Cancer Chemother Pharmacol
DOI 10.1007/s00280-017-3257-1

REVIEW ARTICLE

Concise review of the management of iatrogenic emesis using cannabinoids: emphasis on nabilone for chemotherapy-induced nausea and vomiting

Joseph V. Pergolizzi Jr.[1] · Robert Taylor[1] · Jo Ann LeQuang[1] · Gianpietro Zampogna[1] · Robert B. Raffa[2]

Received: 27 January 2017 / Accepted: 6 February 2017

Abstract Chemotherapy-induced nausea and vomiting (CINV) is a prevalent, distressing, and burdensome side effect of cancer chemotherapy. It is estimated to affect the majority of patients receiving certain anti-cancer drug regimens and can be treatment-limiting, even for life-saving medications. Despite seemingly numerous options, such as antimuscarinic anticholinergics, antihistamines, 5-HT_3 receptor antagonists, dopamine receptor antagonists, and neurokinin-1 receptor antagonists, preventative therapies are often inadequately effective, particularly for "delayed CINV"—leaving an important unmet clinical need. Cannabinoid receptor agonists, by virtue of their unique mechanism of action and efficacy and safety data reported in clinical trials, appear to offer a useful additional option. The mechanistic value of cannabinoids has been well known for many years, but these agents may have been underutilized in the past because of the notoriety and legal status of marijuana. While botanical marijuana contains nearly 500 components, including the psychoactive tetrahydrocannabinol (THC), nabilone is an established, single-entity synthetic cannabinoid receptor agonist that has become the focus of renewed interest. We review the basic pharmacology and clinical trial data of nabilone for use in prophylaxis and treatment of CINV.

Keywords CINV · Emesis · Nabilone · Chemotherapy · Cannabinoids

✉ Jo Ann LeQuang
joann@leqmedical.com

[1] NEMA Research, Inc., 868 106th Ave North, Naples, FL 34108, USA

[2] University of Arizona College of Pharmacy, Tucson, AZ, USA

Introduction: chemotherapy-induced nausea and vomiting (CINV)

CINV is experienced to some degree by about 70–80% of chemotherapy patients. Risk factors vary with the chemotherapeutic drug regimen and individual patient factors [1]. CINV may be under-reported, in that 37% of chemotherapy patients stated that they tried not to complain to healthcare providers about their nausea and vomiting for fear it would show weakness [2]. The majority of oncology patients (63%) said they preferred to limit the number of medications they were taking and said they might have refused antiemetic therapy to reduce polypharmacy [2].

CINV has been categorized as acute, delayed, or anticipatory (when the patient's contemplation of future chemotherapy induces symptoms) [1]. CINV can have a profoundly negative impact on quality of life, can reduce the patient's daily function, and may be extremely distressing to patients and their families. CINV also adversely impacts the healthcare system, in that it may be responsible for incremental costs of $778.58 per patient (from first day of administration through the 5 days following the first cycle of chemotherapy) [3]. Furthermore, CINV can be a treatment-limiting side effect that has the potential to compromise therapeutic goals [4].

In a prospective study of 302 consecutive cancer patients in Europe, CINV was associated with significant emotional distress ($p < 0.05$) and significantly reduced the quality of life ($p < 0.05$) in 54% of the patient population [5]. In a multicenter study of 277 cancer patients undergoing chemotherapy, 39% reported acute nausea, 68% reported delayed nausea, and 12 and 23%, respectively, reported acute or delayed vomiting [6]. About one-third of patients in this study reported that CINV made a substantial negative impact on their daily life.

Published online: 24 February 2017

There are additional health reasons that prompt clinicians to address CINV. CINV may be associated with decreased appetite and reduced caloric intake, which can lead to metabolic disruptions, cachexia, unintended weight loss, anorexia, and dehydration. CINV may decrease a patient's functional capacity and impair his or her ability to attend to basic self-care. For some patients, CINV may be treatment-limiting [7].

Like other forms of nausea and vomiting, CINV is multimechanistic and complex. Nausea and vomiting are regulated in large part by the brain in the area postrema to the nucleus tractus solitarius (NTS) [8]. The NTS oversees functions relating to swallowing, gastric sensation, laryngeal and pharyngeal sensation, baroreceptor function, and respiration. Vagal afferent inputs from the GI tract relating to stomach contents and gastric tone along with neurotransmissions related to emetic signals deliver information to the NTS and from there to a central pattern generator (CPG), which coordinates the emetic sequence and involves the ventral medulla and the hypothalamus. The often-described "vomiting center" of the brain is an oversimplification. Rather, vomiting is regulated by a disperse organization of neurons throughout the medulla and regulated by the CPG [8]. The neurotransmitters implicated in this process include serotonin (5-hydroxytryptamine or 5-HT), dopamine, neurokinin-1 (NK1), and substance P [8]. Antiemetic agents may disrupt this pattern at any of several points. Some agents block receptors in the peripheral ends of vagal afferents, which reduces the brain's ability to perceive and respond to emetic stimuli [8]. Neurokinin-1 receptor (NK1R) antagonists can prevent emesis when they affect the dorsal vagal complex and inhibit vagal motor neurons and, in that way, prevent the necessary fundic relaxation which precedes nausea and emesis [9]. Serotonin and dopamine are able to transmit emesis-related stimuli from the periphery to the brain, and 5-HT receptors are known to play a major role in acute CINV [10]. Chemotherapeutic regimens irritate the GI tract and may damage GI mucosa, triggering the release of specific neurotransmitters such as dopamine, 5-HT, and substance P [11, 12]. These neurotransmitters deliver sensory inputs which are integrated in the dorsal vagal complex, and may activate abdominal muscles, the diaphragm, the stomach, and the esophagus. Thus, chemotherapeutic drugs may activate the emetic pathways via neurotransmitters and neuro-anatomical centers such as the brainstem, the area in the brain postrema near the floor of the fourth ventricle, and by way of vagal nerve afferents that extend from the GI tract into the emetic center to or near the area postrema [8]. Vomiting may occur due to interaction among neurotransmitters and mediators (acetylcholine, dopamine, 5-HT, substance P, prostaglandin, leukotrienes, and/or histamines) [4, 11, 13, 14].

While the mechanisms behind emesis are relatively well elucidated, the mechanisms of nausea are less clearly known. Chemotherapy-induced nausea (CIN) and chemotherapy-induced vomiting (CIV) may occur independently, and pharmacological therapies that control CIV may not improve symptoms of CIN. Compounding this challenge is the fact that nausea is a subjective experience and much more difficult to quantify than discrete emetic events. The neural pathways underlying CIN and CIV may actually be to some degree separate and distinct [15].

Risk factors for postoperative nausea and vomiting (PONV) have been described extensively in the literature [16–21] and have been used to stratify patients for risk of CINV [22]. Female sex, nonsmoking status, prior history of PONV, and the type of anesthesia used in the surgery are associated with an increased risk for PONV [23]. The type of chemotherapy plays a role in CINV risk, in that certain chemotherapeutic regimens are considered more emetogenic than are other regimens. Risk factors for CINV may be further related to the type of CINV involved.

The literature describes three main types of CINV: acute, delayed, and anticipatory (when the patient's contemplation of impending chemotherapy induces symptoms). For example, "acute CINV" (nausea and vomiting that occurs soon after the administration of the chemotherapy, usually defined as from 1 to 6 h) is affected by the patient's age, sex, environment in which the chemotherapy is administered, history of chronic alcoholism (which reduces the risk of acute emesis), history of motion sickness, and history of nausea and vomiting due to other causes [24]. Acute CINV typically resolves within 24 h [25]. "Delayed CINV," generally defined as nausea and vomiting that occurs 16 to 24 h after chemotherapy [24], has been suggested to be the sequelae of acute CINV, emphasizing the importance of preventing acute symptoms [26]. Delayed CINV may occur in up to 58% of patients undergoing moderately or highly emetogenic chemotherapy [3] and can be particularly challenging to treat [25]. Delayed CINV occurs frequently with chemotherapeutic regimens involving cisplatin, carboplatin, cyclophosphamide, or doxorubicin [27]. It is hypothesized that acute CINV is mediated primarily by 5-HT pathways, whereas delayed CINV is mediated by substance P acting at neurokinin-1 (NK1) receptors [28]. "Anticipatory CINV" is a conditioned response in patients who have experienced nausea and vomiting as a result of prior episodes of chemotherapy. These patients may develop symptoms prior to treatment or when contemplating treatment [29].

In addition to these types of CINV, it is also helpful to recognize "breakthrough CINV," a sudden exacerbation of nausea and vomiting against a background of nausea and vomiting. Not all CINV responds to treatment, and

refractory CINV can pose a major challenge to clinical management of the chemotherapy patient [30, 31].

The complexity of nausea and vomiting offers multiple drug targets, which has led to a variety of classes of pharmacological therapy. These include muscarinic cholinergic receptor agonists (scopolamine), histamine receptor antagonists (diphenhydramine, meclizine), dopamine receptor antagonist phenothiazines (for instance, chlorpromazine, prochlorperazine, promethazine), benzamides (metoclopramide, trimethobenzamide), 5-HT receptor antagonists (aprepitant), opioid receptor antagonists, and glucocorticoids [23]. In general, the pharmacological approaches for CINV prophylaxis are the same as those for PONV and CINV. Multimodal antiemetic therapy involving a combination of two or more agents with different mechanisms of action has also been advocated, for example, dexamethasone plus aprepitant [7].

Despite the multiplicity of pharmacotherapeutic options, antiemetic treatment is often inadequate. For example, in a clinical study that evaluated the efficacy of palonosetron and dexamethasone for prevention of CINV with cisplatin therapy, approximately 50% of patients reported emesis [32]. These results align with other clinical trials of antiemetics [33, 34].

Evidence-guided CINV prophylaxis is suboptimal in the US [35] and Europe [36].

Clinical treatment of CINV

There are several evidence-based guidelines for CINV prevention [26, 27, 29, 37–39]. These guidelines generally recommend the use of a selective serotonin receptor antagonist (5-HT3RA) plus a corticosteroid or the same therapy with the addition of neurokinin-1-receptor antagonist (NK1RA) for those receiving moderately to highly emetogenic chemotherapy, respectively [25, 39]. Novel antiemetics (rolapitant, a long-acting NK1-RA) and a fixed-dose combination product of netupitant and palonosetron (NEPA) are being evaluated and show promise [25]. Given the lack of absolute effectiveness by any one agent (particularly for the management of delayed CINV), cannabinoids are emerging as a "new" treatment option. To be sure, cannabinoids are actually older, established treatments. The Food and Drug Administration (FDA) in the US approved a cannabinoid product for antiemesis in 1985 (Marinol®) and nabilone (Cesamet®), which was approved in 1985 but not marketed in the US until 2006.

Cannabinoids

Cannabinoids can be categorized into phytocannabinoids (plant-based), their endogenous counterparts (endocannabinoids), and synthetic products. All have affinity for 7-transmembrane G-protein-coupled membrane-bound receptors. Activation of these receptors is transduced into inhibition of adenylyl cyclase and regulation of transcription factors [40].

The psychoactive properties of marijuana and the potential for misuse have impeded research into the bioactive components of these plants (*Cannabis indica* L., *Cannabis ruderalis* L., and *Cannabis sativa* L.). The value of cannabis as a potential drug source may have been discounted by pharmaceutical companies for fear that the stigma of marijuana and its abuse potential might hinder development of the drug class. Recent changes in regulations and the more favorable public perception of marijuana have focused new light on synthetic and botanical cannabinoids, in particular because of their effective analgesic and antiemetic properties.

The two best-known and most important cannabinoid receptors are CB1 and CB2 [41]. A third type (GPR55 or "type 3") has been postulated [42]. CB1 and CB2 are part of a superfamily of receptors that couple to guanine nucleotide-binding proteins that act as heptahelical receptors (threading seven times through cell membranes) [43]. While it was once thought that CB1 receptors were located mainly in the brain and CB2 receptors in the periphery and immune system, CB1 receptors have been discovered in peripheral tissues of the cardiovascular, reproductive, and gastrointestinal tracts and CB2 receptors have been found in the central nervous system [44]. CB2 receptors are associated mainly with the immune system and hematopoietic cells [45]. CB2 is present in the neuronal system and it appears that expressed in neurons, CB2 effectively mimics the actions of CB1 and thus neuronal CB2 plays a role in conventional neuronal endocannabinoid signaling processes [46]. Research into these receptors, particularly the less well-elucidated CB2 receptors, is ongoing [43, 47]. Synthetic cannabinoids can be designed with varying, and relatively selective, affinities for CB1 and/or CB2 receptors.

The main endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), both of which act on CB1 and CB2 receptors. AEA and 2-AG are produced in response to stress, injury, or ischemia [48]. Activation of CB1 by the endogenous ligands modulates neurotransmission, and thereby reduce pain and are thought to modulate cerebral blood flow [49]. The principal psychoactive constituents of the phytocannabinoid marijuana are the phytocannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) [50].

Dronabinol and nabilone were approved by the FDA for the safe and effective treatment of chemotherapy-induced nausea and vomiting in 1985, yet they may not be featured prominently in guidelines or widely used in clinical practice. Current antiemetic guidelines for chemotherapy

(Multinational Association of Supportive Care in Cancer, the European Society for Medical Oncology, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network) endorse triple therapy for patients receiving cisplatin-based chemotherapeutic regimens; they do not emphasize dronabinol or nabilone [38, 51–53]. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Antiemesis specifically do not include cannabinoids out of both "legal and medical concerns," although some patients may prefer marijuana over other agents to manage CINV symptoms [54]. The omission of cannabinoids does not necessarily reflect a lack of evidence. Indeed, the use of cannabinoids for the treatment of CINV is approved by the FDA [55], although the efficacy and safety of botanical marijuana have not been as thoroughly studied as has synthetic cannabinoids [56].

Botanical marijuana

Botanical marijuana is not approved by the FDA for the treatment of CINV. High-quality botanical research materials may be unavailable or available in limited quantities, hampering investigation. Indeed, the number of investigators working in this area remains comparatively small [57].

However, public perception may be driving change in considering marijuana's therapeutic potentials. In a process described as "reverse drug discovery," anecdotal reports of medical marijuana, particularly smoking it for relief of CINV, were evaluated by scientists who recognized an unmet need for more effective and better tolerated CINV antiemetics [57]. Botanical marijuana presents the opportunity to breed plants with specific concentrations of the desired phytocannabinoids. While there are numerous potential uses for cannabinoids (ranging from treatment of neuropathy, chronic nociceptive pain, spasticity, seizures, and others), its role in CINV prophylaxis may be particularly important owing to the prevalence of cancer, the frequency of CINV, and the unmet medical need to safely and effective treat CINV.Several studies have explored botanical marijuana (smoked or ingested) as CINV prophylaxis. Chang and colleagues reported in 1979 in a placebo-controlled randomized clinical trial that smoked marijuana plus oral THC reduced CINV vs. placebo in patients undergoing high-dose methotrexate therapy [58]; however, a 1981 study found no improvement with smoked marijuana and oral THC over placebo for patients undergoing doxorubicin and cyclophosphamide therapy [59]. Other studies of botanical marijuana smoked for CINV reported it to be effective [50].

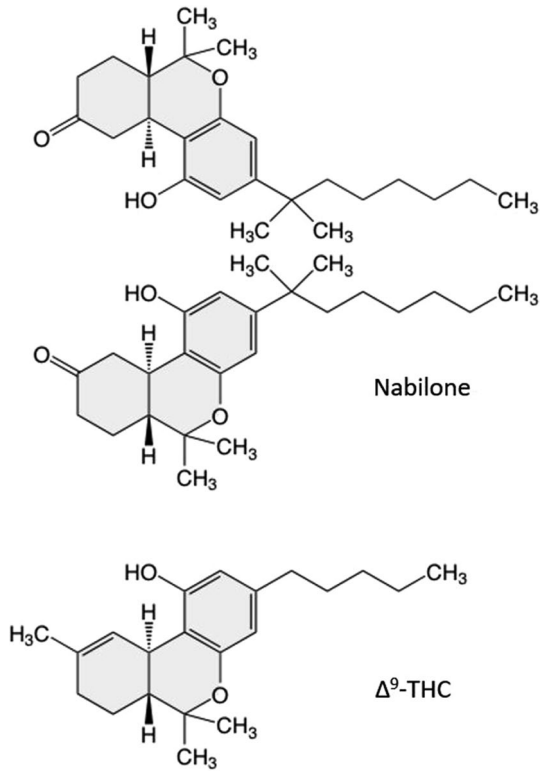

Fig. 1 The chemical structure of the enantiomers of nabilone and Δ^9-THC

Table 1 Overview of nabilone metabolism [61]

Nabilone (CESAMET™)	
Oral dosing	1–2 mg 1–3 h before chemotherapy, and 2 times per day for up to 48 h afterwards
Source	Synthetic Δ^9-THC analog
Formulation	Crystalline powder capsule
Onset of action	60–90 min
Peak plasma concentrations (T_{max})	2 h
Duration of action	8–12 h
Metabolites	Two active metabolites
Clearance	Major excretory pathway is the biliary system

Nabilone pharmacology

Nabilone is a CB1 receptor agonist [60]. It is a synthetic analog of Δ^9-THC (Fig. 1). Oral dosing information is shown in Table 1 [61]. Its antiemetic effect derives from its ability to activate CB receptors in the brain that mediate nausea and vomiting [8, 62].

Clinical efficacy

As nabilone is an older drug, the earliest studies of nabilone's safety, efficacy, and tolerability date back to the 1970s. Many of these early studies have been summarized in two reviews on cannabinoids for CINV prophylaxis [62, 63]. A short overview of the main older studies is shown in Table 2. A recent systematic review and meta-analysis of cannabinoid studies reported on 28 studies ($n = 1772$) that evaluated cannabinoids for CINV prophylaxis, of which 14 assessed nabilone (the others evaluated dronabinol, nabiximol, levonantradol, and THC). All studies suggested that cannabinoids conferred a benefit in CINV prophylaxis compared to either placebo or active comparator drugs, but this difference did not achieve statistical significance in all studies. The average number of patients showing complete response (no nausea or vomiting) was greater with cannabinoids than with placebo [odds ratio (OR) 3.82, 95% confidence interval (CI), range 1.55–9.42, $n = 3$ trials] [64].

One of the earliest nabilone studies was by Herman et al. who tested nabilone's ability to relieve CINV in patients who failed treatment with prochlorperazine [65]. Chemotherapy patients ($n = 13$) were given 1 or 2 mg nabilone every 8 h, a regimen that reduced nausea and vomiting in 77% of patients. About half of the patients reported an "excellent response" or complete resolution of CINV [65]. In a subsequent study by Herman and colleagues, a double-blind comparative crossover of 2 mg nabilone vs. 10 mg prochlorperazine ($n = 113$), found patients had more complete relief of CINV with nabilone than placebo (8 vs. 0%) and greater partial response (72% vs. 32%) [66]. Nabilone's reduction in vomiting vs. prochlorperazine persisted over all five test days.

In another early study published in 1981, Einhorn et al. examined the efficacy of 2 mg nabilone or 10 mg prochlorperazine given every 6 h to 100 cancer patients who received cisplatin-based chemotherapy in a double-blind, randomized crossover trial [67]. Like previous studies, nabilone significantly reduced the severity (based on a 1 to 3 scale, 3 being severe) and the duration of nausea and frequency of vomiting (vomiting episodes were reduced by about 33% on all days). Overall, more patients (75 vs. 17%) chose nabilone over prochlorperazine [67]. In a double-blind crossover study, 34 patients receiving cyclophosphamide, adriamycin, and etoposide chemotherapy for lung cancer were treated with nabilone or prochlorperazine [68]. Treatment consisted of 2 mg twice per day nabilone or 10 mg three times per day prochlorperazine. There was no difference in vomiting episodes on day 1 of treatment; however, there were significant differences on day 2 (15 vs. 43%) and day 3 (0 vs. 27%) for nabilone vs. prochlorperazine, respectively. Patient preference favored nabilone over prochlorperazine during the chemotherapeutic regimen [68].

Nabilone has also been compared to other antiemetics. For example, in a double-blind randomized study, Crawford and Buckman compared 1 mg nabilone every 8 h to 1 mg/kg metoclopramide every 3 h in 32 patients who were undergoing cisplatin treatment for ovarian or germ cell carcinoma [69]. The outcome measures, which included number of vomiting events and vomit volume, failed to reach statistical difference (intra- or inter-patient comparisons). However, the number of cycles with fewer than three associated vomiting episodes was significantly less in the metoclopramide-treated group [69].

In a randomized, open-label, crossover study comparing nabilone plus prochlorperazine to metoclopramide plus dexamethasone in 80 patients, there was no statistical difference between the two groups either in the number of vomiting episodes or in patient preference (31 for nabilone plus prochlorperazine vs. 26 for metoclopramide plus dexamethasone) [70]. In a study analyzing 20 testicular cancer patients undergoing low-dose cisplatin chemotherapy, patients treated with 2×2 mg/day nabilone before chemotherapy had statistically fewer vomiting episodes when compared to 3×150 mg/day alizapride [71]. Significantly fewer vomiting episodes were also noted during a prospective, double-blind randomized study comparing nabilone to domperidone in 38 patients undergoing two cycles of highly emetogenic chemotherapy (cisplatin, adriamycin, ifosfamide) [72].

A retrospective analysis of the use of various cannabinoid products for CINV prophylaxis analyzed 30 papers and conducted five meta-analyses: dronabinol vs. placebo ($n = 185$), dronabinol vs. neuroleptics ($n = 325$), nabilone vs. neuroleptics ($n = 277$), levonantradol vs. neuroleptics ($n = 194$), and patient preference for cannabinoids or other drugs ($n = 1138$) [73]. The meta-analyses demonstrated that cannabinoids were more effective than placebo or other agents in preventing CINV. A quantitative systematic review (30 studies, $n = 1366$) found cannabinoids were more effective CINV antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride, although side effects were more frequent with cannabinoids than with the other agents [63]. Nabilone has been shown to be superior to certain neuroleptics for delaying emesis, but not better than serotonin receptor antagonists [74].

A study of 56 patients receiving radiotherapy treatments for head and neck cancers found that nabilone administered before, during, and 4 weeks following radiation therapy did not relieve symptoms of nausea better than placebo [75]; these results do not align with results found in many other studies that found nabilone was effective in reducing CINV.

Table 2 Summary of nabilone clinical trials for CINV

Year	First author	Study type	Treatment (T) vs. control (C)	*n*	Outcome (treatment vs. control)	Adverse events
1977	Herman	Open	1 or 2 mg nabilone every 8 h	13	Vomiting ↓ in 77% of patients	↑Sedation, dry mouth, dizziness, loss of coordination (mild or moderate) in nabilone arm
1979	Herman	R DB CS	2 mg nabilone every 8 h 10 mg prochlorperazine	113	Vomiting episodes and nausea ↓ in nabilone arm Patients preferred nabilone	Similar types of side effects in both groups, more frequent in nabilone arm
1981	Einhorn	R DB CS	2 mg nabilone every 6 h (T) 10 mg prochlorperazine (C)	80	Vomiting episodes ↓ 33% Duration and severity of nausea ↓ Patients preferred nabilone	Drowsiness, hypotension, "high" ↑ in nabilone arm
1983	Ahmedzai	R DB CS	2 mg nabilone BID (T) 10 mg prochlorperazine 3× per day (C)	34	Vomiting episodes ↓ day 2/3 Patients preferred nabilone ($p < 0.005$)	Similar types of side effects in both groups, more frequent in nabilone arm (common effects: drowsiness, postural dizziness, light-headedness)
1985	Niiranen and Mattson	R DB CS	1 mg nabilone, night before and 1 h before chemotherapy, every 12 h 7.5 mg prochlorperazine, night before and 1 h before chemotherapy, every 12 h	24	Vomiting episodes reduced ($p < 0.05$) No difference between severity of nausea, appetite, or investigator's global assessment on efficacy Patients preferred nabilone ($p < 0.05$)	55% experienced side effects with nabilone (vertigo, decreased coordination, hallucinations) Drop in blood pressure in nabilone arm (not clinically significant)
1987	Niiranen and Mattson	R DB CS	2 mg nabilone BID + 8 mg dexamethasone initial dose 2 mg nabilone BID	40	Vomiting episodes ↓ No difference between severity of nausea or appetite 2/3 of patients preferred combination treatment	Common side effects: vertigo drop in blood pressure
1986	Crawford	R DB CS	Oral nabilone 1 mg every 8 h (T) IV metoclopramide 1 mg/kg every 3 h (C)	32	No difference between: Vomiting episodes Mean vomit volume No. of patients with <3 vomiting episodes per chemo cycle Patient preference < patients <3 episodes during 4 cycles of chemo administered (metoclopramide arm)	Nabilone > drowsiness Metoclopramide > diarrhea
1988	Cunning-ham	R Open CS	Nabilone 2 mg and oral prochlorperazine 5 mg every 12 h Metoclopramide 2 mg/kg loading dose intravenously (IV) then 3 mg/kg as IV infusion over 8 h and dexamethasone 20 mg IV over 3 to 5 min at the time of chemotherapy	80	Complete control of nausea and vomiting in patients (32% vs. 19%, metoclopramide vs. nabilone arm) For 70 crossover patients, emesis on a linear analog scale significantly favored metoclopramide and dexamethasone ($p = 0.02$) No difference in patient preference	Nabilone > dizziness ($p < 0.001$), sedation ($p < 0.0$), dryness of the mouth ($p < 0.001$) and dysphoria ($p < 0.05$)

Table 2 (continued)

Year	First author	Study type	Treatment (T) vs. control (C)	*n*	Outcome (treatment vs. control)	Adverse events
1986	Nierdele	R DB CS	Nabilone (2 × 2 mg/day) (T) Alizapride (3 × 150 mg/day) (C) Both treatments prior to chemotherapy	20	↓ episodes of emesis (T) ($p < 0.01$) More patients on nabilone experienced complete relief ($p < 0.01$) Nabilone shortened the duration of nausea ($p < 0.01$)	Nabilone group had more AE
1986	Pomeroy	R DB CS	1 mg nabilone the night before chemotherapy and 8-hourly on each chemotherapy day for two consecutive cycles of treatment 20 mg domperidone (administration same as nabilone)	38	Nabilone < domperidone: vomiting episodes Nausea and food intake no difference	Drowsiness and dry mouth were reported frequently with both N and D. Dizziness and postural hypotension were more common in the N arm. Other central nervous system effects, including euphoria, confusion, difficulty in talking, and a drunk feeling, were only described with N
2006	Valeant Pharmaceuticals	R DB CS	Cesamet 2 mg BID, 1–3 h before initiation of chemotherapy and in the evening Placebo	6 studies ($n = 129$)	Reduction in vomit frequency ($p < 0.01$) Reduction in nausea severity ($p < 0.001$) Reduction in food intake ($p < 0.001$)	50.1–70% drowsiness, vertigo 20.1–50% dry mouth 10–20% ataxia, decreased concentration, vision disturbance, asthenia headache, sleep disturbance <10% depression, depersonalization
2006	Valeant Pharmaceuticals	R DB CS	Cesamet 2 mg BID Prochlorperazine 10 mg BID	Two studies ($n = 75$)	Reduction in vomit frequency ($p < 0.007$) Reduction in nausea severity ($p < 0.007$) Reduction in food intake ($p < 0.012$)	Vertigo (52 vs. 3%), drowsiness (52 vs. 5%), and dry mouth (36 vs. 2%) occurred more than placebo Vertigo (66 vs. 47%), drowsiness (59 vs. 23%), euphoria (38 vs. 5%), and dry mouth (22 vs. 5%) occurred more with nabilone than prochlorperazine
2006	Valeant Pharmaceuticals	R DB CS	Cesamet 2 mg BID every 6 h as needed Prochlorperazine 10 mg every 6 h as needed	2 studies ($n = 112$)	Reduction in vomit frequency ($p < 0.001$) Reduction in nausea severity ($p < 0.001$) Reduction in food intake ($p < 0.001$)	

AE adverse event(s), *BID* twice daily, *CS* crossover study, *D* domperidone, *DB* double blind, *mg* milligram, *N* nabilone, *R* randomized

Table 3 Summary of safety concerns for nabilone [73]

Contraindications	In patients with a history of hypersensitivity to any cannabinoid
Precautions	Cannabinoids should not be taken with alcohol, sedatives, hypnotics, or other psychotomimetic substances
Side effects	Drowsiness Vertigo Dry mouth Euphoria Ataxia Headache Concentration difficulties

The commercial product Cesamet® (nabilone) was approved by the FDA in 2006 for CINV in cases where other drugs were unable to control such symptoms. Eleven pivotal efficacy trials have been reported, each of which was a double-blind, randomized, crossover study against placebo or prochlorperazine as reference. These trials are described below.

Placebo-controlled fixed-dose trials

Six double-blind randomized crossover studies tested the efficacy of a fixed dose of nabilone vs. placebo in patients ($n=129$) undergoing two cycles of chemotherapy [73]. 2 mg of nabilone was given twice per day, usually 1–3 h before the initiation of chemotherapy plus in the evening. Chemotherapy treatment lasted 1–5 days and the two cycles were separated by 3–6 weeks. The endpoints assessed included number of vomits, nausea severity (0 = none, 1 = mild, 2 = moderate, 3 = severe), food intake/post-therapeutic appetite (0 = none, 1 = less than usual, 2 = usual amount or average, 3 = more than usual), Investigators' Global Impressions of Efficacy (1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor), and Investigators' Global Impressions of Safety (based on the frequency of adverse experiences). Combination of all six trials significantly favored nabilone over placebo for reduction in the number of vomits, reduction in the severity of nausea, and improvement in appetite (food intake) ($p \leq 0.01$). In addition, Investigators' Global Impressions of Efficacy significantly favored nabilone ($p \leq 0.01$): 77% of evaluable patients preferred nabilone vs. 12% placebo vs. 12% no preference. Overall, these studies support an antiemetic efficacy greater than placebo against CINV.

Active-controlled fixed-dose trials

Three double-blind randomized crossover studies tested the efficacy of a fixed dose of nabilone vs. prochlorperazine in patients ($n=75$) undergoing two cycles of chemotherapy [73]. The patients received 2 mg of nabilone twice per day or 10 mg of prochlorperazine twice per day. The dosing schedule, chemotherapy duration, and crossovers time were similar to the placebo-controlled trials described above. Combined analysis of the three trials resulted in a statistical advantage for nabilone over prochlorperazine in the overall reduction in the number of vomits, reduction in the severity of nausea, and improvement in appetite (food intake) ($p \leq 0.012$). Investigator's Global Impressions of Efficacy and rating on safety significantly favored nabilone over prochlorperazine ($p \leq 0.012$ and $p=0.003$, respectively). Overall, 73.3% of the patients preferred nabilone, whereas only 20% preferred prochlorperazine even though the latter experienced significantly fewer side effects.

Active-controlled flexible-dose trials

Two double-blind randomized crossover studies tested the efficacy of a flexible dose of nabilone vs. prochlorperazine in patients ($n=112$) undergoing two cycles of chemotherapy [73]. The dosing regimen consisted of 2 mg of nabilone every 6 h or 10 mg of prochlorperazine every 6 h. Treatment times during the day and chemotherapy duration were similar to the studies described above, except that the chemotherapy cycles were 2–4 weeks apart. Frequency of vomiting was reduced by 42%, along with reduced nausea in the nabilone group compared to placebo. In addition, appetite was better in the nabilone group ($p<0.001$).

Nabilone safety

In many of the clinical trials, nabilone treatment or pretreatment was associated with a higher incidence of adverse events than were the placebo group. Common side effects included drowsiness, dizziness, dry mouth, and euphoria. These were mostly considered mild or moderate, and in a majority of the studies, these effects did not prevent patients from requesting nabilone treatment (see Table 3). In the 11 trials conducted for Cesamet™, drowsiness and vertigo were experienced in about 50–70% of the patients taking 2 mg/day dose and increased to >70% in patients taking 4 mg/day. Dry mouth occurred in approximately 20–50% of the patients. Other adverse effects (including ataxia, decreased concentration, vision disturbance,

asthenia headache, and sleep disturbance) occurred in about 10–20% of the patients [73].

Conclusion

The prevalence of CINV among chemotherapy patients and the burden it represents to patients and their families underscore an important clinical need. While numerous antiemetic therapies exist, there is no therapy that is completely effective in all patients. Thus, clinicians require a robust armamentarium of agents to use, rotate, or combine to prevent CINV and the even-more challenging delayed CINV. The role of cannabinoids in the treatment of CINV is not new and has been studied since the 1970s, although research has been hampered by the negative connotations of marijuana. Cannabinoids have a mechanism of action that is different from the conventional pharmacologic classes of antiemetics in use such as the antimuscarinic anticholinergics, antihistamines, 5-HT_3 receptor antagonists, dopamine receptor antagonists, or neurokinin-1 receptor antagonists. Cannabinoid receptor agonists, by virtue of their unique mechanism of action and published efficacy and safety data from clinical trials, appear to represent a useful additional option for consideration in the management of emesis. These "new old" drugs, in particular nabilone, are worthy of further consideration as important alternatives in the management of CINV. Synthetic cannabinoids can be designed with varying, and relatively selective, affinities for CB1 and/or CB2 receptors.

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