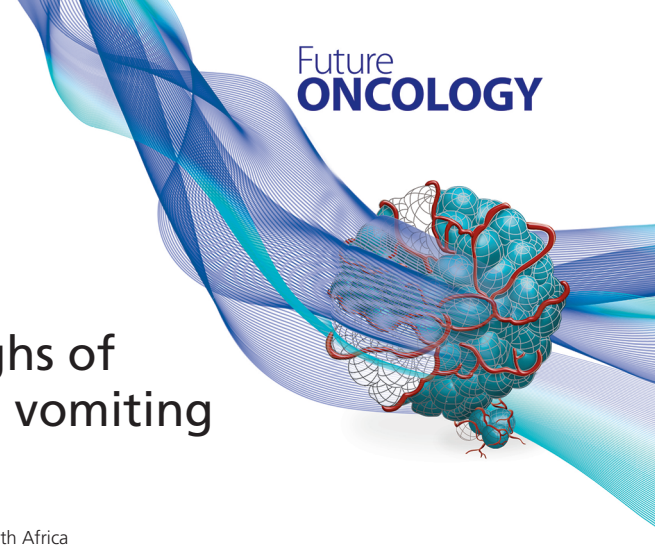
Review

For reprint orders, please contact: reprints@futuremedicine.com



Cannabinoids: the lows and the highs of chemotherapy-induced nausea and vomiting

Toni Leigh Mortimer*,[1], Tom Mabin[2] & Anna-Mart Engelbrecht[1]

[1]Department of Physiological Sciences, Stellenbosch University, Stellenbosch, 7600, South Africa

[2]Department of Medicine, Division of Cardiology, University of Cape Town, Observatory, 7925, South Africa

*Author for correspondence: tonigoldswain@gmail.com

Despite remaining one of the most widely abused drugs worldwide, *Cannabis sativa* exhibits remarkable medicinal properties. The phytocannabinoids, cannabidiol and Δ-9-tetrahydrocannabinol, reduce nausea and vomiting, particularly during chemotherapy. This is attributed to their ability to reduce the release of serotonin from enterochromaffin cells in the small intestine, which would otherwise orchestrate the vomiting reflex. Although there are many preclinical and clinical studies on the effects of Δ-9-tetrahydrocannabinol during nausea and vomiting, little is known about the role that cannabidiol plays in this scenario. Since cannabidiol does not induce psychotropic effects, in contrast to other cannabinoids, its use as an anti-emetic is of great interest. This review aims to summarize the available literature on cannabinoid use, with a specific focus on the nonpsychotropic drug cannabidiol, as well as the roles that cannabinoids play in preventing several other adverse side effects of chemotherapy including organ toxicity, pain and loss of appetite.

First draft submitted: 18 July 2018; Accepted for publication: 20 November 2018; Published online: 5 February 2019

Keywords: cannabidiol • cannabinoids • chemotherapy • nausea • vomiting

Cannabidiol & tetrahydrocannabinol

Cannabis sativa can be considered one of the most controversial plants in society. On one hand, cannabis remains the most widely abused drug in the USA [1], but on the other hand, cannabis use is associated with undeniable medicinal benefits. The term cannabinoid refers to all the ligands that bind to the cannabinoid receptors, CB1 and CB2. Two of the main phytocannabinoids are Δ-9-tetrahydrocannabinol (Δ-9-THC), known for its psychoactive effects, and cannabidiol (CBD), which is devoid of psychotropic activity. CBD has been shown to exhibit anti-epileptic, anti-inflammatory, anti-emetic and neuroprotective activity [2]. Although CBD and Δ-9-THC are associated with cannabis, these molecules are not biosynthesized by the plant. Instead *C. sativa* produces CBDA and tetrahydrocannabinolic acid from a 'stem cell' cannabigerolic acid. When triggered by heat, CBDA and tetrahydrocannabinolic acid undergo decarboxylation, resulting in decarboxylated CBD and Δ-9-THC [3].

Cannabinoids make up a large part of the growing cannabis market due to the role that they play in remedying several conditions; however, despite many forms being devoid of psychotropic activity, the pharmaceutical industry operates in a gray legal area. As a result, there are still major gaps in our understanding of the benefits and mechanisms behind the relief that cannabinoids provide. Some of the applications of cannabinoids span from pain and inflammation to treatment of depression and psychosis [4,5]; however, this review will provide insight into the role that cannabinoids play in reducing nausea and vomiting, frequently experienced by cancer patients undergoing chemotherapy.

Chemotherapy-induced nausea & vomiting

Cancer is associated with high mortality rates across the globe, regardless of economic groups. In 2012, there was an estimated 14.1 million new cancer cases worldwide [6]. The majority of affected individuals will experience symptoms of their cancer, or side effects from their treatments, which consequently reduce their quality of life and their completion of cancer therapies. The importance of managing these symptoms and side effects is emphasized by the projected increase in new cases of 50% by the year 2020. Of the most commonly reported side effects, nausea

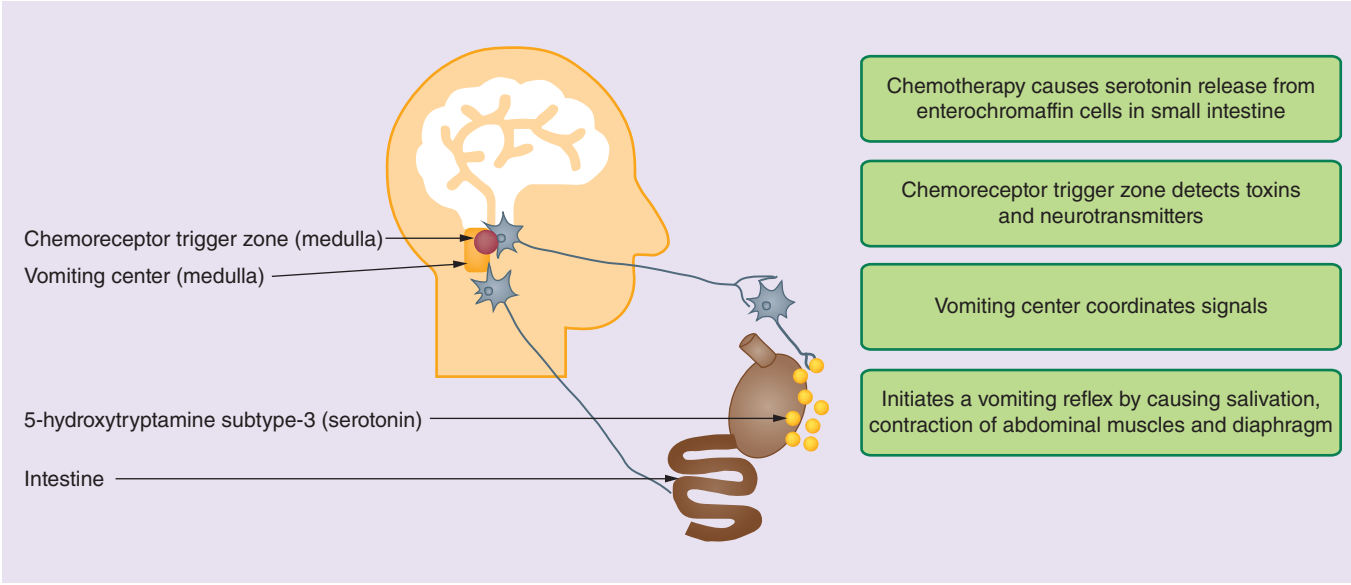


Figure 1. Schematic of the vomiting reflex. The vomiting reflex involves regions in the medulla known as the vomiting center and the chemoreceptor trigger zone, as well as nerve fibers from the small intestines. These detect neurotransmitters or toxins and send signals to the brain to initiate a vomiting response.

and vomiting are at the forefront of reducing adherence to chemotherapy and patient performance. In fact, 70–80% of patients undergoing chemotherapy will experience chemotherapy-induced nausea and vomiting (CINV) [7]. This can be accompanied by the psychological (demeaning, anticipatory nausea), physical (rib fracture, esophageal tears and dental erosion) and metabolic (dehydration, loss of appetite) side effects of nausea and vomiting, further adding the overall reduced quality of loss experienced by these individuals [8].

The pathophysiology of CINV is multifactorial and complex, occurring as a result of a complicated network of pathways, neurotransmitters and receptors between the CNS and the GI tract [9]. In short, the mechanisms behind CINV involve the vomiting center, a region in the medulla that coordinates signals from several sources, the chemoreceptor trigger zone (CTZ), a region in the medulla known as the *area postrema* which detects toxins or neurotransmitters in the blood and at last, visceral afferent nerve fibers of the small intestine (Figure 1). These nerve fibers also send signals to the CTZ which, in turn, stimulates efferent fibers in the vomiting center to initiate the vomiting reflex. Serotonin/5-HT_3 and its receptor have been shown to play a key role during CINV. Chemotherapy triggers the release of 5-HT_3 from enterochromaffin cells in the small intestine, which then binds to vagal afferent nerve fibers in the GI tract. Afferent nerve fibers then transmit this signal to the CTZ. These signals are processed in the vomiting center, which sends efferent signals to the abdominal muscles, the stomach and the diaphragm. This works in concert with other neurotransmitters such as dopamine, to escalate nausea and induce vomiting – a natural reflex to protect the body from toxins [8,10,11]. Chemotherapeutic drugs are agents with strong emetic activity and inhibit DNA synthesis and kill cells at any stage of the cell cycle. Dying enterochromaffin cells may release substances that induce the release of serotonin or the cytotoxic agents may have a direct damaging effect on the mucosa of the stomach, leading to 5-HT_3 release. Studies using animal models have indicated severe mucosal damage of the ileum and jejunum after high-dose chemotherapy, most likely via oxidative stress [12], which was directly proportional to the severity of emesis [13,14].

CINV is classified into several groups depending on the time of onset: acute, delayed, anticipatory, refractory and breakthrough CINV. Acute CINV occurs within 24 h of treatment and is believed to be mediated via the serotonin pathway; therefore, a 5-HT_3 receptor antagonist such as ondansetron and a corticosteroid are the best combination for prevention [15]. Delayed CINV occurs more than 24 h after chemotherapy and is mediated by the substance P pathway, a group of peptides known as tachykinins [16–18]. Anticipatory CINV is a learned response, and occurs prior to re-administration, in response to a previous negative experience, therefore, the generally prescribed anti-emetics provide no relief. Breakthrough CINV is the nausea or vomiting that occurs despite anti-emetic treatment and is managed with rescue medications such as dopamine receptor antagonists, 5-HT_3 receptor antagonists and

cannabinoids. Refractory CINV is classified as the vomiting that occurs with subsequent treatment, after the anti-emetics used in previous cycles of chemotherapy have been ineffective [19]. Although anti-emetics did provide an important breakthrough in oncology, the incidence of CINV still remains unacceptably high, emphasizing the need for alternative anti-emetic relief. Since CBD does not induce intoxicating effects, it may be an effective cannabinoid for the treatment of CINV.

Cannabinoids & chemotherapy-induced nausea & vomiting

Cannabinoids can be administered sublingually, orally or topically, inhaled, smoked, consumed with food or brewed into a tea [20]. Δ-9-THC is marketed as dronabinol, the generic name for a naturally occurring isomer, and nabilone, a synthetic analog of Δ-9-THC which binds to and agonizes the CB1 receptor [21]. The route of administration affects the bioavailability, efficacy and toxicity of cannabinoids, as those that are inhaled become active within 3–5 min and are associated with intense, long-lasting euphoria. In contrast, when taken orally, the onset of action is slow and euphoria is less pronounced [22]. Dronabinol becomes effective approximately 1 h after administration, with peak activity after 2–4 h. The elimination of dronabinol also varies, as dronabinol metabolites have been detected in urine and feces 5 weeks after administration of a single dose [19].

The Asian musk shrew *(Suncus murinus)* provides a good model for studying the effects of cannabinoids on nausea and vomiting, as this species experiences both conditions (as opposed to rats and mice which are not capable of vomiting) [23]. The musk shrew retches and vomits in response to most emetic drugs. Shrews were injected with a vehicle, Δ-9-THC or CBD 10 min prior to receiving lithium chloride. Lithium chloride is used in conditioned rejection reactions, in which the consumption of a flavor linked to an emetic substance results in nausea and vomiting. Δ-9-THC suppressed vomiting in a dose-dependent manner, whereas CBD only suppressed vomiting at low concentrations [24]. Furthermore, 5 mg/kg of CBD has been shown to suppress conditioned gaping in rats and vomiting in shrews [25]. The mechanism of action of CBD is currently unknown; however, it has been suggested that it may act through an unidentified cannabinoid receptor, as CB receptors in the brain bind Δ-9-THC but not CBD. In addition, synthetic cannabinoid antagonists block the actions of Δ-9-THC but not of CBD [26]. Blocking the CB1 receptor induces vomiting, suggesting that stimulation of this receptor by 9-THC may be responsible for its anti-emetic effect [27]. CBD has been demonstrated to antagonize some of the adverse effects of THC including intoxication, sedation and tachycardia [28]. CBD may also act as an antagonist of 5-HT_{1A}, by competing for 5-HT_{1A} receptor binding [29]. Furthermore, considering that Δ-9-THC has been reported to reverse the effects of 5-HT_3 receptor agonists (thereby reducing vomiting), CBD may prevent nausea and vomiting in a similar manner [30,31]. Through allosteric inhibition of the 5-HT3 receptor, CBD may exert its anti-emetic effects (Figure 2).

Cannabinoids have been approved by the US FDA for the treatment of CINV; however, according to a recent review conducted by Garcia & Shamliyan, the evidence regarding the harm versus benefit of cannabinoid use is largely insufficient [32]. Evidence is also controversial, as several clinical guidelines report conflicting recommendations. The American Society of Clinical Oncology Focused Guideline Update: Anti-emetics, 2015 states that FDA-approved cannabinoids are recommended for the treatment of nausea and vomiting that is resistant to standard anti-emetic therapies; however, evidence remains insufficient regarding treatment with medical marijuana in place of the tested and approved cannabinoids, dronabinol and nabilone [33]. The National Comprehensive Cancer Network Antiemesis Guidelines 2017 recommend cannabinoids (dronabinol 5–10 mg orally every 4–6 h or nabilone 1–2 mg orally, twice daily) among other anti-emetic drugs, when the other drugs become insufficient to control symptoms [34]. The Multinational Association of Supportive Care in Cancer: 2011 does not recommend the use of cannabinoids, as they have only moderate efficacy and significant adverse effects such as marked sedation and extrapyramidal reactions [35]. Dronabinol use has been found to prevent or reduce CINV [36,37]; however, as it contains the psychoactive component of *C. sativa*, dronabinol use results in similar side effects as those noted in marijuana users, notably drowsiness, dizziness and mood changes.

In a meta-analysis of 28 studies, Whiting *et al.* reported that all 28 studies suggested more benefit through the use of cannabinoids than with comparative anti-emetics and placebos [38]. Furthermore, the average number of patients displaying complete prevention of nausea and vomiting was greater with cannabinoid use than with the placebo. Of importance, however, is that the use of cannabinoids resulted in greater adverse effects compared with the controls. These effects included dysphoria, depression, paranoia and hypotension [39]. In a meta-analysis conducted by Rocha *et al.*, dronabinol showed statistically significant improvement in anti-emetic efficacy when compared with the comparative anti-emetic [40]. Meiri *et al.* investigated the efficacy of dronabinol versus ondansetron (an anti-emetic drug) in reducing CINV [41]. During the 2–5 days after receiving chemotherapy, patients were administered

10.2217/fon-2018-0530

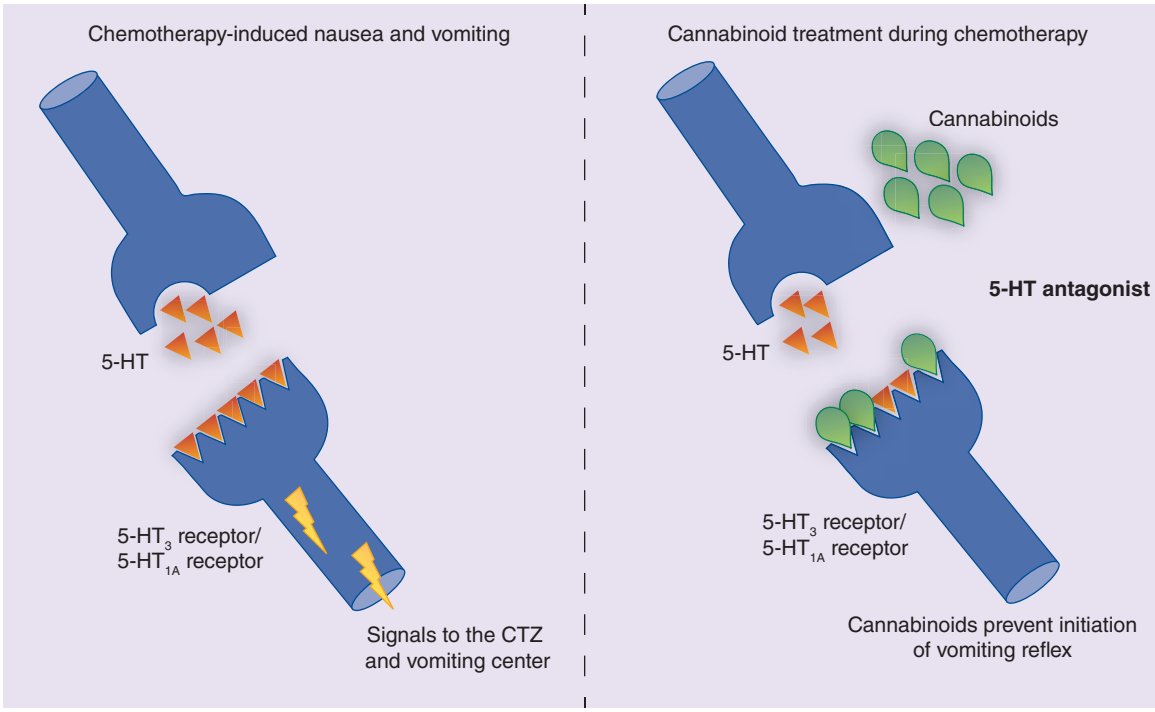


Figure 2. Illustration of the possible mechanisms of the anti-emetic effects of cannabinoids. 5-HT is released from damaged enterochromaffin cells in the small intestine, binding to afferent nerve fibers which transmit signals to the CTZ. These signals are processed in the vomiting center, which initiates the vomiting reflex.
CTZ: Chemoreceptor trigger zone.

up to 20 mg dronabinol, either alone, or in combination with ondansetron. The efficacy of dronabinol alone was similar to that of ondansetron alone, and the combination of the two drugs did not result in a greater benefit. It was also reported that the overall quality of life reported by patients was higher in the group that received dronabinol compared with the other treatment groups. In 18 crossover trials included in a meta-analysis conducted by Tramèr *et al.*, 76 and 61% of patients preferred cannabinoids over placebo or comparative anti-emetics, respectively [39].

In a trial by Chang *et al.*, 15 patients receiving high-dose methotrexate were administered oral (Δ9-THC in sesame oil) or smoked Δ-9-THC for the treatment of nausea and vomiting [42]. Δ-9-THC was administered at a dose of 10 mg/m^2 every 3 h, for a total of five doses. Δ-9-THC was significantly more effective than the placebo at reducing retching and vomiting and the degree and duration of nausea. When plasma Δ-9-THC concentrations were <5.0 ng/ml, 5.0–10.0 ng/ml and >10.0 ng/ml, the incidences of nausea and vomiting were 44, 21 and 6%, respectively. Sedation was noted in 80% of the subjects, while others experienced short-lasting episodes of tachycardia, anxiety and depression. In a later study by the same group, Δ-9-THC did not significantly reduce nausea or vomiting during Doxorubicin treatment when compared with the control, and it was concluded that the anti-emetic properties of Δ-9-THC might only be effective against certain types of chemotherapeutic drugs [43]. In a randomized, crossover trial, four out of 20 patients preferred smoked cannabis over dronabinol, seven preferred dronabinol and nine had no preference [22,44]. Finally, a study on Sativex® (a sublingually delivered whole-plant extract containing a 1:1 ratio of Δ-9-THC and CBD) found that 71% of patients displayed a complete anti-emetic response to cannabinoids when compared with only 22% that received the placebo, both in conjunction with standard anti-emetic treatment [45]. Each spray push delivered in Sativex® contained 2.7 mg of THC and 2.5 mg of CBD, with an average of 4.8 sprays per day. Although there are other studies investigating the effects of Δ-9-THC on CINV [20,39,46,47], there are no reports on the evaluation of CBD alone in human patients [48]. Much of the widely available information on the Internet is largely assumptive, with the authors drawing conclusions based on animal studies and not on clinical evidence. In fact, Mechoulam and colleagues have even patented the use of CBD and its homologs in the treatment of nausea and vomiting, stating that the term 'subject' refers to a human, dog, cat, horse, primate or fowl, when their study was solely based on rat experimentation [49]. In this study, Parker, Mechoulam & Schlievert examined the anti-emetic effects of CBD in a rat model of CINV, in which CBD

interfered with lithium chloride-induced conditioned rejection reactions, indicating a reduction in nausea [50]. This may suggest that CBD has therapeutic value as an anti-emetic, warranting further research in human subjects.

Medical marijuana contains more than 60 pharmacologically active cannabinoids, with the primary active cannabinoids being Δ-9-THC and CBD [51,52]. Although several states have legalized its use, the adverse effects of medical marijuana should not be ignored. These include effects on the cardiovascular, respiratory and central nervous systems, an increase in the level of carcinogens (when smoked), myocardial infarction, stroke, atrial fibrillation, dizziness, difficulty sleeping, delayed gastric emptying and immunosuppression [53,54]. In fact, there are reports of gastrointestinal discomfort following cannabinoid use, as both animals and humans may experience constipation and suppressed defecation [4,55–57]. Acutely, marijuana increases heart rate and blood pressure, while long-term use is associated with a decrease in blood pressure, and bradycardia. However, there has been no clear association between marijuana use and hospitalization due to cardiovascular disease. Whether these marijuana-induced effects on the cardiovascular system are sufficient to trigger infarction is still under debate, however, the evidence does leave cause for concern. In addition, it is difficult for pathologists to decide whether an individual with cardiovascular disease has died from marijuana smoking or alongside marijuana smoking. Smoke from marijuana contains more carcinogenic compounds than smoke from a tobacco cigarette. Despite the lack of epidemiological studies displaying a relationship between marijuana use and lung disease, there is evidence to suggest that marijuana may increase the risk of adverse respiratory effects [51].

Despite these unwanted side effects, cannabinoids are known for their safety, and there has never been a documented death from an overdose of cannabinoids [58,59]. Musty & Rossi reported the results of six state-run clinical trials consisting of 748 patients who smoked marijuana and 345 patients who used oral THC capsules [60]. Of the patients who smoked marijuana prior to and after chemotherapy, 70–100% experienced a reduction in nausea and vomiting. Of the patients who used oral THC capsules, 76–88% also experienced relief. Söderpalm, Schuster & De Wit examined the anti-emetic effect of smoked marijuana cigarettes (8.4 and 16.9 mg Δ-9-THC) compared with the anti-emetic drug, ondansetron in healthy volunteers [61]. Nausea and vomiting were induced by syrup of ipecac, a fast-acting emetic that induces the release of serotonin in the GI tract. Δ-9-THC significantly reduced nausea but was only modestly effective at reducing vomiting compared with ondansetron.

Δ-8-THC is a double bond isomer of Δ-9-THC, prepared from CBD. These compounds are identical in stereochemistry and chemical behavior, but Δ-8-THC is more resistant to oxidation and less potent in terms of psychotropic activity than Δ-9-THC [62]. When administered to young children with different hematologic cancers treated with a variety of anticancer drugs, Δ-8-THC could be administered at considerably higher doses (18 mg/m^2) than the doses of Δ-9-THC generally administered to adults (5–10 mg/m^2), without any major side effects [36,62]. In addition, vomiting was completely prevented, regardless of the type of chemotherapy protocol. In a very recent study by Pertwee *et al.*, CBDA methyl ester, a synthetic analog of CBDA, resulted in 5-HT$_{1A}$ receptor-mediated suppression of nausea in rats [63]. The authors reported that the methyl ester form was more potent than CBDA at enhancing 5-HT$_{1A}$ receptor activation, thereby inhibiting signs of nausea and anxiety. Suppression of nausea was induced by the methyl ester form at a low dose of 0.1 μg/kg, whereas the lowest effective dose of CBDA was 1 μg/kg. This was assessed using the conditioned gaping model. When WAY100635, a 5-HT$_{1A}$ antagonist, was administered, suppression of nausea was blocked, indicating that this effect is mediated via the 5-HT$_{1A}$ receptor. Since CBDA is a major constituent of cannabis, it is possible that CBDA may mediate the anti-emetic and anti-nausea effects of cannabis, however, further human clinical research is required.

In an effort to shed light on the controversial market of CBD, the Brightfield Group (a strategic market firm), in partnership with HelloMD (America's largest online community of medical cannabis patients, experts, brands and retailers), collected data from over 2400 HelloMD community members, to analyze their experiences of CBD. The results of this study indicated that three out of four cannabis users use CBD products, and 42% of CBD users have stopped using traditional medications. In addition, 66% of CBD users indicated that CBD products are more effective at relieving medical conditions than the traditional over-the-counter products. However, the results showed that CBD was used to treat anxiety in 65% of users compared with only 26% who turn to CBD for nausea. This study summarized by stating that those looking to manufacture CBD should focus on the perceived advantages of the product, further highlighting the prematurity of the concept of using CBD to treat various ailments. Although there are emerging benefits of using CBD and other cannabinoids as anti-emetic drugs, substantial research is still required before definitive conclusions can be made regarding their effectiveness [64].

10.2217/fon-2018-0530

Other pharmacological actions of cannabinoids during chemotherapy

Organ toxicity

Doxorubicin is one of the most widely utilized chemotherapeutic drugs, however, its clinical success is limited by the development of dose-dependent cardiotoxicity [65]. The mechanism behind cardiotoxicity is complex, involving oxidative stress, mitochondrial dysfunction, dysregulation of signaling pathways, activation of apoptosis and necrosis and inflammation. Reactive oxygen species can induce damage to lipid membranes, the mitochondria, DNA and cellular proteins, all of which will contribute to apoptosis or necrosis of the cell [66]. Hao *et al.* examined the effects of CBD in a mouse model of Doxorubicin-induced cardiomyopathy [67]. Mice were administered a single high dose of Doxorubicin 1.5 h after receiving 10 mg/kg CBD. The CBD was continued daily for 5 days, after which hemodynamic, biochemical and histological assessments were made. CBD was found to attenuate the levels of Doxorubicin-induced lactate dehydrogenase and creatine kinase, markers of tissue injury, and cardiac dysfunction, which was indicated by an improvement in ejection fraction. CBD increased glutathione peroxidase activity and reduced lipid peroxidation and the expression of reactive oxygen species. Doxorubicin reduced the mRNA expression of several markers of mitochondrial biogenesis such as PGC1-α, PPAR-α and UCP2 and UCP3, whereas CBD largely prevented this. CBD also reduced apoptotic cell death, as indicated by a reduction in caspase activity, PARP cleavage and DNA fragmentation. Finally, it was found that CBD reduced the myocardial mRNA expression of inflammatory markers such as TNF-α.

Similarly to the mechanisms responsible for CBD's cardioprotective effects, Pan *et al.*, 2009 reported a reduction in oxidative stress, inflammation and cell death by CBD in a model of nephrotoxicity [68]. CBD attenuated cisplatin-induced renal dysfunction in mice, indicated by lower levels of creatinine, most likely by reducing apoptosis and necrosis, inflammation and oxidative stress. It is thought that cannabinoids act as potent antioxidants to antagonize oxidative stress [69]. These effects occur independently of the CB1 and CB2 receptors, as CBD has very limited affinity for these receptors [70]. This is supported by experiments that were performed on neuronal cells derived from CB1 knock-out mice; CBD still exerted protective effects against oxidative stress in a cell line devoid of the CB1 receptor [71]. Instead, CBD activates several other receptors and second messengers to carry out its pharmacological effects. An example of this is PPAR-γ, which mediates some of the neuroprotective, anti-inflammatory and cardiovascular effects of cannabinoids [72]. In addition to their effects on organs such as the heart and kidneys, chemotherapeutic drugs can result in gastrointestinal adverse effects such as constipation or diarrhea, which are often overlooked side effects. Research shows that cannabinoids may relieve the diarrhea associated with 5-fluorouracil treatment [57,73], a drug that can result in diarrhea rates of up to 80% [74], possibly by reducing gastric hypermotility [57].

Chemotherapy-induced neuropathic pain

One of the additional side effects of chemotherapy is the development of peripheral neuropathic pain. Although the exact mechanism is not yet understood, chemotherapeutic agents induce mitochondrial dysfunction and impair DNA synthesis, leading to oxidative stress and inflammation and the spontaneous activation of peripheral nerve fibers [75]. King *et al.* examined whether CBD was effective at preventing chemotherapy-induced mechanical sensitivity in mice [76]. They reported a significant reduction in mechanical sensitivity following CBD treatment, an effect that was shown to be synergistic, when Δ-9-THC was co-administered. One of the mechanisms behind this effect may be a result of suppressed calcium conductance and subsequent reduction of neuronal excitability [77]. Furthermore, activation of the 5-HT_{1A} receptor was shown to be necessary for the anti-neuropathic effects of CBD, as this receptor plays an important role in modulating the pain pathway. Indeed, administration of a 5-HT_{1A} receptor antagonist blocked the protective effect offered by CBD [78]. CBD acts as an agonist for the 5-HT_{1A} receptor, thereby regulating the rate of firing of 5-HT_{1A} afferents, to reduce the release and bioavailability of 5-HT_{1A} [2,29].

Appetite stimulation

It is common knowledge that individuals who suffer from cancer experience significant weight loss [79]; therefore, the appetite-stimulating effects of cannabinoids may be beneficial in this context. Despite being approved by the FDA as an appetite stimulant for HIV-induced anorexia, there is currently insufficient evidence to support the use of cannabinoids in cancer-related anorexia [80]. In a randomized clinical trial evaluating a cannabis extract and dronabinol for the treatment of cancer-related anorexia–cachexia syndrome, neither of the compounds were found to affect appetite or quality of life [81]. In an open-label study, 13 out of 18 patients reported improved

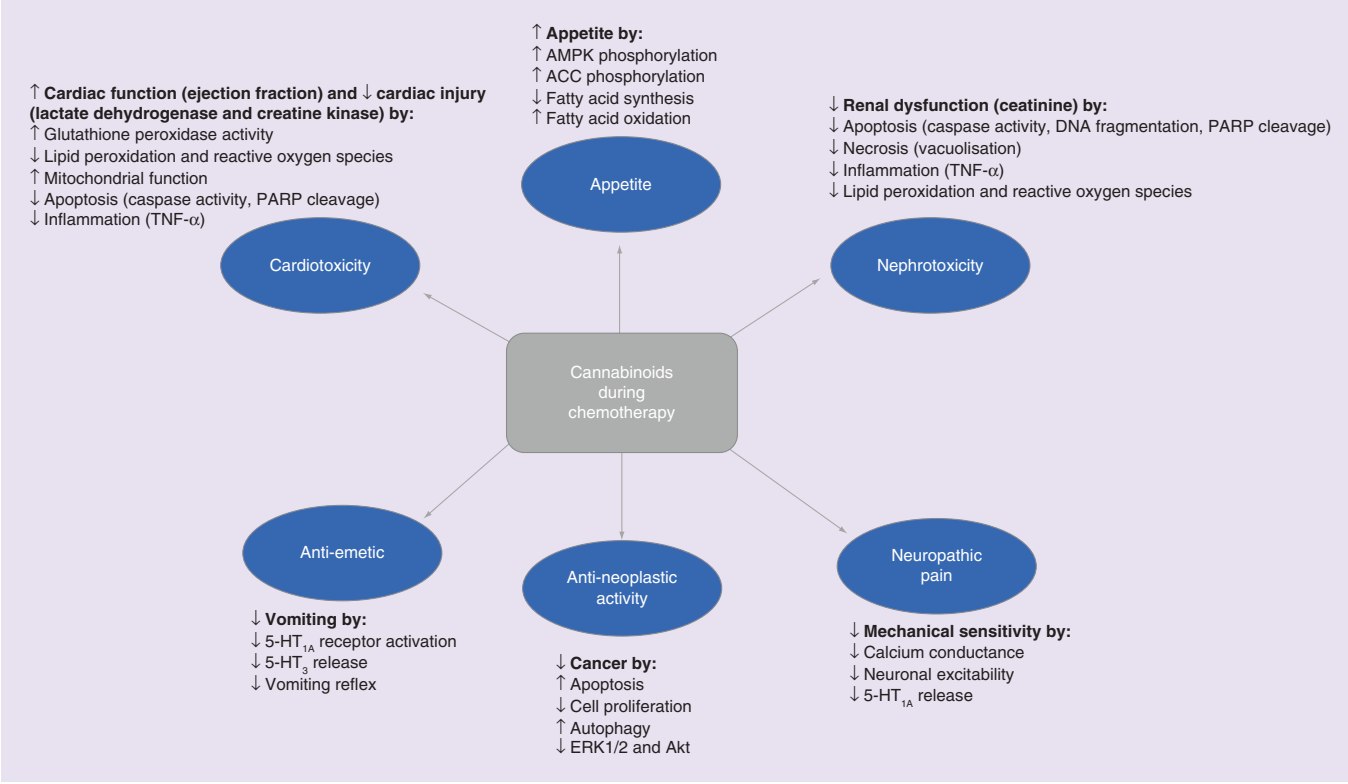


Figure 3. Summary of the potential mechanisms by which cannabinoid treatment is beneficial during chemotherapy. Cannabinoid use during chemotherapy may prevent cardio- and nephrotoxicity, pain and vomiting, and promote food intake. Cannabinoids may also exhibit anti-neoplastic activity.

appetite with dronabinol [46], while in a double-blind crossover study, treatment with Δ-9-THC led to significant weight gain, whereas individuals who received the placebo experienced continued weight loss [55], although this was thought to be attributed to fluid retention. Clearly, more controlled studies are required to determine whether cannabinoids do indeed stimulate food intake during chemotherapy. The mechanism behind cannabinoid-induced feeding may involve AMPK, an enzyme that functions as a fuel sensor to regulate energy balance. It has been shown that treatment with Δ-9-THC results in an increase in AMPK activity in the hypothalamus [82]. AMPK then phosphorylates acetyl-CoA carboxylase, thereby inhibiting fatty acid synthesis and promoting fatty acid oxidation. The increase in fatty acid oxidation reduces lipid stores, signaling fuel deprivation which, in turn, stimulates appetite (Figure 3). The fact that cannabinoids may target more than just emesis further highlights their potential as an adjuvant therapy, as a single compound may have the ability to alleviate multiple symptoms and side effects concurrently. Since patients will be more likely to adhere to their treatments, better prognosis, reduced morbidity and improved quality of life will emerge.

Anti-neoplastic activity

Besides alleviating the side effects of chemotherapy, cannabinoids may exert a chemotherapeutic effect. Experimental studies have shown that when cannabinoids activate the CB receptors, tumor cell proliferation is inhibited, apoptosis is initiated, and metastasis is prevented [83,84]. Although discussion of these chemotherapeutic effects is beyond the scope of this review, the CB receptor-dependent mechanisms for antineoplastic activity involve the inhibition of ERK1/2 and Akt, resulting in reduced cell proliferation. Activation of the CB1 receptor can also lead to cell cycle arrest and therefore the activation of apoptosis. A CB receptor-independent mechanism involves the induction of autophagy, which then also activates apoptotic cell death of cancer cells [85]. These anti-cancer effects, together with the anti-emetic potential of cannabinoids, may improve prognosis, reduce morbidity and improve overall quality of life.

Nausea & vomiting in other conditions

Many individuals are at risk of motion sickness during air, road or sea travel, which may lead to nausea and vomiting. Acute motion sickness is thought to occur because of an intense brain–gut interaction during stress – an interaction that is regulated by the endocannabinoid system. This system comprises the CB1 and CB2 receptors, endocannabinoid ligands such as anandamide and several enzymes responsible for uptake and degradation [86]. Choukèr *et al.* studied the activity of the endocannabinoid system during parabolic flight maneuvers [87]. Blood endocannabinoid levels (anandamide) were measured before the start of the parabolic maneuvers, after 10, 20 and 30 parabolas, after termination of the maneuvers and 24 h later. The subjects who developed motion sickness displayed significantly lower endocannabinoid levels. The mRNA expression of CB1, but not CB2, was also significantly lower in the subjects with motion sickness compared with those without, demonstrating that nausea may be associated with impaired endocannabinoid activity. Therefore, enhancing endocannabinoid signaling with phytocannabinoids such as CBD may be an alternative treatment strategy in individuals that are unresponsive to the currently available treatments.

Adherence to antiretroviral therapy is critical for the successful control of HIV, however, a large proportion of patients discontinue treatment because of adverse side effects like nausea and vomiting. De Jong *et al.* performed a cross-sectional survey to identify an association between marijuana smoking and adherence to antiretroviral treatment [88]. Their data suggested that the use of medical marijuana may facilitate antiretroviral adherence in patients with nausea. Similarly, in an anonymous mail survey conducted by Sidney, 66% of HIV-positive or AIDS patients reported using cannabis to reduce nausea [89].

During pregnancy, many women will experience some nausea and vomiting that can vary from mild to extreme, such as *hyperemesis gravidarum* [90]. In a study by Westfall *et al.*, a survey was conducted on women who were using medical cannabis [91], and 68% of the respondents who had experienced nausea during pregnancy reported cannabis use to treat the condition, rating it as 'extremely effective'.

Table 1 summarizes some of the currently available information on cannabis use, as well as the type of cannabinoid administered with the associated outcomes. The table is presented in chronological order, which demonstrates how investigations into CBD as an anti-emetic occurred much later (2002) than Δ-9-THC (1979), highlighting how much more information and research is necessary before valid conclusions can be drawn.

Drug interactions & hyperemesis

CYP3A4 and CYP2D6 are important liver enzymes involved in the oxidation and metabolism of toxins or drugs [92]. CBD is a potent inhibitor of CYP3A4 and CYP2D6 [93], therefore administration of CBD may result in increased serum concentrations of warfarin [94], anticonvulsants [95], antiretrovirals [96] and others, while medical cannabis may have no effect on the pharmacokinetics of chemotherapy drugs [97]. Nevertheless, further research is required to elucidate drug interactions.

Despite the beneficial effects of cannabinoid use on nausea and vomiting, recent reports have indicated that chronic use can lead to a toxic condition of cyclic nausea and vomiting known as cannabinoid hyperemesis [98]. Vomiting resolves after abstaining from cannabis use, and those who use cannabis again suffer from recurring symptoms [99]. Although the mechanism behind this toxic effect is still unclear, one of the mechanisms reported stems from how Δ-9-THC is lipid soluble and deposits in the body's fat stores. This results in a long elimination half-life, subsequent accumulation of Δ-9-THC in the body and higher toxic levels in the blood stream, especially in response to stress or fasting [100]. It has also been reported that hyperemesis may occur due to the dysregulation of peripheral enteric nerves, resulting in delayed gastric emptying and abdominal pain [56]; however, only 30% of patients experienced delayed gastric emptying and as such, this mechanism remains controversial [57]. Cannabinoids might also disrupt the thermoregulatory equilibrium of the hypothalamus, which is why hot bathing may provide relief to suffering individuals [98].

Conclusion

Although the purpose of this manuscript was to review the known preclinical and clinical investigations of CBD as a treatment for nausea and vomiting, the majority of the available literature was based on the psychoactive component of marijuana, Δ-9-THC. This highlighted the known therapeutic benefits of Δ-9-THC, but more importantly, the lack of evidence surrounding the use of CBD, identifying a large gap in the current knowledge. Clinical evidence on the use of CBD for the treatment of CINV is virtually nonexistent. Despite the efforts of dedicated individuals and institutions, properly controlled clinical trials remain rare. The current knowledge about

Table 1. A summary of the case studies, preclinical and clinical reports of cannabinoid use during nausea and vomiting.

Study (year)	Model	Cannabinoid/drug	Dose	Diagnosis	Outcome	Ref.
Chang *et al.* (1979)	Humans	Δ-9-THC in sesame oil Δ-9-THC smoked	10 mg/m^2 × 5 17.4 mg	CINV (methotrexate)	↑ Efficacy compared with placebo	[42]
Chang *et al.* (1981)	Humans	Δ-9-THC in sesame oil Δ-9-THC smoked	10 mg/m^2 × 5 17.4 mg	CINV (doxorubicin)	No reduction of CINV	[43]
Chan *et al.* (1987)	Humans	Nabilone	1 mg × 3 (daily)	CINV	↑ Efficacy compared with anti-emetics	[47]
Lane *et al.* (1991)	Humans	Dronabinol	10 mg × 4	CINV	↑ Efficacy compared with anti-emetics	[46]
Abrahamov *et al.* (1995)	Humans	Δ-8-THC in oil	18 mg/m^2	CINV	Vomiting completely prevented	[62]
Tramèr *et al.* (2001)	Humans	Dronabinol Nabilone	10–12 mg/m^2 × 4 1–5 mg	CINV	↑ Efficacy compared with anti-emetics	[39]
Söderpalm *et al.* (2001)	Healthy humans	Δ-9-THC smoked	8.4 and 16.9 mg	Ipecac-induced nausea and vomiting	↓ Nausea, modest ↓ in vomiting	[61]
Parker *et al.* (2002)†	Sprague–Dawley rats	CBD	2.5 mg/ml	LiCl gaping (nausea)	↓ Gaping	[50]
Westfall *et al.* (2006)	Humans	Smoked marijuana	Unknown	Morning sickness	Rated extremely effective	[91]
Parker *et al.* (2006)†	Asian musk shrew	Δ-9-THC CBD	3 mg/kg 5 mg/kg	LiCl rejection (nausea)	↑ Efficacy compared with anti-emetics	[24]
Meiri *et al.* (2007)	Humans	Dronabinol	20 mg	Nausea and vomiting	Similar anti-emetic effectiveness, improved QoL	[41]
Rocha *et al.* (2008)	Humans (meta-analysis)	Dronabinol	10–12 mg/m^2 × 4	Nausea and vomiting	↑ Efficacy compared with anti-emetics	[40]
Choukèr *et al.* (2010)	Humans	NA	NA	Motion sickness	↓ Endocannabinoid activity	[87]
Duran *et al.* (2010)†	Humans	Δ-9-THC CBD (Sativex®)	12.9 mg 12 mg	Nausea and vomiting	↑ Efficacy compared with placebo	[45]
Rock *et al.* (2011)†	Sprague-Dawley rats	CBD	5 mg/kg	Conditioned gaping (nausea)	Suppressed conditioned gaping	[25]
Rock *et al.* (2011)†	Asian musk shrew	CBD	5 mg/kg	LiCl rejection (nausea)	Suppressed vomiting	[25]
Whiting *et al.* (2015)	Humans (meta-analysis)	Dronabinol Nabilone Δ-9-THC	5–30 mg/day 0.5–8 mg/day 5–60 mg/day	Nausea and vomiting Nausea and vomiting CINV	Suppressed nausea/vomiting better than placebo and anti-emetics	[38]

†Studies that specifically make use of CBD.
CBD: Cannabidiol; CINV: Chemotherapy-induced nausea and vomiting; LiCl: Lithium chloride; NA: Not applicable; THC: Tetrahydrocannabinol; QoL: Quality of life.

10.2217/fon-2018-0530

the pharmacological actions of CBD in the context of nausea and vomiting is limited; however, based on the enormous body of evidence for CBD use in other conditions [101], controlled clinical trials may shed light on its true potential. Propelled by public support, politics and the media, despite limited scientific evidence, patients are still largely self-medicating as they explore the use of cannabis as a treatment strategy. Cannabinoids, both natural and synthetic, have been shown to reduce nausea and vomiting by competing for the serotonin receptor. In addition, these compounds may prove to exert benefits that extend beyond CINV, such as limiting the organ toxicity and pain that commonly accompanies chemotherapy. Considering that CBD has demonstrated beneficial effects in animal models of emesis, as well as in other conditions in humans, it is likely that CBD will prove to be an effective anti-emetic agent and has the potential to drastically improve the quality of life of cancer patients. However, investors, self-medicators, social media addicts and physicians should get down from this high about CBD until carefully conducted long-term clinical research has been carried out.

Future perspective

Considering the current evidence surrounding the use of Δ-9-THC as an anti-emetic and CBD for the treatment of various other conditions, it is highly likely that the market for and research of CBD will explode in the near future. Not only will this diminish the illegal implications of its use, but also bring to light the mechanisms surrounding its benefits. The stigma surrounding cannabis use should fall away over time, leading to a larger community of both prescribers and users. In preparation for the clinical trials that will ensue, large amounts of money will also be invested in this industry. In the end, we will probably see that this herbal remedy performs with even higher efficacy than conventional medicine.

Acknowledgements

The authors would like to thank L Kruger for his valuable discussion.

Financial & competing interests disclosure

The authors acknowledge funding support from the Cancer Association of South Africa (CANSA), National Research Foundation (NRF) and the South African Medical Research Council (SAMRC). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Cannabidiol & tetrahydrocannabinolic acid

- *Cannabis sativa* remains a widely abused drug worldwide.
- Cannabidiolic acid and tetrahydrocannabinolic acid are produced from 'stem cell' cannabigerolic acid.
- When triggered by heat, CBDA and tetrahydrocannabinolic acid undergo decarboxylation, resulting in CBD and Δ-9-THC.
- CBD is nonpsychoactive.
- Research into the effects of CBD during nausea and vomiting is lacking.

Chemotherapy-induced nausea & vomiting

- Cancer is associated with high mortality rates.
- Majority of affected individuals experience symptoms of their cancer, or side effects from treatments.
- A total of 70–80% of patients undergoing chemotherapy experience chemotherapy-induced nausea and vomiting.
- Mechanism involves vomiting center, chemoreceptor trigger zone and visceral afferent nerve fibers of the small intestine.
- Acute, delayed, anticipatory, refractory and breakthrough.

Cannabinoids reduce chemotherapy-induced nausea & vomiting

- Administered sublingually, orally or topically, inhaled, smoked, consumed with food or brewed.
- Preclinical and clinical studies with synthetic Δ-9-THC have often had better outcomes than when the generally prescribed anti-emetics are used.
- Only a single human study using CBD as an anti-emetic – CBD proved more effective than the placebo, in conjunction with anti-emetics.
- The anti-emetic effects are possibly mediated via the inhibition of 5-HT3 release.
- A total of 42% of CBD users have stopped using traditional medications.
- A total of 66% of CBD users indicated that CBD products are more effective than traditional products.

Cannabinoids prevent other adverse effects of chemotherapy

- Increased cardiac function and reduced cardiac injury.
- Reduced renal dysfunction.
- Mechanisms involve reduced apoptosis, inflammation and oxidative stress.
- Appetite promotion involves AMP-activated protein kinase and increased fatty acid oxidation.
- Pain relief is afforded by reduced neuronal excitability.

Drug interactions & hyperemesis

- CBD is a potent inhibitor of CYP3A4 and CYP2D6 – liver enzymes.
- May result in increased serum concentrations of certain drugs.
- Chronic cannabinoid use can lead to cyclic vomiting known as cannabinoid hyperemesis.
- Δ-9-THC is lipid soluble and deposits in the body's fat stores.
- Long elimination half-life, and a subsequent accumulation.

Conclusion

- Lack of evidence surrounding the use of CBD and nausea/vomiting.
- Properly controlled clinical trials remain rare.
- Patients are still largely self-medicating.

References

Papers of special note have been highlighted as: • of interest

1. SAMHSA. National Survey on Drug Use and Health: detailed tables. (2015). www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.htm
2. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med. Hypotheses* 66(2), 234–246 (2005).
3. Burstein SH. The cannabinoid acids: nonpsychoactive derivatives with therapeutic potential. *Pharmacol. Ther.* 82(1), 87–96 (1999).
4. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 45(1), 50–52 (2006).
5. Koppel BS, Brust JCM, Fife T *et al.* Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 82(17), 1556–1563 (2014).
6. Ferlay J, Soerjomataram I, Dikshit R *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. Cancer* 136(5), 359–386 (2015).
7. Wiser W, Berger A. Practical management of chemotherapy-induced nausea and vomiting. *Oncology* 19(5), 637–645 (2005).

10.2217/fon-2018-0530

- **Introduces chemotherapy-induced nausea and vomiting (CINV), indicating its prevalence, and discuss the various categories and mechanisms behind this condition.**

8. Sanger G, Andrews P. A history of drug discovery for treatment of nausea and vomiting and the implications for future research. *Front. Pharmacol.* 9(September), 1–35 (2018).
9. Navari RM, Aapro M. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. *N. Engl. J. Med.* 374(14), 1356–1367 (2016).

- **Also discusses CINV, but provides insight into the treatment strategies for the condition. Cannabinoids are discussed briefly.**

10. Aapro M. CINV: still troubling patients after all these years. *Support. Care Cancer* 26(1), 5–9 (2018).
11. Bayo J, Fonseca PJ, Hernando S *et al.* Chemotherapy-induced nausea and vomiting: pathophysiology and therapeutic principles. *Clin. Transl. Oncol.* 14(6), 413–422 (2012).
12. Bhattacharyya A, Chattopadhyay R, Mitra S *et al.* Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. *Physiol. Rev.* 94, 329–354 (2014).
13. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Malave JJ. Changes in serotonin metabolism in cancer patients: its relationship to nausea and vomiting induced by chemotherapeutic drugs. *Br. J. Cancer* 66(January), 198–203 (1992).
14. Gunning SJ. Cisplatin induces biochemical and histological changes in the small intestine of the ferret. *Br. J. Pharmacol.* 90, 135 (1987).
15. Higgins GA, Kilpatrick GJ, Bunce KT, Jones BJ, Tyers MB. 5-HT3receptor antagonists injected into the area postrema inhibit cisplatin-induced emesis in the ferret. *Br. J. Pharmacol.* 97(1), 247–255 (1989).
16. Hesketh P. Chemotherapy-induced nausea and vomiting. *N. Engl. J. Med.* 358, 2482–2494 (2008).
17. Hargreaves R, Ferreira JCA, Hughes D *et al.* Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Ann. N. Y. Acad. Sci.* 1222(1), 40–48 (2011).
18. Chawla SP, Grunberg SM, Gralla RJ *et al.* Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 97(9), 2290–2300 (2003).
19. May MB, Glorde AE. Dronabinol for chemotherapy-induced nausea and vomiting unresponsive to antiemedics. *Cancer Manag. Res.* 8, 49–55 (2016).
20. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids – an international cross-sectional survey on administration forms. *J. Psychoactive Drugs* 45(3), 199–210 (2013).
21. Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2005–2009. *Cannabinoids* 5, 1–21 (2010).
22. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *J. Ethnopharmacol.* 105, 1–25 (2006).
23. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev. Bras. Psiquiatr.* 30(3), 271–280 (2008).
24. Parker LA, Kwiatkowska M, Mechoulam R. Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in *Suncus murinus*: an animal model of anticipatory nausea and vomiting. *Physiol. Behav.* 87(1), 66–71 (2006).
25. Rock EM, Goodwin JM, Limebeer CL *et al.* Interaction between non-psychotropic cannabinoids in marihuana: effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews. *Psychopharmacology (Berl.)* 215(3), 505–512 (2011).
26. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J. Clin. Pharmacol.* 42(11), 11–19 (2002).
27. Darmani NA. Δ9-Tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid CB1 receptor antagonist/inverse agonist SR 141716A. *Neuropsychopharmacology* 24(2), 198–203 (2001).
28. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br. J. Pharmacol.* 163(7), 1344–1364 (2011).
29. Rock EM, Bolognini D, Limebeer CL *et al.* Cannabidiol, a nonpsychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT 1A somatodendritic autoreceptors in the dorsal raphe nucleus. *Br. J. Pharmacol.* 165(8), 2620–2634 (2012).
30. Himmi T, Dallaporta M, Perrin J, Orsini J-C. Neuronal responses to Δ9-tetrahydrocannabinol in the solitary tract nucleus. *Eur. J. Pharmacol.* 312(3), 273–279 (1996).
31. Yang K, Galadari S, Isaev D, Petroianu G, Shippenberg TS, Oz M. The nonpsychoactive cannabinoid cannabidiol inhibits *Xenopus laevis* oocytes. *J. Pharmacol. Exp. Ther.* 333(2), 547–554 (2010).
32. Garcia JM, Shamliyan TA. Cannabinoids in patients with nausea and vomiting associated with malignancy and its treatments. *Am. J. Med.* 131, 1–5 (2018).

- **Discusses the use of cannabinoids during chemotherapy and highlights the quality of evidence available for various cannabinoids compared with traditional anti-emetic drugs. Also provides the recommended clinical guidelines, which clearly demonstrate the controversial and conflicting nature of cannabinoid use.**

33. Hesketh PJ, Kris MG, Basch E *et al.* Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* 35(28), 3240–3261 (2017).
34. Berger MJ, Ettinger DS, Aston J *et al.* NCCN Guidelines Insights: Antiemesis, Version 2.2017. *J. Natl Compr. Cancer Netw.* 15(7), 883–893 (2017).
35. Jordan K, Roila F, Molassiotis A, Maranzano E, Clark-Snow RA, Feyer P. Antiemetics in children receiving chemotherapy. MASCC/ESMO guideline update 2009. *Support. Care Cancer.* 19(Suppl. 1), 37–42 (2011).
36. Sallan S, Zinberg N, Frei E. Antiemetic effect of Delta-9-tetrahydrocannabinol receiving cancer chemotherapy. *N. Engl. J. Med.* 293(16), 795–797 (1975).
37. Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG. Recent clinical experience with dronabinol. *Pharmacol. Biochem. Behav.* 40(3), 695–700 (1991).
38. Whiting PF, Wolff RF, Deshpande S *et al.* Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 313(24), 2456–2473 (2015).

- **Conducts a systematic review of the benefits and adverse effects of cannabinoids. This assisted with making clear what was already known and where the gaps in the knowledge lie.**

39. Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *Br. Med. J.* 323(7303), 16–21 (2001).
40. Rocha FCM, Stefano SC, Haiek RDC, Oliviera LMQR, Da Silviera DX. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur. J. Cancer Care (Engl).* 17(5), 431–443 (2008).
41. Meiri E, Jhangiani H, Vredenburgh J *et al.* Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr. Med. Res. Opin.* 23(3), 533–543 (2007).
42. Chang A, Shiling D, Stillman R *et al.* Delta-9-tetrahydrocannibinol as an antiemetic in cancer patients receiving high-dose methotrexate. *Ann. Intern. Med.* 91, 819–824 (1979).
43. Chang A, Shiling D, Stillman R *et al.* Prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 47, 1746–1751 (1981).
44. Levitt M, Faiman C, Hawks R, Wilson A. Randomized doubleblind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. *Proc. Am. Soc. Clin. Oncol.* 91 (1984).
45. Duran M, Pérez E, Abanades S *et al.* Preliminary efficacy and safety of an oromucosal standardized cannabis extract in nausea and vomiting. *Br. J. Clin. Pharmacol.* 70(5), 656–663 (2010).

- **Conducts a study on humans using a combination of CBD and THC. To our knowledge, this is the only human study that uses CBD to reduce nausea and vomiting. It therefore provides important information that animal studies cannot do.**

46. Lane M, Vogel C, Ferguson J *et al.* Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J. Pain Symptom Manage.* 6(6), 352–359 (1991).
47. Chan H, Correia J, Macleod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 79(6), 946–952 (1987).
48. Sharkey KA, Darmani NA, Parker LA. Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. *Eur. J. Pharmacol.* 722(1), 134–146 (2014).
49. Raphael Mechoulam, Parker L, Breuer A. Anti-nausea and anti-vomiting activity of cannabidiol compounds. (2002). https://patents.google.com/patent/US8119697B2/en
50. Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport* 13(5), 567–570 (2002).
51. ElSohly M. *Marijuana and the Cannabinoids.* Humana Press, Inc. NJ, USA (2007).
52. Kramer J. Medical marijuana for cancer. *Cancer J. Clin.* 65(2), 109–122 (2015).
53. Seamon MJ, Fass JA, Maniscalco-Feichtl M, Abu-Shraie NA. Medical marijuana and the developing role of the pharmacist. *Am. J. Heal. Pharm.* 64(10), 1037–1044 (2007).
54. Walsh D, Nelson K, Mahmoud F. Established and potential therapeutic applications of cannabinoids in oncology. 11(3), 137–143 (2003).
55. Bhargava H. Potential therapeutic applications of naturally occuring and synthetic cannabinoids. *Gen. Pharmacol.* 9, 195–213 (1978).
56. Simonetto DA, Oxentenko AS, Herman ML, Szostek JH. Cannabinoid hyperemesis: a case series of 98 patients. *Mayo Clin. Proc.* 87(2), 114–119 (2012).
57. Uranga JA, Vera G, Abalo R. Cannabinoid pharmacology and therapy in gut disorders. *Biochem. Pharmacol.* (May), 0–1 (2018).
58. Sutton I, Daeninck P. Cannabinoids in the management of intractable chemotherapy-induced nausea and vomiting and cancer-related pan. *J. Support. Oncol.* 4(10), 531–535 (2006).

59. Ware MA, Wang T, Shapiro S, Collet JP. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *J. Pain* 16(12), 1233–1242 (2015).

60. Musty RE, Rossi R. Effects of smoked cannabis and oral δ 9 -tetrahydrocannabinol on nausea and emesis after cancer chemotherapy: a review of state clinical trials. *J. Cannabis Ther.* 1(1), 29–56 (2001).

61. Söderpalm AHV, Schuster A, De Wit H. Antiemetic efficacy of smoked marijuana: subjective and behavioral effects on nausea induced by syrup of ipecac. *Pharmacol. Biochem. Behav.* 69(3–4), 343–350 (2001).

62. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology. *Life Sci.* 56(23), 2097–2102 (1995).

63. Pertwee RG, Rock EM, Guenther K *et al.* Cannabidiolic acid methyl ester, a stable synthetic analogue of cannabidiolic acid, can suppression of nausea and anxiety in rats. 175(1), 100–112 (2018).

64. BrightfieldGroup, HelloMD. Understanding cannabidiol: summary report. https://daks2k3a4ib2z.cloudfront.net/595e80a3d32ef41bfa200178/59946cd0990f530001342c7a_CBD_-_HelloMD_Brightfield_Study_-_Summary_Report_-_FINAL.pdf

- **This report puts information and statistics into laymen's terms and provides insight into cannabinoid use, according to the public. It illustrated medicinal preferences (cannabinoids preferred over traditional medicine) and reported on the usage rates of cannabinoids.**

65. Carvalho F, Burgeiro A, Garcia R, Moreno A, Carvalho R, Oliveira P. Doxorubicin-induced cardiotoxicity: from bioenergetic failure and cell death to cardiomyopathy. *Med. Res. Rev.* 34(1), 106–135 (2014).

66. Ott M, Gogvadze V, Orrenius S, Zhivotovsky B. Mitochondria, oxidative stress and cell death. *Apoptosis* 12(5), 913–922 (2007).

67. Hao E, Mukhopadhyay P. Cannabidiol protects against doxorubicin-induced cardiomyopathy by modulating mitochondrial function and biogenesis. *Mol. Med.* 21(1), 38–45 (2015).

68. Pan H, Mukhopadhyay P, Rajesh M, Patel V, Mukhopadhyay B, Gao B. Cannabidiol attenuates cisplatin-induced nephrotoxicity by decreasing oxidative/nitrosative stress, inflammation, and cell death. *J. Pharmacol. Exp. Ther.* 328(3), 708–714 (2009).

69. Chen Y, Buck J. Cannabinoids protect cells from oxidative cell death: a receptor-independent mechanism. *J. Pharmacol. Exp. Ther.* 293(3), 807–812 (2000).

70. Pertwee R. The diverse CB1 and CB2 receptor pharmacology of three plant cannainoids: D9-tetrahydrocannabinol, cannabidiol and D9-tetrahydrocannabivarin. *Br. J. Pharmacol.* 153, 199–215 (2008).

71. Marsicano G, Moosmann B, Hermann H, Lutz B, Behl C. Neuroprotective properties of cannabinoids against oxidative stress: role of the cannabinoid receptor CB1. *J. Neurochem.* 80(3), 448–456 (2002).

72. O'Sullivan SE. An update on PPAR activation by cannabinoids. *Br. J. Pharmacol.* 173(12), 1899–1910 (2016).

73. Abalo R, Uranga JA, De Andrés IPR, Girón R, Vera G. May cannabinoids prevent the development of induced diarrhea and intestinal mucositis? Experimental study in the rat. *Neurogastroenterol. Motil.* 29, 1–14 (2017).

74. McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-induced constipation and diarrhea: pathophysiology, current and emerging treatments. *Front. Pharmacol.* 7(November), 1–14 (2016).

75. Hu P, McLachlan EM. Macrophage and lymphocyte invasion of dorsal root ganglia after peripheral nerve lesions in the rat. *Neuroscience* 112(1), 23–38 (2002).

76. King KM, Myers AM, Soroka-Monzo AJ *et al.* Single and combined effects of Δ9-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. *Br. J. Pharmacol.* 174(17), 2832–2841 (2017).

77. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics* 6(4), 713–737 (2009).

78. Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT 1A receptors without diminishing nervous system function or chemotherapy efficacy. *Br. J. Pharmacol.* 171(3), 636–645 (2014).

79. Fearon K, Strasser F, Anker SD *et al.* Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol.* 12(5), 489–495 (2011).

80. Jett J, Stone E, Warren G, Cummings KM. Cannabis use, lung cancer, and related issues. *J. Thorac. Oncol.* 13(4), 480–487 (2018).

81. Strasser F, Luftner D, Possinger K *et al.* Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, Phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabi. *J. Clin. Oncol.* 24(21), 3394–3400 (2006).

82. Kola B, Hubina E, Tucci SA *et al.* Cannabinoids and ghrelin have both central and peripheral metabolic and cardiac effects via AMP-activated protein kinase. *J. Biol. Chem.* 280(26), 25196–25201 (2005).

83. Dariš B, Verboten MT, Knez Ž, Ferk P. Cannabinoids in cancer treatment: therapeutic potential and legislation. *Bosn. J. Basic Med. Sci.* 1–10 (2018).

84. Sarfaraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H. Cannabinoids for cancer treatment: progress and promise. *Cancer Res.* 68(2), 339–342 (2008).

85. Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. *Oncotarget* 5(15), 5852–5872 (2014).

86. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: from the early to the latest concepts. *Best Pract. Res. Clin. Endocrinol. Metab.* 23(1), 1–15 (2009).

87. Choukèr A, Kaufmann I, Kreth S *et al.* Motion sickness, stress and the endocannabinoid system. *PLoS ONE* 5(5), 1–7 (2010).

88. de Jong BC, Prentiss D, McFarland W, Machekano R, Israelski DM. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *J. Acquir. Immune Defic. Syndr.* 38(1), 43–46 (2005).

89. Sidney S. Marijuana use in HIV-positive and AIDS patients: results of an anonymous mail survey. *Cannabis Ther. HIV/AIDS* 67, 35–41 (2001).

90. Jueckstock JK, Kaestner R, Mylonas I. Managing hyperemesis gravidarum: a multimodal challenge. *BMC Med.* 8(46), 1–12 (2010).

91. Westfall R, Janssen P, Lucas P, Capler R. Survey of medicinal cannabis use among childbearing women: patterns of its use in pregnancy and retroactive self-assessment of its efficacy against 'morning sickness'. *Complement. Ther. Clin. Pract.* 12, 27–33 (2006).

92. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. *Am. Fam. Physician.* 76(3), 391–396 (2007).

93. Yamaori S, Okamoto Y, Yamaoto I, Watanabe K. Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drg Metab. Dispos.* 39(11), 2049–2056 (2011).

94. Yamaori S, Koeda K, Kushihara M, Hada Y, Yamamoto I, Watanabe K. Comparison in the *in vitro* inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metab. Pharmacokinet.* 27(3), 294–300 (2012).

95. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 56(8), 1246–1251 (2015).

96. Kosel BW, Aweeka FT, Benowitz NL *et al.* The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *Aids* 16(4), 543–550 (2002).

97. Engels FK, de Jong FA, Sparreboom A *et al.* Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* 12(3), 291–300 (2007).

98. Allen JH, De Moore GM, Heddle R, Twartz JC. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. *Gut* 53(11), 1566–1570 (2004).

99. Donnino MW, Cocchi MN, Miller J, Fisher J. Cannabinoid hyperemesis: a case series. *J. Emerg. Med.* 40(4), e63–e66 (2011).

100. Gunasekaran N, Long LE, Dawson BL *et al.* Reintoxication: the release of fat-stored Δ9- tetrahydrocannabinol (THC) into blood is enhanced by food deprivation or ACTH exposure. *Br. J. Pharmacol.* 158(5), 1330–1337 (2009).

101. IACM. Clinical studies and case reports (2018). www.cannabis-med.org/studies/study.php?search=&sort=medication