related receptor targets. Several of these studies are reviewed in the following sections.

Patients with cancer often fearfully anticipate the prospect of many potential negative consequences resulting from cancer chemotherapy. At or near the top of their concerns is chemotherapy-induced nausea and vomiting (CINV) (11). Among patients with cancer, CINV is a common adverse effect that impacts not only quality of life but also treatment outcomes. When CINV goes untreated, it affects upward of 60% to 80% of patients with cancer. It is important to address these issues from both prevention and treatment standpoints so that patients remain adherent to their regimens. The primary medication options for prevention and treatment of CINV include serotonin 5-HT3 receptor antagonists, neurokinin NK1 receptor antagonists, and corticosteroids. Other medications used, but to a lesser extent, include dopamine antagonists, benzodiazepines, cannabinoids, and olanzapine (12). Antiemetic guidelines are published by several major cancer organizations, including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and jointly by the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC). One notable difference among the guidelines is the consideration of cannabinoids. In the ASCO and MASCC–ESMO guidelines, cannabinoids are not listed as antiemetic alternatives (13), whereas the NCCN guidelines list cannabinoids as options for breakthrough and/or refractory CINV (14).

Dronabinol, or Marinol, was the first of only 3 cannabinoids to receive FDA approval in the United States. Dronabinol is manufactured as a capsule containing Δ9-tetrahydrocannabinol (THC) in sesame oil. It was approved by the FDA in 1985 for the treatment of CINV. The preclinical and clinical research on THC that culminated in the FDA's 1985 approval was supported primarily by the National Cancer Institute, in collaboration with the pharmaceutical company Unimed (Marietta, GA). Dronabinol is synthesized in the laboratory rather than extracted from the plant. Its manufacture is complex and expensive because of the numerous steps needed for purification. The poor solubility of Marinol in aqueous solutions and its high first-pass metabolism in the liver account for its poor bioavailability; only 10% to 20% of an oral dose reaches the systemic circulation (15). Variation in individual responses for THC is highest and bioavailability is lowest following oral administration (16). The most common adverse events associated with dronabinol are anxiety, confusion, depersonalization, dizziness, euphoria, dysphoria, somnolence, and thinking abnormalities (17). In 2 key clinical trials, central nervous system adverse events occurred in about one-third of patients, but only a small percentage discontinued the drug because of adverse effects (18,19). Lowering the dose of dronabinol can minimize side effects, especially dysphoria (20).

Dronabinol was initially placed on schedule II, designated for medically approved substances that have high potential for abuse. Unimed later petitioned the US Drug Enforcement Administration (DEA) to reschedule dronabinol from schedule II to schedule III, which is reserved for medically approved substances that have some potential for abuse. Evidence used to support this petition included data provided by researchers at the Haight Ashbury Free Clinic of San Francisco, which found no evidence of abuse or diversion of dronabinol by their patients. Dronabinol's low abuse potential is attributed to its slow onset of action, its dysphoric effects, and other factors (21). Hence, the DEA rescheduled dronabinol to schedule III in 1999.

In summary, mounting evidence strongly suggests clinical utility of the use of cannabis-based medicines for the cancer patient. This collection of writings discusses the history of cannabinoid research as it pertains to therapeutic potential and highlights recent and current preclinical investigation into the application of cannabis-based pharmacotherapies for cancer treatment–related adverse effects, namely CIPN and CINV.

The Endocannabinoid System and Cancer Pain

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Opioid analgesics remain the mainstay for cancer pain management, even though the quality of evidence for efficacy is disappointingly low. In addition to this, side effects associated with opioid use are dose limiting in at least 10% to 20% of patients (22). Cannabis or other cannabinoid-based treatment strategies are emerging as a therapeutic option for cancer pain; however, evidence of efficacy is also sparse.

The histories of opium and cannabis show intriguing parallels. For both plants, the isolation and chemical characterization of their active constituents—morphine and THCs, respectively—were followed by the discovery of cell surface receptors that mediate their effects and ultimately by the identification of endogenous molecules, opioid peptides and endocannabinoid

lipids, which normally engage such receptors. However, there is also an important historical divergence. Preparations derived from opium and cannabis were used as analgesics, among other indications, and were both listed in the US and European pharmacopeias until the late 1930s and early 1940s. At this time, cannabis became a controlled substance, and its medical use was first hampered and then ended altogether, first with the passage of the Marihuana Tax Act of 1937 and then the Controlled Substances Act of 1970. These statutes were based largely on political and social factors rather than new scientific evidence. Although public opinion regarding cannabis has changed dramatically over the past 50 years, social stigma and legal constraints have remained and slowed down the pace of cannabis science.

This progress was slowed down but not completely halted. In 2017, the National Academies of Sciences, Engineering, and Medicine published a report, entitled "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research." In its 468 pages, 15 conclusions and 4 recommendations were offered, including the following: "There is substantial evidence that cannabis is an effective treatment for pain in adults" (23). The choice of the adjective *substantial* was deliberate and intended to indicate that more work is needed for the evidence to be considered conclusive. Moving the needle of evidence from substantial to conclusive would require a massive investment in research, time, and financial support; however, the authors believe it is worthwhile for several reasons.

First, the clinical evidence available is, after all, already substantial. Noyes et al. (24), in 1975, tested oral THC on 10 patients with pain associated with advanced cancer in a randomized, double-blind, placebo-controlled, single-dose trial and reported mild to moderate analgesia. Cannabis was also shown in a randomized placebo-controlled trial to be effective at attenuating painful HIV-associated sensory neuropathy (25). Some of the most persuasive examples of clinical evidence of cannabinoids for pain treatment include placebo-controlled, randomized clinical trials for the sublingual spray nabiximols, containing THC and cannabidiol (CBD) in a 1:1 ratio. At least 9 randomized controlled studies have been completed with nabiximols for the treatment of pain. Overall, these studies demonstrated significant improvement in chronic neuropathic pain compared with a placebo (26).

Second, there is a demonstrated role of the endocannabinoid system in the regulation of pain transmission and a preponderance of preclinical research to show that exogenous cannabinoids can modulate pain perception and pathophysiology. Pain processing occurs within the peripheral and central nervous systems, and cannabinoid receptors are located all along this pathway, from the tips of primary sensory afferents to the dorsal root ganglia, from the thalamus to the S1 somatosensory cortex. For a comprehensive review of the distribution of the cannabinoid receptors and enzymes associated with endocannabinoid synthesis and degradation in pain pathway, see Finn et al. (27). A wealth of rodent pain modeling demonstrates the modulation of nociceptive transmission and antinociceptive effects following exogenous cannabinoid administration, a review of which is outside the scope of this monograph. Most relevant to the central thesis of this presentation, we now know that endogenous cannabinoids, such as endogenous opioids, mediate stress-induced analgesia, but through distinct pathways (28). Overall, the endogenous opioid and cannabinoid systems serve nonoverlapping but converging functions in pain control. This begs the question: Can opioid-cannabinoid interactions be leveraged to obtain better analgesia? A 2017 review of the opioid-sparing effect of cannabinoids in animal models concluded that "seventeen of the nineteen pre-clinical studies provided evidence of synergistic effects from opioid and cannabinoid administration. Our meta-analysis indicated that the median effective dose (ED_{50}) of morphine administered in combination with THC was 3.6 times lower than the ED_{50} of morphine alone" (29). These results should encourage us to pursue high-quality, controlled clinical trials directed at measuring the potential opioid-sparing effects of cannabinoids.

Lastly, taken in its totality, the health risks posed by cannabinoid use are lower than those posed by opioids. A 17th century physician, John Jones, wrote in his book *The Mysteries of Opium Revealed* that the "effects of suddenly leaving off the uses of opium after a long use thereof are great and even intolerable distress, anxieties and depression of spirit, which commonly end in a most miserable death, attended with strange agonies, unless men return to the use of opium, which soon raises them again and certainly restores them" (30). In the more aseptic but equally harsh terms of statistics, data from the Centers for Disease Control and Prevention show that 49 860 Americans died of opioid overdose in 2019 alone. The numbers accrued during the 2020 coronavirus pandemic are unlikely to be better.

This is not to dismiss the issues associated with problematic cannabis use. Cannabis use disorder is included in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, published in 2013, recognizing that prolonged use of cannabis can result in loss of control over use and the emergence of distinct withdrawal signs when such use is stopped. However, although reports of cannabis use disorder have been on the rise, this condition is not associated with the extreme physiological effects caused by the opioids. As of 2018, there have been no reported overdose deaths related to cannabis use, excluding a rise in accidental ingestion deaths of cannabis edibles in children, as well as deaths from severe dehydration and renal failure associated with cannabis hyperemesis syndrome. For a comparison of the impact of cannabis vs opioid use on overall mortality, no association was reported for cannabis use and all-cause mortality, whereas opioid use is associated with significant excess mortality (31).

In summary, a strong foundation of preclinical research supports the potential for cannabis-based medicines for the treatment of pain, based on a robust and expanding understanding of the role of the endogenous cannabinoid system in pain regulation and the effects of exogenous cannabinoids on nociception. Even though these discoveries parallel much of how the opioid receptor system was discovered and characterized, opioids remain a mainstay for pain management, including cancer-associated pain, whereas to date, no cannabis-based pharmacotherapies have been approved for the treatment of pain, and cannabis itself remains a schedule I substance. This is especially noteworthy given that clinical data do exist regarding efficacy for chronic pain; however, obstacles remain that stymy further much needed clinical research, and the safety profile of cannabis shows significant advantages over that of opioid analgesics. More high-quality randomized controlled clinical trials are the logical next step to move the needle on transitioning from substantial to conclusive evidence that cannabinoid-based medicines deserve to regain their place in the armamentarium for the treatment of pain.

Targeting the Endogenous Cannabinoid System to Treat Chemotherapy-Induced Peripheral Neuropathy: Leads From Preclinical Studies

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The brain produces at least 2 naturally occurring cannabis-like chemicals, known as endogenous cannabinoids, and expresses 2 known G protein-coupled receptors that are responsive to assorted phytocannabinoids present in cannabis, known as the cannabinoid CB1 and CB2 receptors (32). The eCB anandamide, also known as N-arachidonoylethanolamine (AEA), was first isolated from porcine brain in 1992 (33). AEA activates CB1 and CB2 receptors, acting as a partial agonist, as well as activating the transient receptor potential receptor 1 (34). AEA plays a role in energy regulation (35), and changes in AEA levels have been associated with a range of pathologies (36,37). The endocannabinoid 2-arachidonoylglycerol (2-AG) is 1000-fold more abundant in the central nervous system compared with AEA, with much higher efficacy for cannabinoid receptors (34). 2-AG plays a role in several physiological functions, including its role in synaptic plasticity (38,39). These endogenous cannabinoids are synthesized on demand, act as retrograde signaling molecules, and are rapidly degraded by specific enzymatic pathways (34).

Much of the research from my laboratory for more than 10 years has focused on the enzymatic pathway regulating 2-AG, which is produced by 2 enzymes that are similar in structure—diacylglycerol lipase alpha and beta (DAGLα and DAGLβ, respectively). Several enzymes are responsible for the degradation of 2-AG, the most notable of these being monoacylglycerol lipase (MAGL), into arachidonic acid, the precursor of prostaglandins and other inflammatory mediators (34). Therefore, levels of this short-acting endocannabinoid can be regulated in at least 3 ways: interfering with DAGLα, DAGLβ, or MAGL activity. DAGLα is expressed centrally and can regulate the role of 2-AG in learning, memory, and synaptic plasticity (34). DAGLβ is more highly expressed in the periphery and contributes to inflammatory responses; its inhibition has been shown to decrease pain and inflammation in a variety of animal models (40).

My laboratory has begun investigating the effects of modulating these enzymatic pathways in a mouse model of CIPN using 2 approaches: 1) elevation of 2-AG levels via inhibition of MAGL (41) and 2) reduction of 2-AG biosynthesis via inhibition of DAGLβ.

In the mouse model of CIPN, mice are given a series of injections of the taxane chemotherapeutic paclitaxel (4 injections totaling 8 mg/kg every other day), which result in the development of measurable increases in mechanical and thermal sensitivity of the hind paws (42). In this model, the MAGL inhibitors, JZL184 and MJN110, dose-dependently reverse paclitaxel-induced mechanical sensitivity (41). Complementary genetic and pharmacological approaches revealed that the antiallodynic effects of each drug require cannabinoid receptors CB1 and CB2. MJN110 reduced paclitaxel-mediated increased expression of monocyte chemoattractant protein-1 and phospho-p38 MAPK in dorsal root ganglia as well as monocyte chemoattractant protein-1 in spinal dorsal horn. Whereas the antinociceptive effects of high dose JZL184 (40 mg/kg) underwent tolerance following 6 days of repeated dosing, repeated administration of a threshold dose (ie, 4 mg/kg) completely reversed paclitaxel-induced allodynia without the development of tolerance (41).

Using the mouse model of CIPN described above, we are currently investigating the effects of DAGLβ inhibition, which results in decreases of 2-AG and arachidonic acid production in macrophages. The DAGLβ inhibitor KT109 was used, and although this compound shows good selectivity for DAGLβ over DAGLα, it shows poor ability to cross the blood-brain barrier. As a consequence, the effects of this drug administration targets peripheral 2-AG levels. As with inhibition of MAGL, administration of the DAGLβ inhibitor KT109 significantly reduced paclitaxel-induced mechanical sensitivity. Importantly, these antiallodynic effects did not undergo tolerance following repeated administration at 40 mg/kg. Lastly, unpublished results showed that paclitaxel administration elicited hyperexcitability of primary afferent neurons isolated from the dorsal root ganglia of treated mice and that this effect was also reversed by administration of KT109.

Ultimately, it is important to determine whether pharmacological interventions to treat CIPN will alter the chemotherapeutic efficacy of cancer treatment regimens. Results from our laboratory showed that neither the MAGL inhibitor JZL184 nor the DAGLβ inhibitor KT109 altered cancer growth or interfered with paclitaxel-induced antiproliferation or apoptosis in the A549 human lung cancer line.

In summary, this line of research demonstrates that biosynthetic and catabolic 2-AG-regulating enzymes reverse paclitaxel-induced allodynia through distinct mechanisms. Repeated administration of a low dose of a MAGL inhibitor results in a retention of antinociceptive effects with a low dose, but tolerance to these effects occurs with a high dose, and repeated administration of even a high dose of the DAGLβ inhibitor was not associated with the development of antinociceptive tolerance. In addition, these MAGL or DAGLβ inhibitors did not affect proliferation or apoptosis of human lung cancer cells in vitro and did not interfere with the in vitro antineoplastic effects of paclitaxel. In future studies, it will be important to examine whether inhibition of DAGLβ or MAGL offers protection from the development of CIPN, as well as whether these strategies translate to the treatment of CIPN in patients.

Cannabinoid-Based Treatment Strategies for Pain Associated With Cancer

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In the early 1940s, University of Chicago, Urbana, scientist Dr Roger Adams identified and synthesized 2 phytocannabinoids—CBD and cannabinol—and was awarded a patent for the isolation of CBD in 1942. Through his research and that of Israeli scientist Raphael Mechoulam and others, it was determined that the phytocannabinoid THC was the "psychoactive" component of *C. sativa*. However, research into the pharmacological properties of CBD in both rodents and humans continued at a somewhat slow but steady pace until the early 2000s. Moving forward, research into the pharmacological and potential therapeutic effects of CBD has increased steeply, with nearly 1000 publications listed in PubMed in the year 2020.

During these past 20 years, investigations have centered on potential mechanisms of action and therapeutic applications of CBD, with the vast majority of this work being carried out in vitro or using animal models. Currently, the most well-established pharmacological effect associated with CBD is as an antiseizure agent. Several recent large-scale clinical trials have led to FDA approval in 2018 of the CBD therapeutic Epidiolex for the treatment of rare childhood seizure disorders. Also in 2018, the passage of the Agriculture Improvement Act (also known as the US Farm Bill) included the Hemp Act, which designates cannabis containing less than 0.3% THC as hemp and thus decouples it from schedule I drug status of cannabis. In this rapidly changing landscape, another emerging potential therapeutic effect of CBD is for the treatment of chronic pain.

Historical data report and contemporary research confirms that CBD is not frankly analgesic. However, beginning in the mid-2000s,

CBD has been looked upon as a potential treatment for chronic pain, based largely on its purported anti-inflammatory actions, coupled with potential mechanisms of action that would support its efficacy for this application, as well as a groundswell of anecdotal reports. For example, proposed mechanisms of action of CBD supported by the literature include interactions with serotonin 5-HT1A receptors, transient receptor potential (TRP) channels, glycine channels, the adenosine receptor system, intracellular Ca^{2+} handling, and reactive oxygen species (43). Importantly, binding data show that unlike THC, CBD shows negligible affinity for the canonical CB1 and CB2 receptors. At the time that our laboratory became interested in the therapeutic potential of CBD, 2 preclinical studies were published suggesting that CBD showed antineuropathic effects in rodent models of hyperalgesia (44,45).

Based on the above, our laboratory investigated the effect of prophylactic CBD administration on paclitaxel-induced mechanical sensitivity in female C57Bl/6 mice. The same paclitaxel dosing regimen was used as described above (experimental days 1, 3, 5, and 7), and prior to each paclitaxel injection, mice were pretreated with either CBD (2.5-10 mg/kg) or vehicle. We reported that paclitaxel-induced mechanical sensitivity was prevented by administration of CBD. This effect was reversed by co-administration of the 5-HT1A receptor antagonist WAY 100635 but not the CB1 receptor antagonist SR141716 or the CB2 receptor antagonist SR144528. Additionally, we conducted studies to determine whether CBD impacted the chemotherapeutic efficacy of paclitaxel in an in vitro MTT assay using breast cancer cells. In this assay, CBD was more potent and efficacious when compared with paclitaxel, and CBD plus paclitaxel combinations produced synergistic inhibition of breast cancer cell viability in comparison with either agent alone (46).

In a follow-up study, our group tested the hypothesis that CBD may interact synergistically with THC to prevent the development of paclitaxel-induced mechanical sensitivity (47). This line of research was inspired by a concept called the "entourage effect," a proposed mechanism by which cannabis compounds other than THC act synergistically with it to modulate the pharmacological effects of the plant. Although this concept is well accepted among many groups interested in *C. sativa* pharmacology, very few published experimental investigations existed at the time. To determine the nature of potential interactive effects of CBD and THC in this model, paclitaxel-treated mice were pretreated with CBD (0.625-20.0 mg/kg), THC (0.625-20.0 mg/kg), or CBD plus THC (0.04 + 0.04-20.0 + 20.0 mg/kg), and mechanical sensitivity was assessed on days 9, 14, and 21. Both CBD and THC alone attenuated mechanical allodynia in mice treated with paclitaxel. Very low, ineffective doses of CBD and THC alone were synergistic when given in combination, resulting in nearly a 10-fold shift in the potency of the combination compared with either phytocannabinoids alone. The implications of this research are that CBD may be potent and effective at preventing the development of chemotherapy-induced peripheral neuropathy, and its clinical use may be enhanced by co-administration of low doses of THC. These treatment strategies would increase the therapeutic window of cannabis-based pharmacotherapies. Further research is warranted to understand the mechanisms underlying this synergy.

Most recently, this research has been extended to investigating other minor cannabinoids and terpenes found in *C. sativa*. For example, β-caryophyllene (BCP) is a sesquiterpene found in cannabis and several other plant species such as black pepper, clove, rosemary, and hops. The pharmacological properties of BCP have been studied for decades and include antioxidant, anti-inflammatory, antimicrobial, cardioprotective, and neuroprotective effects (for a review, see reference 48). Gertsch et al. (49) in 2008 reported the selective CB2 receptor agonist activity of BCP in nanomolar concentrations. The effects of BCP alone and in combination with CBD were tested in the CIPN model. C57Bl/6 mice were treated with paclitaxel and vehicle or BCP, CBD, or a combination of BCP and CBD (by oral gavage, days 1, 3, 5, and 7) 15 minutes prior to paclitaxel injection. Mechanical allodynia was assessed on days 0 and 14. On days 14 and 15, mice were euthanized, and the L1-L4 regions of the spinal cord were collected and then stained for the microglial marker Iba1. Several doses of CBD and BCP, either alone or in combination, prevented the onset of mechanical sensitivity, but unlike combinations of CBD and THC, the interactive effect of CBD and BCP was additive. Microglial cell bodies of paclitaxel-treated animals were larger than those of the control groups and were irregularly shaped, whereas microglia of the cannabinoid-treated and vehicle groups were smaller and had a morphology characteristic of homeostatic microglia. In light of the findings with microglial activation, these treatments may affect the central sensitization of pain through glial cell-dependent mechanisms. It may also be concluded, based on the finding that CB1/CB2 receptor agonist THC synergized with CBD, whereas the CB2 receptor-selective BCP did not, that the CB1 receptor is a viable candidate for the synergy observed with CBD and THC. Future experiments will be conducted to explore a wider range of minor cannabinoids and terpenes.

Lastly, our laboratory has characterized the behavioral pharmacological effects of the CBD structural analogue KLS-13019 under a Small Business Technology Transfer Research (STTR) grant awarded to myself and KannaLife Sciences, Inc, by the National Institute on Drug Abuse. We reported that like CBD, either intraperitoneal (IP) or oral KLS-13019 prevented the development of the mechanical sensitivity associated with paclitaxel administration. In contrast to CBD, KLS-13019 was also effective at reversing established mechanical sensitivity. Because KLS-13019 binds to fewer biological targets, these findings can bring us closer to identifying molecular mechanisms shared by the 2 compounds, as well as those unique to KLS-13019 (50).

Taken together, there is compelling preclinical evidence to support the development of cannabinoid-based pharmacotherapies for the treatment of CIPN. The 3 most important overarching questions to be answered moving forward will be 1) which cannabinoid(s) will be best for the treatment of CIPN, 2) should and will there be different cannabinoid-based treatment strategies for the prevention vs the treatment of CIPN, and 3) what are the potential interactive effects with anti-tumor effectiveness of cancer treatment? Regarding which cannabinoid-based treatment strategy will prove to be the most efficacious, researchers and clinicians need to increase larger scale clinical trials to explore select plant-derived and synthetic molecules, as well as distinct cannabis cultivars with known phytocannabinoid and terpene profiles. Neuroprotective, anti-inflammatory, and antiallodynic reports of cannabinoids in rodent models of pain and other neurological diseases abound, but it remains frustratingly unclear whether these effects will translate to the clinic on a large scale.

CBD Acid (CBDA) and CBDA Methyl Ester (CBDA-ME)—Highly Effective Treatments for Nausea and Vomiting Using Preclinical Animal Models

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Cannabinoids have been shown to be effective treatments for the side effect of nausea and vomiting in cancer patients (51). To study the preclinical efficacy of cannabinoids on nausea and vomiting in the laboratory, my laboratory uses 2 animal models (52,53). The first is used to measure the effect of the cannabinoid on toxin-induced vomiting in *Suncus murinus*, or the house musk shrew; these animals retch and vomit in response to the administration of a toxin, such as lithium chloride (LiCl). The second measure, conditioned gaping in rats, assesses the effect of the cannabinoid on toxin-induced nausea. Although rats cannot vomit, they do show conditioned gaping in response to the administration of a flavor that is paired with an illness-inducing agent like LiCl, and they will also show conditioned gaping responses upon reexposure to a context that has been previously paired with LiCl-induced illness. My laboratory uses conditioned gaping rather than conditioned taste avoidance (CTA) because gaping is a more selective measure of nausea. Taste avoidance is produced by almost all drugs paired with a flavor—even rewarding drugs. Also, unlike CTA, conditioned gaping is produced only by emetic drugs. Also, unlike CTA, conditioned gaping is attenuated by antiemetic drugs, whereas CTA is not. Topographically, the conditioned gape in rats requires similar musculature as the shrew retch, just before the shrew vomits. Therefore, conditioned gaping is a standard measure used to evaluate whether a drug reduces or produces nausea (52).

Our group used the preclinical conditioned gaping model to determine whether cannabinoids reduce the acute nausea and anticipatory nausea (54,55) that are both experienced by chemotherapy patients. To test whether the compound is effective against acute nausea, rats are pretreated with a cannabinoid before pairing a saccharin-flavored solution with LiCl. If the cannabinoid effectively reduces LiCl-induced illness, the rats will not show conditioned gaping in a subsequent drug-free test trial. To test whether the compound is effective against anticipatory nausea, the rats are first given a number of pairings in a distinctive context (a black plexiglass box) with LiCl to induce conditioned gaping and then they are given a cannabinoid prior to the context in the absence of LiCl. Below, the effects of cannabis compounds (THC, CBD, CBDA, CBDA-ME) on nausea using these preclinical models are described.

Δ9-tetrahydrocannabinol

Anecdotal reports from patients indicating that smoking cannabis relieved their chemotherapy-induced nausea and vomiting prompted oncologists to begin looking at the antinausea and antivomiting effects of cannabis. Indeed, nabilone (THC in an oral suspension capsule) is an FDA-approved treatment for chemotherapy-induced nausea and vomiting in humans. We have shown a dose-dependent reduction in LiCl-induced vomiting in the *Suncus murinus* at doses ranging from 3 mg/kg to 20 mg/kg (52). THC is also effective in treating nausea using both the acute and chronic preclinical model of conditioned gaping (52, 56) at doses ranging from 1 mg/kg to 10 mg/kg (IP). However, at the higher doses, THC is sedating in rats. Because THC is sedating and intoxicating, it may not be the best treatment for chemotherapy-induced nausea and vomiting, although these effects may be beneficial for some patients.

Cannabidiol

The *C. sativa* plant does not just contain THC, it contains several other cannabinoids, which, unlike THC, are not intoxicating. One such compound is CBD. Interestingly, CBD does not bind to the typical cannabinoid receptors; however, a number of CBD's other behavioral effects, such as reducing anxiety, have been shown to be 5-HT_{1A}–receptor mediated. CBD displaces 8-OH-DPAT (the classic 5-HT_{1A} receptor agonist) from the 5-HT_{1A} receptor at micromolar (16 μM) concentrations (57).

CBD (5 mg/kg, IP) effectively reduces nicotine, lithium, and cisplatin (chemotherapy agent)–induced vomiting by a 5-HT_{1A} mechanism of action (58). However, CBD also reduces LiCl-induced acute nausea in the preclinical conditioned gaping model (58–61) in both male and female rats at 5 mg/kg (IP). There was no gender difference in efficacy. CBD also reduced LiCl-induced anticipatory nausea in rats (1-10 mg/kg, IP) by a 5-HT_{1A} mechanism.

The central mechanism for the efficacy of CBD appears to be agonism of 5-HT_{1A} somatodendritic autoreceptors in the dorsal raphe nucleus (DRN). When administered systemically, 5-HT_{1A} agonists inhibit serotonergic cell firing in the DRN (62), decreasing serotonin levels in terminal regions (63). We have recently found that when administered systemically, CBD suppresses LiCl-induced elevation of serotonin in the interoceptive insular cortex (the site responsible for the triggering of nausea) (64). We also found that central administration of a 5-HT_{1A} receptor antagonist into DRN prevented the antinausea effect of CBD (58). CBD appears to act on these central 5-HT_{1A} receptors in the DRN to ultimately reduce the release of nausea-inducing serotonin to forebrain regions (64).

Unfortunately, CBD has a limited window of efficacy in treating nausea: doses of 0.5-5.0 mg/kg are effective, with higher doses being ineffective (60). As a treatment for vomiting, CBD actually potentiates both LiCl- (53) and cisplatin (65)–induced vomiting in the *Suncus murinus* at higher doses of 20-40 mg/kg (IP). Therefore, CBD may not be the ideal therapeutic. Importantly, unlike THC, CBD does not impair locomotor activity (60).

CBD Acid and CBDA Methyl Ester

CBDA is the acidic precursor to CBD that is present in the fresh *C. sativa* plant. Upon heating or normal drying of the plant, CBDA is decarboxylated to CBD. CBDA is 1000 to 10 000 times more potent than CBD in reducing LiCl-induced vomiting, acute nausea, and anticipatory nausea (66,67). Doses as low as 1 μg/kg (IP) effectively reduced LiCl-induced acute and anticipatory nausea. The antinausea and antivomiting effects of CBDA are mediated by their action as an indirect 5-HT_{1A} agonist (66).

CBDA is easily decarboxylated to CBD. To surmount this, Raphael Mechoulam's laboratory synthesized CBDA-ME, which is more resistant to conversion to CBD as compared with CBDA. Our group found that CBDA-ME also produced antinausea and antivomiting effects at even lower doses (0.1 μg/kg, IP) than CBDA, by a 5-HT_{1A} mechanism of action with no effect on locomotor activity (68).

Preclinical Translational Studies With CBD, CBDA, and CBDA-ME

To utilize these compounds in the clinical setting to manage nausea, their effectiveness when administered subcutaneously, chronically, and in repeated trials must be established using the preclinical models. We recently reported that chronic (daily over 7 days) administration of CBD (5 mg/kg), CBDA (1 μg/kg), or CBDA-ME (1 μg/kg) reduced LiCl-induced acute nausea in the rat gaping model without the development of tolerance to the

treatment (61). Also, the efficacy of the treatment did not diminish across repeated trials. The mechanism of action, even after chronic administration, was indirect agonism of the 5-HT_{1A} receptor. Finally, chronic administration of CBD (5 mg/kg, subcutaneously) also maintained effectiveness against LiCl-induced vomiting in the *Suncus murinus*. CBDA-ME is a highly effective antinausea/antivomiting cannabinoid compound that should be evaluated in human clinical trials for chemotherapy-induced nausea and vomiting.

Closing Remarks

Substantial preclinical evidence shows that cannabinoid-based treatment strategies may help to mitigate cancer chemotherapy-associated adverse effects, as demonstrated by the above summarized bodies of research, among others. Translation of the promising results seen with cannabinoid-based treatment strategies in preclinical models of CIPN and CINV will take a concerted effort from basic scientists, clinical trial experts, and pain experts and oncologists to move the needle and empirically determine that these approaches offer a safe and effective intervention option for current and potential sufferers of these significant and sometimes cancer treatment–limiting adverse effects of chemotherapeutics.

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