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Cannabinoids in the Treatment of Chemotherapy-Induced Nausea and Vomiting: Beyond Prevention of Acute Emesis

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Abstract Chemotherapy-induced nausea and vomiting (CINV) remains a significant problem in the care of cancer patients. Although the use of serotonin (5-HT_3) receptor antagonists, as well as neurokinin-1 inhibitors, has reduced rates of acute emesis, many patients still experience acute vomiting; moreover, these agents have reduced efficacy in preventing nausea, delayed CINV, and breakthrough CINV. Nausea, in particular, continues to have a major—and often overlooked—impact on patients' quality of life. Optimizing the treatment for CINV likely will involve combinations of agents that inhibit the numerous neurotransmitter systems involved in nausea and vomiting reflexes. Cannabinoids are active in many of these systems, and two oral formulations, dronabinol (Marinol) and nabilone (Cesamet), are approved by the US Food and Drug Administration for use in CINV refractory to conventional antiemetic therapy. Agents in this class have shown superiority to dopamine receptor antagonists in preventing CINV, and there is some evidence that the combination of a dopamine antagonist and cannabinoid is superior to either alone and is particularly effective in preventing nausea. The presence of side effects from the cannabinoids may have slowed their adoption into clinical practice, but in a number of comparative clinical trials, patients have expressed a clear preference for the cannabinoid, choosing its efficacy over any undesired effects. Improvement in antiemetic therapy across the entire spectrum of CINV will involve the use of agents with different mechanisms of action in concurrent or sequential combinations, and the best such combinations should be identified. In this effort, the utility of the cannabinoids should not be overlooked.

Despite therapeutic advances over the past 20 years, chemotherapy-induced nausea and vomiting (CINV) remains an important cause of morbidity in patients with active cancer and continues to influence the treatment decisions of oncologists and patients. When poorly controlled, CINV can influence the patient's willingness to accept scheduled chemotherapy or the oncologist's treatment plan, thereby compromising tumor control and patient survival. Even when patients persevere through treatment, CINV can negatively impact quality of life (QOL) and result in multiple morbidities that complicate management and increase treatment costs, including anorexia and nutritional deficits. These continuing challenges are prompting investigations into new classes of medications for the control of CINV as well as a re-examination of how existing agents may be best combined to optimize treatment outcomes.

CINV in the 5-HT_3 Antagonist Era: Continuing Challenges

CINV is commonly categorized as *anticipatory* (before the next cycle of chemotherapy), *acute* (occurring within minutes to hours after the start of treatment), *delayed* (> 24 hours after the start of treatment), *breakthrough* (occurring despite prophylaxis), and *refractory* (recurring in subsequent cycles; Table 1).[1] The introduction of the serotonin (5-hydroxytryptamine$_3$; 5-HT_3)-receptor antagonists represented a significant advance in the prevention of acute CINV, opening the door to the administration of more aggressive and effective chemotherapy regimens. As a class, these agents have been effective in controlling acute emesis and have a highly favorable side-effect profile. However, as our experience with these agents has matured, we have come to recognize that they have a narrower spectrum of activity than was initially anticipated.[2] Their efficacy has not been demonstrated for anticipatory CINV—except when they control acute CINV in previous courses of chemotherapy—and their value as rescue therapy has been disappointing.[3] Even when used

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Table 1

Types of Chemotherapy-Induced Nausea and Vomiting

TYPE	CHARACTERISTICS
Anticipatory	• Occurs before next chemotherapy visit • Nausea more common than vomiting
Acute	• Usually occurs within minutes to hours after chemotherapy administration • Commonly resolves within first 24 hours • Intensity peaks after 5–6 hours
Delayed	• Develops > 24 hours after chemotherapy administration • Emesis associated with cisplatin peaks at 48–72 hours; can last 6–7 days
Breakthrough	• Occurs despite prophylactic treatment and/or requires rescue therapy • Can be acute or delayed
Refractory	• Occurs during chemotherapy cycles after prophylaxis and/or rescue therapy have failed in earlier cycles

for the prevention of acute CINV due to highly emetogenic chemotherapy (HEC), optimal efficacy is achieved only with the concomitant use of dexamethasone and other adjuvant medications.[4] Moreover, in many studies of CINV, efficacy of the 5-HT_3 antagonists has been determined from the first or second course of therapy; reports are now emerging that this efficacy, even in combination with a corticosteroid, may decline over successive treatment courses.[5,6]

Not withstanding these shortcomings, the greatest disappointment with the first-generation 5-HT_3 antagonists (eg, ondansetron, granisetron [Kytril], dolasetron [Anzemet], tropisetron) has perhaps been their limited efficacy in controlling delayed CINV. An early trial reported by Olver et al[7] showed no difference between treatment with placebo and ondansetron with regard to delayed CINV in patients receiving cisplatin-based therapy; delayed nausea and delayed emesis occurred in 73% and 67% of placebo patients, respectively, and in 73% and 68% of patients receiving ondansetron, respectively. The addition of dexamethasone to ondansetron somewhat improved control, with delayed nausea and delayed emesis occurring in 55% and 51% of patients, respectively. In a more recent study, Grunberg et al[8] reported that among patients treated with a 5-HT_3 antagonist and dexamethasone, delayed vomiting occurred in approximately 30% of patients receiving moderately emetogenic chemotherapy (MEC) and 50% of the patients receiving HEC; delayed nausea occurred in approximately 50% and 60%, respectively. Further reports have questioned the efficacy and cost-effectiveness of continuing 5-HT_3 antagonist therapy beyond the initial 24 hours of chemotherapy.[9]

Palonosetron (Aloxi), considered by some to be a second-generation 5-HT_3 antagonist due to its higher receptor-binding affinity and longer elimination half-life, was superior to dolasetron in controlling delayed CINV in patients receiving MEC.[10] A complete response (no emesis and no use of rescue medication) was seen in 63% and 53% of patients during the acute period and 54% and 39% during the delayed period for palonosetron (0.25 mg) and dolasetron (100 mg), respectively. For patients receiving HEC, the comparative advantage of palonosetron was diminished, as it fared no better than ondansetron plus dexamethasone for acute or delayed CINV.[11] Even with the addition of the neurokinin-1 (NK_1; substance P) receptor antagonist aprepitant (Emend) to a 5-HT_3 antagonist (ondansetron) and dexamethasone, CINV remains a problem. In a trial of patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy, a number of patients receiving the combination regimen with aprepitant failed to achieve a complete response for acute (17%) and delayed (32%) CINV, and 47% of the aprepitant-treated patients experienced delayed nausea.[12]

Nausea: Overlooked and Undertreated

Despite improvements in emesis control, the 5-HT_3 antagonists have not decidedly improved control of nausea.[13] Following treatment with these agents, the difference in the CINV experienced by patients receiving HEC and MEC is typically defined more by the occurrence of emesis than nausea, the prevalence of the latter being more comparable between chemotherapy groups. First-line preventive regimens (eg, 5-HT_3 antagonists + aprepitant + dexamethasone alone or in combination) have often been disappointing in controlling nausea, particularly delayed nausea, which occurs twice as frequently as acute nausea. Although the addition of aprepitant and palonosetron to the treatment regimen has improved the control of emesis, the results for control of nausea remain less favorable. Unfortunately, the challenges of controlling chemotherapy-induced nausea are even greater than those for chemotherapy-induced emesis—nausea is less well understood at the neurochemical level, the paucity of animal models poses greater difficulties to basic research, and the results of treatment generally have been less successful.[4] To meet this challenge, novel adjuvant medications, such as the cannabinoids, likely will need to be incorporated into existing treatment regimens, with the outcomes then compared against the current standards.

It is not uncommon for patients receiving 5-HT_3 antagonists to experience significant nausea, even as they enjoy good control against emesis. In a study of patients receiving adjuvant therapy for breast cancer who were treated with a 5-HT_3 antagonist plus dexamethasone, Lee et al[14] found acute nausea in 46.7% of patents and delayed nausea in 81.5% after the first cycle of chemotherapy and in 45.0% and 73.9%, respectively, after the second cycle. Another study[15] showed that despite 5-HT_3 antagonist/dexamethasone treatment, acute nausea occurred in 32% and delayed nausea occurred in 59% of patients receiving platinum- (50%) or anthracycline-based (30%) chemotherapy. Although anthracyclines are often considered moderately emetogenic, they are associated with significant nausea; in a study by Hickok et al[16] in patients receiving antiemetic therapy with ondansetron/dexamethasone, acute and delayed moderate-to-severe nausea occurred in 10.3% and 34.9%, respectively, of patients receiving carboplatin; 21.3% and 57.4%,

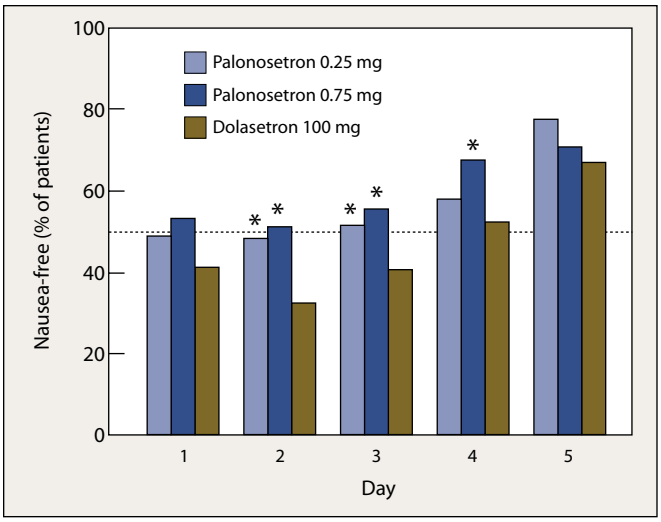

Figure 1 Proportion of Patients Who Remained Nausea-Free

Patients received moderately emetogenic chemotherapy.

* $P < 0.05$ for palonosetron versus dolasetron (chi-squared test).

Reproduced with permission from Eisenberg et al.[10]

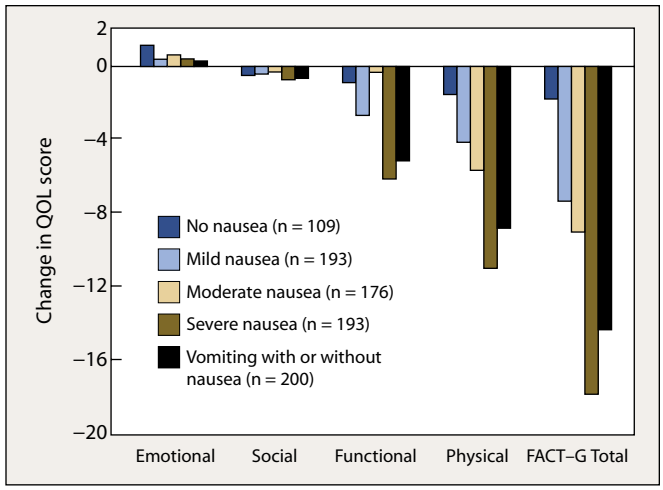

Figure 2 Impact of Nausea and Vomiting on Patient Quality of Life (QOL)

Data are from Hickok et al.[25] Abbreviation: FACT–G = Functional Assessment of Cancer Therapy–General

respectively, of those receiving cisplatin; and 41.4% and 66.2%, respectively, of those receiving doxorubicin.

For patients receiving palonosetron, the treatment results appear only marginally better for control of nausea. In a phase III trial of patients receiving HEC, palonosetron was associated with acute nausea (sufficient to interfere with daily life) in 26% of patients and delayed nausea in 45%, versus 34% and 54%, respectively, for ondansetron.[11] Another phase III trial in patients receiving MEC showed that palonosetron was associated with more patients being nausea-free than was dolasetron, although 50% or more of patients still experienced nausea during the days following chemotherapy (Figure 1).[10] The addition of aprepitant to antiemetic therapy did not reduce significant nausea. In a trial of breast cancer patients receiving MEC, Warr et al[17] found that nausea, which caused a greater than minimal impact on daily life, occurred in 49.5% of patients receiving ondansetron/dexamethasone and in 46.5% of patients who received aprepitant/ondansetron/dexamethasone. Preliminary data on the investigational agent casopitant has revealed similar findings,[18,19] suggesting that the NK_1 antagonists as a class may have little value in preventing delayed chemotherapy-induced nausea.

IMPACT ON QOL

The occurrence of chemotherapy-induced nausea and its impact on QOL are often overlooked—possibly because vomiting is an objective and dramatic event, whereas nausea is a subjective experience and is commonly suffered in silence. Recent data show that health professionals dramatically underestimate the frequency of nausea compared with patient reports.[6,20] For example, a study by Grunberg and colleagues[8] showed that in patients receiving HEC, the physician/nurse estimates versus patient reports were 34% versus 33% for acute nausea but 39% versus 60% for delayed nausea; the discrepancies were even larger in patients receiving MEC, with estimates of 24% versus 37% for acute nausea and 24% versus 52% for delayed nausea. Similarly, a Taiwanese study reported by Liau et al[20] showed physician/nurse estimates versus patient reports of 39% versus 55% for acute nausea and 44% versus 74% for delayed nausea in patients receiving MEC.

The need to do a better job in recognizing and treating nausea is evident from the impact of this symptom on patient distress and QOL measures. In identical surveys performed in 1983, before the advent of 5-HT_3 antagonists, and in 1995, after these agents had been widely adopted into clinical practice, the order of side effects most distressing to patients receiving emetogenic chemotherapy changed from 1) vomiting, 2) nausea, and 3) loss of hair in 1983 to 1) nausea, 2) loss of hair, and 3) vomiting in 1995.[21] These studies emphasize that even with effective antiemetic therapy, nausea remains highly distressing to patients and may be even more distressing than the experience of actual emesis. Studies further suggest that nausea has a more deleterious impact on QOL and the patients' sense of well-being than emesis whether patients are receiving MEC or HEC.[22–24]

In a recent study by Hickok et al[25] of patients receiving therapy with doxorubicin, overall QOL as measured by the Functional Assessment of Cancer Therapy–General (FACT–G) scale and physical and functional well-being components decreased in the 4 days following chemotherapy infusion, with no change seen in emotional or social well-being scores. A stepwise linear regression analysis predicting change in QOL showed that severity of nausea entered first and accounted for a significant 24% of variance in QOL reduction ($P < 0.001$); the occurrence of vomiting accounted for a nonsignificant < 1% of additional variance, with no other factors significantly predicting the decrease in QOL. Similar results were obtained when the relative influence

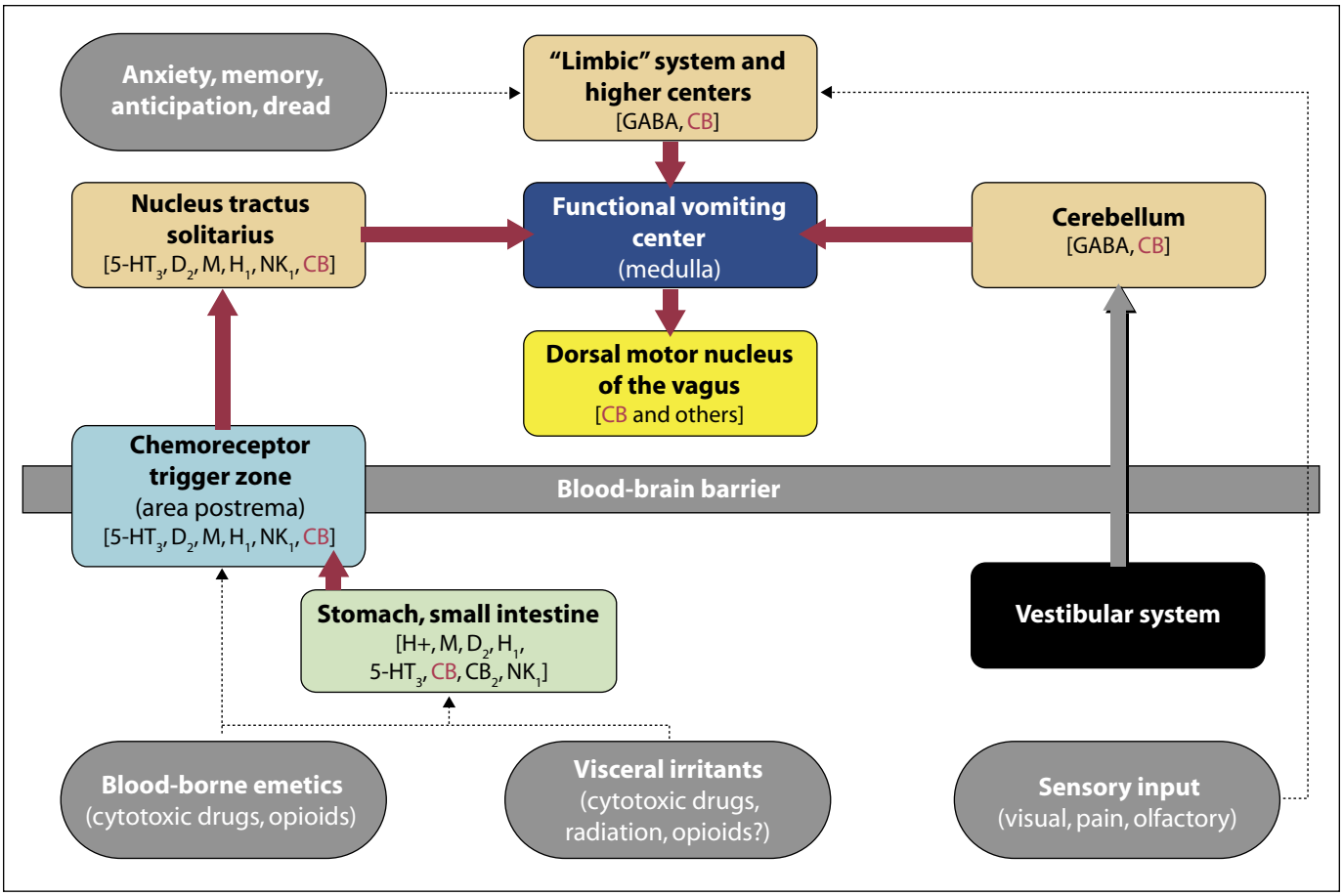

Figure 3 Multiple Systems Involved in the Pathogenesis of Chemotherapy-Induced Nausea and Vomiting

Abbreviations: GABA = gamma-aminobutyric acid; CB = cannabinoid; 5-HT_3 = 5-hydroxytryptamine$_3$ (serotonin); NK = neurokinin; D = dopamine; H = histamine; H+ = hydrogen ion

of nausea and vomiting on physical and functional decline was evaluated. As shown in Figure 2,[25] patients rated severe nausea as having a worse effect on QOL than vomiting with or without nausea. The investigators concluded that nausea severity, not the occurrence of vomiting, was the primary factor in perceived decline in QOL, and that nausea severity should be a primary outcome measure in studies evaluating antiemetic treatment efficacy. Reports further suggest that nausea duration may even result in even greater distress and QOL impairments than nausea severity.[23,24] Indeed, when patients are asked whether they would rather experience a few vomiting episodes associated with mild, temporary nausea or no emesis but moderate nausea most of the day, most indicate the former. Perhaps it is not surprising that reduction of nausea rather than emesis has been shown to guide patient preference of antiemetic treatment.[26]

Pathophysiology of CINV: New Therapeutic Opportunities

The need for improved strategies in prevention and treatment of CINV is highlighted by its complex pathophysiology, shown schematically in Figure 3. In brief, emetogenic messages converging from the gastrointestinal system, circulation, and higher brain centers are processed in parallel via multiple pathways within the brainstem using a variety of neurotransmitters, including serotonin, dopamine, neurokinin, histamine, endorphins, acetylcholine, gamma-aminobutyric acid, and cannabinoids. Although the neurochemical systems and pathways mediating chemotherapy-induced emesis are reasonably well understood, those for nausea are less well defined.[4,27] It is this multiplicity of neurotransmitter systems that helps explain why complete control of chemotherapy-induced emesis still eludes our grasp and why control of nausea lags even farther behind. Another explanation for this gap may reside in our therapeutic focus on neurotransmitter antagonists. Recently, Sanger and Andrews[4] suggested that neurochemical agonists, such as the cannabinoids, are a "relatively neglected area of antiemetic research."

Pharmaceutical cannabinoids have been approved for the treatment of CINV since the 1980s. The utility of this class of agents has been overshadowed, however, by the efficacy of the 5-HT_3 receptor antagonists in preventing acute emesis and by a disproportionate focus on prevention of this symptom—rather than nausea or delayed CINV, for example—as a

primary measure of treatment efficacy. A significant, if somewhat older, body of literature supports the value of cannabinoids in reducing CINV, and given the deficiencies of current therapies, an expansion of their role in treatment should be the subject of active investigation.

As indicated in Figure 3, cannabinoid binding occurs at multiple pivotal control points for nausea and emesis, suggesting that cannabinoids do have a significant neuromodulatory function in ameliorating these symptoms. Cannabinoid receptors of the CB_1 type are present throughout the central nervous system, and CB_2 receptors were thought to be localized exclusively in the periphery, primarily on immunocytes and mast cells. Recent evidence suggests that CB_2 receptors are also present on brainstem neurons and may have a role in mediating the cannabinoid effects on emesis.[28] Whether through CB_1 receptor agonism alone or with CB_2 binding, cannabinoids directly and indirectly affect serotonin, neurokinin, dopamine, and opioid activity, and all of these neurotransmitters play a critical role in mediating the emetogenic response to toxins (as well as the response to nociception).[29] CB_1 receptors are particularly abundant in the area postrema, nucleus tractus solitarius (solitary nucleus), and dorsal motor nucleus—key detection, integration, and efferent sites within the brainstem for emetogenic stimuli.[28] Cannabinoids have long been used for their anti-anxiety and distress-relieving effects, and although limbic system modulation of central processing may be less important for emesis than for nausea, such activity may be linked to anticipatory and even delayed CINV.[3,30,31] Finally, like the 5-HT_3 antagonists and perhaps dexamethasone, cannabinoids also appear to stabilize enterochromaffin cells in the gut, thereby decreasing the vagal input to the brainstem regions coordinating nausea and vomiting.

Role of Cannabinoids in CINV

Despite public interest in the medicinal potential of cannabis, this botanic is restricted from therapeutic use by Federal law, and the scientific data supporting cannabis use in the treatment of CINV are of marginal value.[32] The oral cannabinoids nabilone (Cesamet) and dronabinol (Marinol) are approved by the US Food and Drug Administration for use in CINV refractory to conventional antiemetic therapy and are recognized for use as breakthrough treatment by the National Comprehensive Cancer Network.[1] However, it is well-recognized that the optimal efficacy of most antiemetic agents is achieved when they are prescribed prophylactically rather than in a rescue situation. The vast majority of studies supporting the use of cannabinoids in CINV were conducted in such a setting, suggesting that they also should be prescribed earlier rather than later in the treatment course. The diverse effects of the cannabinoids on the multiple subsystems involved in the control of nausea and vomiting suggest their inclusion in rational pharmacologic approaches to the prevention of acute and delayed CINV. Combining agents with different mechanisms of action is recognized as the optimal approach to management of nausea and vomiting.[1,33]

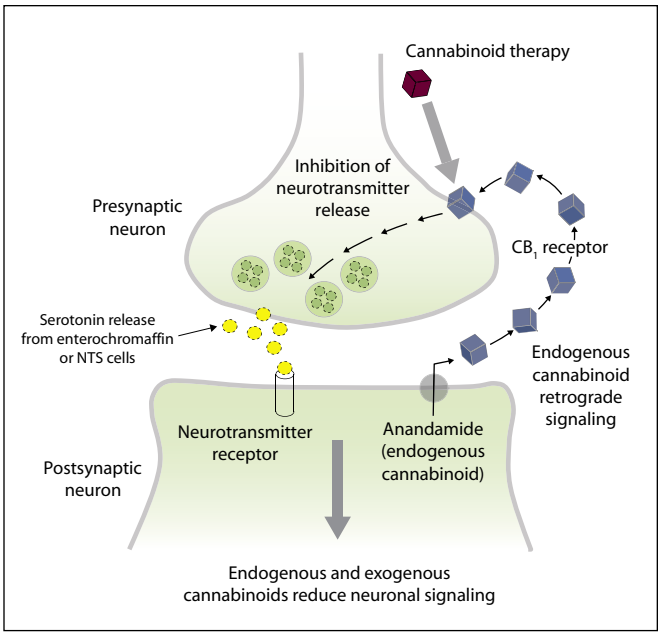

Figure 4 Mechanism of Action of the Cannabinoids

Endogenous cannabinoids are produced in response to overstimulation of postsynaptic nerves. They then serve to modulate or inhibit the excitation of presynaptic nerve cells. Exogenous cannabinoids mimic these effects of inhibition of the presynaptic nerves.

Abbreviation: NTS = nucleus tractus solitarius; CB = cannabinoid

As noted previously, the antiemetic activity of cannabinoids is related to interaction with receptors located in enteric vagal afferents and the brainstem. In the gastrointestinal tract, cannabinoids may subserve similar functions to the 5-HT_3 antagonists in diminishing vagal excitation by the serotonin released from enterochromaffin cells, though effects on other neurotrasmitters (eg, acetylcholine) may also be of importance.[34] In the brainstem, they have overlapping modulatory activity with NK_1 inhibitors, and dopamine-2 receptor antagonists. The identified sites of activity lie principally within the dorsal vagal complex, which appears to serve as the integration center for direct (systemic toxin) and indirect (vagal mediated) emetogenic stimuli. This area includes the nucleus tractus solitarius; area postrema (chemoreceptor trigger zones); and the dorsal motor nucleus of the vagus, the latter serving as the efferent or motor center, which initiates the actual emetic process.[28] Additional cannabinoid binding has been shown in the limbic areas and cerebellar-vestibular system, functional brain regions that contribute to setting the "thermostat" for the control of nausea and emesis.[2,27,35] At the cellular level, cannabinoids appear to exert their effects through the presynaptic inhibition of neurotransmitter release, either from the enterochromaffin cells in the viscera or the central vagal afferents in the dorsal vagal complex (Figure 4).[29]

The two available cannabinoids, dronabinol and nabilone, are both well absorbed orally but differ with regard to their formulation and pharmacokinetics. Dronabinol is formulated with sesame seed oil; thus, it is contraindicated in patients with

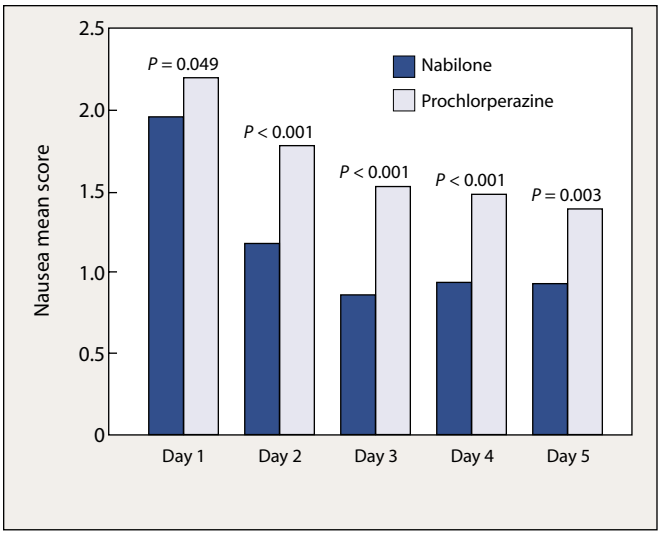

Figure 5 Effect of Nabilone and Prochlorperazine on the Severity of Nausea in Patients Receiving Primarily Cisplatin-based Chemotherapy

The scoring system of the patients' subjective evaluation of nausea was 0 = none; 1 = mild, activity not limited; 2 = moderate, activity limited; 3 = severe, bedridden with nausea for more than 2 hours.

Adapted from Einhorn et al[43]

hypersensitivity to sesame seed oil and probably also in those with peanut allergies, since there is a significant cross-reactivity between these substances. Dronabinol has a somewhat shorter time to onset of effect, whereas nabilone has a longer duration of effect, likely due to an active metabolite, and is dosed twice daily, compared with 4–6 times daily for dronabinol.[36–38] Both drugs are primarily metabolized via the cytochrome P450 (CYP) 2C9 isoenzyme, with a lesser contribution by the 3A4 enzyme. Although neither is an inducer of CYP enzymes, inhibition of 3A4 has been observed with dronabinol, warranting attention to potential drug-drug interactions with the many therapeutic agents that are metabolized by CYP3A4.

Most comparative studies of nabilone and dronabinol are older studies, performed in concert with drug development and approval processes. A systematic review of 30 randomized, comparative studies (16 with nabilone, 13 with dronabinol, 1 levonantradol) reported by Tramer et al[39] in 2001 showed that cannabinoids reduced nausea and vomiting more than placebo or active controls, including mostly antidopaminergic agents. Against active controls (prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine [Torecan], haloperidol, domperidone, or alizapride), cannabinoids were more effective in preventing vomiting (relative risk [RR], 1.38; 95% confidence interval [CI], 1.18–1.62; number needed to treat for complete control of vomiting = 6) and in preventing nausea (RR, 1.28; 95% CI, 1.08–1.51; number needed to treat for complete control of nausea = 8). In crossover trials, patients preferred cannabinoids for future chemotherapy cycles over both placebo (RR, 5.67; 95% CI, 3.95–8.15) and active (RR, 2.39; 95% CI, 2.05–2.78) comparators. Dysphoria was the most troublesome side effect noted, with approximately 11% of patients withdrawing from treatment due to side effects.

TRIALS WITH PROCHLORPERAZINE

As occurred with the cannabinoids, the success of 5-HT_3 antagonists in reducing acute emesis may also have obscured the value of the dopamine antagonists, as single agents or as combination therapy, in the prevention of nausea or other types of CINV (eg, anticipatory, delayed). For example, although 5-HT_3 antagonists may reduce acute vomiting more than prochlorperazine, there are a number of studies indicating that the latter is at least as effective in preventing delayed nausea. In a trial in patients receiving doxorubicin,[40] delayed nausea was less frequent in patients receiving daily prochlorperazine versus a short-acting 5-HT_3 antagonist (71% vs 79%; $P < 0.05$) and significantly fewer prochlorperazine-treated patients required rescue therapy (21% vs 34%; $P < 0.0001$). Similar results were reported by Lindley et al[41]; patients treated with prochlorperazine had lower average delayed nausea scores than did patients treated with ondansetron. In an uncontrolled study of olanzapine (Zyprexa), an atypical dopamine antagonist,[42] an apparent benefit was seen when this agent was added prophylactically and throughout the treatment course to a combination of granisetron and dexamethasone.

Multiple studies have examined the relative benefits of prochlorperazine versus the cannabinoids. In a crossover comparison of nabilone versus prochlorperazine in patients receiving primarily cisplatin-based chemotherapy, nabilone significantly reduced both the frequency of vomiting and the severity of nausea on each of days 1 to 5 following chemotherapy (Figure 5).[43] In this trial, 75% of patients preferred nabilone and 21% preferred prochlorperazine ($P < 0.001$). This trial was also notable in that it is one of the few cannabinoid studies that provided data on both acute and delayed CINV. Unlike the results typically seen with the 5-HT_3 antagonists, nausea control with both agents was superior in the delayed versus the acute setting. In another early comparative trial in patients with severe CINV,[44] response in terms of partial or complete relief of CINV symptoms occurred in 80% of patients receiving nabilone versus 32% of those receiving prochlorperazine ($P < 0.01$), and complete response occurred in 8% versus 0%, respectively. Nabilone had a significantly superior response rate in controlling both nausea ($P < 0.01$) and vomiting ($P < 0.001$). In this trial, too, 75% of patients preferred nabilone, with 15% preferring prochlorperazine ($P < 0.001$).

NEWER STRATEGIES

Most comparative studies of cannabinoids are old, but as interest in this class of agents resurfaces because of an improved understanding of the mechanisms involved in nausea/vomiting as well as the unmet challenges of CINV, new studies are being initiated. One recent small study compared dronabinol with ondansetron in patients receiving MEC or HEC.[45] Rates of total response (nausea intensity < 5 mm on a visual

analogue scale, no vomiting/retching, and no rescue medication) were 54% with dronabinol, 58% with ondansetron, and 20% with placebo. Rates of absence of nausea were 71% with dronabinol, 64% with ondansetron, and 15% with placebo (Figure 6).[45] The dronabinol group had the lowest nausea intensity on a visual analogue scale (10.1 mm vs 24.0 mm with ondansetron and 48.4 mm with placebo) and the lowest mean number of vomiting/retching episodes (0.2 vs 1.3 with ondansetron and 1.3 with placebo). A combination dronabinol/ondansetron arm in this study had rates of response and absence of nausea that were lower than with either agent alone, and nausea intensity and mean vomiting/retching episodes were between those seen with dronabinol and ondansetron—perhaps giving pause to further examination of combined treatment with 5-HT_3 antagonists and cannabinoids.

Combination therapy with a cannabinoid and prochlorperazine has shown results superior to those observed with single-agent treatment. In another older study, the combination of dronabinol and prochlorperazine was significantly more effective than either agent administered alone.[46,47] Nausea occurred in 29% of patients receiving the combination compared with 47% of dronabinol-treated patients and 60% of prochlorperazine-treated patients; vomiting occurred in 35% with the combination, 41% with dronabinol, and 55% with prochlorperazine. Both the severity and duration of nausea were significantly reduced with the combination regimen compared with dronabinol alone ($P < 0.001$ vs $P = 0.02$) and with prochlorperazine alone ($P < 0.001$ vs $P < 0.001$). The duration of vomiting episodes was also decreased with combined treatment (median, 1 minute vs 2 minutes with dronabinol and 4 minutes with prochlorperazine). The addition of prochlorperazine to dronabinol also decreased the number of dropouts encountered with dronabinol alone. A study of nabilone and prochlorperazine showed that in patients receiving MEC, this combination was slightly better than the combination of high-dose metoclopramide and dexamethasone in providing complete control of nausea and vomiting and was preferred by a higher percentage of patients ($P = 0.013$).[48] Such findings suggest that combinations of a cannabinoid and dopamine antagonist such as prochlorperazine or olanzapine should be further evaluated in the treatment of CINV.

SIDE EFFECTS AND LIMITATIONS

Though the benefits of cannabinoids in treating CINV seem well established, their adoption into clinical practice has been slowed by the occurrence of side effects.[49–52] The principal side effects of concern have varied from study to study but generally include dysphoria, drowsiness, dizziness, and dry mouth. In the review by Tramer et al,[39] approximately 11% of patients dropped out of cananbinoid treatment due to side effects versus 2% in the placebo groups. Despite the side effects, patients expressed a clear preference for the cannabinoid in a number of trials,[44,51,52] a phenomenon also reported in the systemic review by Tramer et al.[39] Typically, the basis of patient preference was the superior efficacy of the cannabinoid over the comparator agent, usually prochlorperazine.

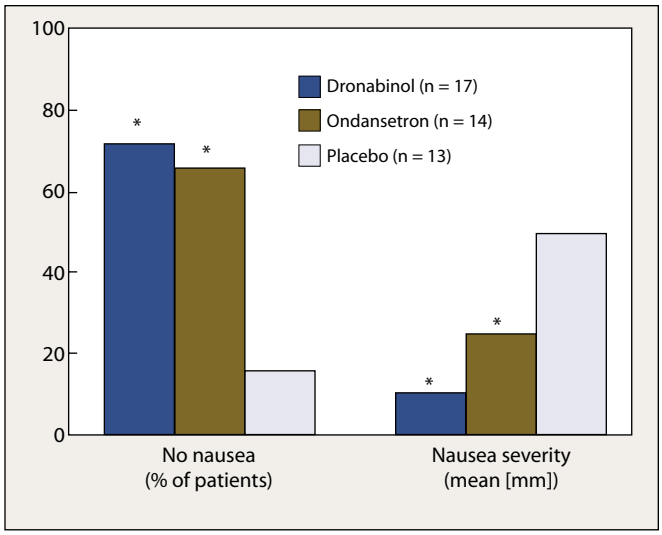

Figure 6 Absence of Nausea and Nausea Severity with Dronabinol, Ondansetron, and Placebo after MEC or HEC

Proportion of patients with absence of nausea and nausea severity on visual analogue scale (lower = less severe, higher = more severe) with dronabinol, ondansetron, and placebo after MEC or HEC. *$P \leq 0.05$ versus placebo.

Abbreviations: MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy

Adapted from Meiri et al[45]

Since cannabinoid side effects are a barrier, at least for some patients and clinicians, to the broader acceptance of cannabinoids in CINV treatment, several studies have examined the potential of combination therapy to mitigate such effects. Two studies, for example, reported that the addition of prochlorperazine decreased the frequency of dysphoric effects associated with cannabinoid treatment,[46,48] and the addition of dexamethasone was also found to reduce the hypotension sometimes seen with cannabinoids, while also improving efficacy.[51]

The limitations of the existing body of clinical cannabinoid research in CINV must also be acknowledged. The vast majority of studies were performed with study methodologies very different from those in use today; they often failed to stratify treatments according to the emetogenicity of the chemotherapeutic agents used and failed to delineate between acute and delayed symptoms. Since the composite data reveal that cannabinoids are clearly efficacious in the treatment of CINV, and these clinical data are buttressed by a strong neurophysiologic rationale for their use, recognition of these limitations should not deter clinicians from the appropriate adoption of cannabinoids into CINV therapeutic regimens. It should be noted that the clinical data in support of prochlorperazine for the management of CINV are equally as dated and that this agent has often been found inferior to the cannabinoids in its clinical value. These factors have not deterred the broad acceptance of prochlorperazine into the CINV treatment armamentarium nor the development of research that has better elucidated the comparative benefits of this agent versus

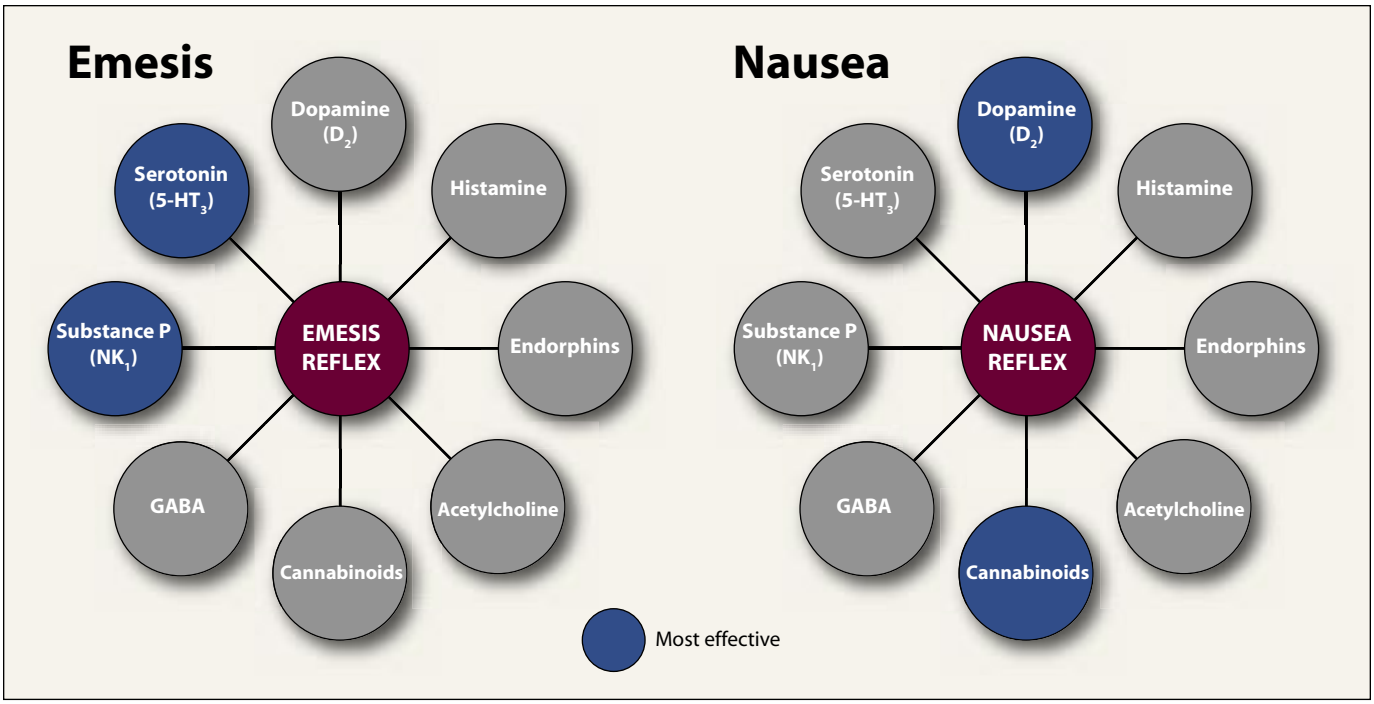

Figure 7 Hypothesis: Different Neuromodulators May Mediate Nausea and Emesis

Many different neurotransmitters are involved in the modulation of emesis, but only those agents that affect the serotonin, neurokinin (NK), dopamine (intravenous metoclopramide), and cannabinoid receptors are approved by the US Food and Drug Administration for the management of chemotherapy-induced nausea and vomiting. Abbreviation: GABA = gamma-aminobutyric acid

5-HT_3 antagonists.[40,41] Seen in this light, the limitations of prior cannabinoid research should spur additional inquiry into how these agents can be best positioned in the nausea and vomiting treatment paradigm for the benefit of patients who continue to suffer the distress of unrelieved CINV. Currently, such a trial is being conducted with nabilone under the auspices of the International Oncology Network.

Conclusion

CINV presents patients and oncologists with many challenges. The 5-HT_3 antagonists may be the best treatments available for preventing acute vomiting, but nausea, delayed CINV, and refractory CINV remain significant problems—nausea, in particular, having a profound impact on patient QOL. There is evidence that prochlorperazine, olanzapine, and the cannabinoids may offer improvements over 5-HT_3 antagonists in preventing nausea, that cannabinoids are better than dopamine antagonists in preventing CINV, and that the combination of these latter two classes of medications is better than either alone. It has been hypothesized that the neuromodulators most active in mediating emesis are serotonin and substance P (NK_1) and that those most active in nausea are dopamine and cannabinoids (Figure 7). The time has come to investigate the best use of the therapies we have available to optimize antiemetic treatment across the entire spectrum of CINV, including an appropriate focus on preventing nausea. This endeavor will involve agents with different mechanisms of action, used in concurrent or sequential combinations, with the best such combinations identified. In this effort, the utility of the cannabinoids should not be overlooked.

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