

## REVIEW ARTICLE

## DRUG THERAPY

## Chemotherapy-Induced Nausea and Vomiting

Paul J. Hesketh, M.D.

From Caritas St. Elizabeth's Medical Center, Boston. Address reprint requests to Dr. Hesketh at Caritas St. Elizabeth's Medical Center, HOQ Rm. 224, 736 Cambridge St., Boston, MA 02135, or at phesketh@massmed.org.

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THE SUPPORTIVE CARE OF PATIENTS RECEIVING ANTINEOPLASTIC TREATMENT has dramatically improved over the past two decades. The development of effective means to prevent nausea and vomiting arising from chemotherapy serves as one of the most important examples of this progress. Patients beginning cancer treatment consistently list chemotherapy-induced nausea and vomiting as one of their greatest fears.<sup>1,2</sup> Inadequately controlled emesis impairs functional activity and quality of life for patients, increases the use of health care resources, and may occasionally compromise adherence to treatment.<sup>3-5</sup> New insights into the pathophysiology of chemotherapy-induced nausea and vomiting, a better understanding of the risk factors for these effects, and the availability of new antiemetic agents have all contributed to substantial improvements in emetic control. This review focuses on our current understanding of chemotherapy-induced nausea and vomiting and the status of pharmacologic interventions for their prevention and treatment.

## BACKGROUND

The likelihood that nausea and vomiting will develop after chemotherapy treatment depends on several factors. Two of these factors are sex and age, with female patients<sup>6-9</sup> and younger patients<sup>6</sup> being at greater risk. In addition, patients who have a high pretreatment expectation of severe nausea are more likely to have nausea after chemotherapy.<sup>10</sup> Conversely, patients with a history of high alcohol consumption have a lower risk of chemotherapy-induced nausea and vomiting.<sup>8,9</sup>

Treatment-related factors such as chemotherapy dose<sup>7</sup> and emetogenicity<sup>11</sup> are also relevant. Of all the known predictive factors, the intrinsic emetogenicity of a given chemotherapeutic agent is the predominant factor and should serve as the primary consideration in guiding antiemetic treatment. In 1997, a schema that assigned intravenously administered chemotherapeutic agents to five levels of emetogenicity was proposed.<sup>12</sup> This schema was modified in 2004 at an expert consensus conference,<sup>13</sup> with agents divided into four emetogenic levels (high, moderate, low, and minimal) (Table 1). Recent evidence-based guidelines for antiemetic treatment reflect acceptance of this modified schema as the new standard for defining the emetogenicity of intravenously administered chemotherapeutic agents.

Another critical factor that led to the rational evolution of treatment for chemotherapy-induced nausea and vomiting was the recognition of distinct emetic clinical syndromes. Most important in this regard was the concept of acute as compared with delayed emesis, first identified with use of the agent cisplatin. In the absence of effective antiemetic prophylaxis, virtually all patients receiving cisplatin will have nausea and vomiting 1 to 2 hours after receiving chemotherapy.<sup>14</sup> At approximately 18 to 24 hours, the emesis typically subsides, only to recur and reach a second peak at approximately 48 to 72 hours after receipt of the agent.<sup>15</sup> On the basis of the

**Table 1. Emetogenic Levels of Intravenously Administered Antineoplastic Agents.\***

Level 1 (minimal risk, <10%)	Level 2 (low risk, 10–30%)	Level 3 (moderate risk, 31–90%)	Level 4 (high risk, >90%)
Bevacizumab	Bortezomib	Carboplatin	Carmustine
Bleomycin	Cetuximab	Cyclophosphamide	Cisplatin
Busulfan	Cytarabine ( $\leq 100$ mg/m <sup>2</sup>	( $\leq 1.5$ g/m <sup>2</sup> )	Cyclophosphamide
Cladribine	of body-surface area)	Cytarabine (>1 g/m <sup>2</sup> )	(>1.5 g/m <sup>2</sup> )
Fludarabine	Docetaxel	Daunorubicin	Dacarbazine
Vinblastine	Etoposide	Doxorubicin	Mechlorethamine
Vincristine	Fluorouracil	Epirubicin	Streptozocin
Vinorelbine	Gemcitabine	Idarubicin	
	Ixabepilone	Ifosfamide	
	Lapatinib	Irinotecan	
	Methotrexate	Oxaliplatin	
	Mitomycin		
	Mitoxantrone		
	Paclitaxel		
	Pemetrexed		
	Temsirolimus		
	Topotecan		
	Trastuzumab		

\* Percentages indicate the risk of vomiting with intravenously administered antineoplastic agents in the absence of anti-emetic prophylaxis.

cisplatin model, emesis occurring within the first 24 hours has been defined as acute, and emesis occurring more than 24 hours later as delayed.<sup>16</sup> A number of agents other than cisplatin, including cyclophosphamide, carboplatin, and the anthracyclines, can cause delayed emesis.<sup>17</sup> Optimal preventive strategies for chemotherapy-induced nausea and vomiting depend on recognition of the intrinsic emetogenicity of a chemotherapeutic agent as well as an understanding its potential to induce acute or delayed emesis. The incidence of anticipatory emesis, a third emetic syndrome, has decreased in recent years. Anticipatory emesis represents a learned response conditioned by the severity and duration of previous emetic responses to chemotherapy.<sup>18</sup> As strategies for controlling emesis have improved, the frequency of anticipatory emesis has decreased.

#### NEUROPHYSIOLOGY OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The vomiting reflex is present in many animal species, ranging from fish to higher mammals, and has been viewed from an evolutionary perspective as a protective mechanism against ingested toxins. The general mechanisms involved in this highly complex reflex have been elaborated in a number of reviews.<sup>19–21</sup> In humans, the motor-reflex re-

sponse of vomiting is often but not always preceded by an unpleasant sensation termed “nausea.” There is debate about whether various characteristic behaviors observed in animals represent a “nausea equivalent.” The central nervous system plays a critical role in the physiology of nausea and vomiting, serving as the primary site that receives and processes a variety of emetic stimuli. The central nervous system also plays a primary role in generating efferent signals which are sent to a number of organs and tissues in a process that eventually results in vomiting.<sup>22</sup>

#### MECHANISMS

Some of the mechanisms through which chemotherapy induces nausea and vomiting have gradually become elucidated over the past 25 years. Three key components involving areas in the hindbrain and the abdominal vagal afferents have been identified (Fig. 1). Pioneering studies conducted by Wang and Borison nearly 60 years ago proposed the concept of a central site (vomiting center) located in the medulla that serves as a final common pathway for processing all afferent impulses that can initiate emesis.<sup>23</sup> It is now thought that an anatomically discrete vomiting center is unlikely to exist.<sup>24</sup> Rather, a number of loosely organized neuronal areas within the medulla probably interact to coordinate the emetic reflex.<sup>21,25</sup> The neurons coordinating the complex series of events that

occur during emesis have been termed the “central pattern generator.”<sup>26,27</sup>

Studies conducted in laboratory animals provide evidence of the importance of two primary sources of afferent input to the key hindbrain areas that can initiate the emetic reflex after exposure to chemotherapy. Abdominal vagal afferents appear to have the greatest relevance for chemotherapy-induced nausea and vomiting.<sup>28</sup> A variety of receptors, including 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>), neurokinin-1, and cholecystokinin-1, are located on the terminal ends of the vagal afferents.<sup>29</sup> These receptors lie in close proximity to enteroendocrine cells located in the gastrointestinal mucosa of the proximal small intestine, which contains a number of local mediators, such as 5-hydroxytryptamine (5-HT), substance P, and cholecystokinin. Antineoplastic agents, through either direct mucosal or blood-borne mechanisms, stimulate enteroendocrine cells to release mediators, which then bind to the appropriate receptors on the adjacent vagal fibers, leading to an afferent stimulus that terminates in the dorsal brain stem, primarily in the nucleus tractus solitarius, and subsequently activates the central pattern generator. Among the various local mediators, 5-HT, located in the enterochromaffin cells, is believed to play the most important role. At present, this vagal-dependent pathway is considered the primary mechanism by which most chemotherapeutic agents initiate acute emesis.

A second possible source of afferent input, identified by Borison and colleagues, is the area postrema, a circumventricular structure located at the caudal end of the fourth ventricle.<sup>30,31</sup> Since the blood–brain barrier is relatively permeable in this region of the brain, the area postrema may be accessible to humoral stimuli in either blood or cerebrospinal fluid. The area postrema has commonly been termed a “chemoreceptor trigger zone.”<sup>32</sup> Studies in animal models have demonstrated that opioids and dopaminergic agonists can induce emesis when they bind to this site.<sup>33,34</sup> It is conceivable that gut-derived peptides and metabolites of chemotherapeutic agents also induce emesis in part through binding at this site. However, such potential mechanisms remain to be investigated in detail.

Other proposed sources of stimuli that result in chemotherapy-induced nausea and vomiting are centers of the higher central nervous system lo-

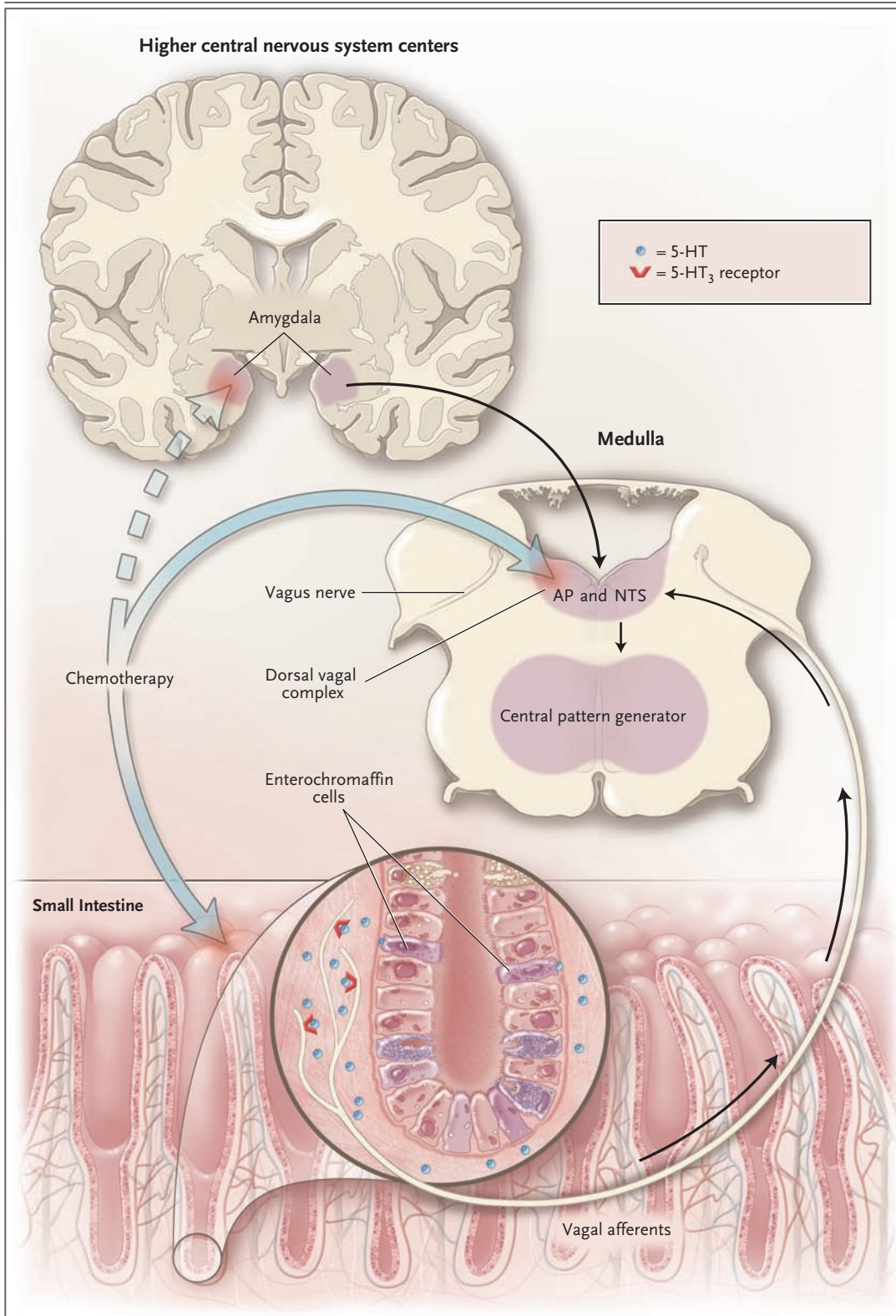
**Figure 1 (facing page). Pathways by Which Chemotherapeutic Agents May Produce an Emetic Response.**

Antineoplastic agents may cause emesis through effects at a number of sites. The mechanism that is best supported by research involves an effect on the upper small intestine (bottom of figure). After the administration of chemotherapy, free radicals are generated, leading to localized exocytotic release of 5-hydroxytryptamine (5-HT) from the enterochromaffin cells; 5-HT then interacts with 5-hydroxytryptamine<sub>3</sub> (5-HT<sub>3</sub>) receptors on vagal afferent terminals in the wall of the bowel. Vagal afferent fibers project to the dorsal brain stem, primarily to the nucleus tractus solitarius (NTS), and, to a lesser extent, the area postrema (AP), the two parts of the brain referred to collectively here as the dorsal vagal complex. Receptors for a number of neurotransmitters with potentially important roles in the emetic response are present in the dorsal vagal complex. These include the neurokinin-1, 5-HT<sub>3</sub>, and dopamine-2 receptors, which bind to substance P, 5-HT, and dopamine, respectively. Efferent fibers project from the dorsal vagal complex to the final effector of the emetic reflex, the central pattern generator, which is an anatomically indistinct area occupying a more ventral location in the brain stem. Receptors for other locally released mediators, such as substance P, cholecystokinin, and prostaglandins, are also present on the vagal afferent terminals. However, the extent to which these mediators are involved at this peripheral site is unknown. Antineoplastic agents may also induce emesis through an interaction with the area postrema within the dorsal vagal complex. The area postrema is a circumventricular organ located at the caudal end of the floor of the fourth ventricle, which is accessible to blood and cerebrospinal fluid–borne emetic stimuli. Other potential sources of efferent input that result in emesis after chemotherapy include a number of structures in the temporal lobe, such as the amygdala. Evidence for this pathway is less well established than for other proposed sites of chemotherapeutic action.

cated in structures in the limbic forebrain, such as the amygdala.<sup>35-37</sup>

**NEUROTRANSMITTERS**

Investigations over the past three decades have gradually elucidated the clinical significance of several neurotransmitters in the emetic process. The neurotransmitters dopamine, 5-HT, and substance P all appear to play important roles.<sup>22,38,39</sup> Early investigations focused on the dopamine D<sub>2</sub> receptors; dopaminergic antagonists such as the phenothiazines and butyrophenones were among the first agents with demonstrated antiemetic efficacy.<sup>40,41</sup>





In the past 20 years, one of the most important advances in research on chemotherapy-induced nausea and vomiting has been the recognition of the critical role played by 5-HT. Of the multiple 5-HT receptors identified to date, the 5-HT<sub>3</sub> receptor appears to be most important in the acute phase of chemotherapy-induced nausea and vomiting.<sup>39,42</sup> Selective antagonists of the 5-HT<sub>3</sub> receptor are currently the single most effective class of antiemetics for the prevention of acute chemotherapy-induced nausea and vomiting. The 5-HT<sub>3</sub> receptors are in both central locations (area postrema and nucleus tractus solitarius) and peripheral locations (vagal afferents) that are potentially relevant to chemotherapy-induced nausea and vomiting.<sup>43,44</sup> Several lines of evidence suggest that antagonism of 5-HT binding to 5-HT<sub>3</sub> receptors on vagal afferents constitutes the predominant mechanism by which the 5-HT<sub>3</sub> antagonists exert their antiemetic effect.<sup>39,45</sup>

During the past two decades, multiple studies have suggested that substance P may also be a relevant neurotransmitter in chemotherapy-induced nausea and vomiting.<sup>46</sup> It is a member of a group of peptides known as the tachykinins, which serve a number of regulatory functions.<sup>47</sup> Three mammalian tachykinins have been isolated to date — substance P, neurokinin A, and neurokinin B, which preferentially bind to the receptors neurokinin-1, neurokinin-2, and neurokinin-3, respectively.<sup>47,48</sup> Neurokinin-1 receptors are widely distributed throughout the central nervous system, including the area postrema and the nucleus tractus solitarius, and are also found in peripheral sites such as the gastrointestinal tract.<sup>49</sup> Carpenter and colleagues demonstrated that administration of substance P to dogs could induce emesis.<sup>33</sup> Subsequent evaluation of a number of selective neurokinin-1-receptor antagonists in animal models revealed substantial antiemetic efficacy across a broad spectrum of emetic stimuli.<sup>50,51</sup> There is evidence suggesting that the neurokinin-1 antagonists have a central site of action.<sup>52</sup> Studies in ferrets have revealed that neurokinin-1 antagonists that cannot cross the blood-brain barrier are not effective in preventing cisplatin-induced emesis.<sup>52</sup> Although neurokinin-1 antagonists may have a peripheral site of action as well, experimental evidence in support of such a mechanism is lacking.

Endocannabinoids constitute a fourth class of neurotransmitters that appear to be relevant to chemotherapy-induced nausea and vomiting. Unlike dopamine, 5-hydroxytryptamine, and sub-

stance P, which have a proemetic role, the endogenous cannabinoids exert an agonistic antiemetic effect. A number of clinical trials have shown that synthetic cannabinoids have antiemetic efficacy in patients with chemotherapy-induced nausea and vomiting.<sup>53</sup>

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## ANTIEMETIC AGENTS

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A wide variety of antiemetic agents are available for the prevention and treatment of chemotherapy-induced nausea and vomiting. These agents can be classified according to the therapeutic index of their usefulness as high (Table 2) or low (Table 3).

### AGENTS WITH A HIGH THERAPEUTIC INDEX

#### 5-HT<sub>3</sub> Antagonists

The introduction of selective 5-HT<sub>3</sub>-receptor antagonists in the early 1990s revolutionized the management of chemotherapy-induced nausea and vomiting. Currently, five 5-HT<sub>3</sub> antagonists are widely available: ondansetron (Zofran, Glaxo-SmithKline), granisetron (Kytril, Roche), dolasetron (Anzemet, Sanofi-Aventis), tropisetron (Navoban, Novartis), and a more recently introduced agent, palonosetron (Aloxi, MGI Pharma). These drugs form the cornerstone of prophylactic therapy for chemotherapy with moderate to high emetic potential. Multiple prospective, randomized trials have demonstrated the therapeutic equivalence of the four older 5-HT<sub>3</sub> antagonists, a finding supported by a number of meta-analyses.<sup>54-56</sup> As a class, these agents have few adverse effects of their own and no limiting toxicity at typical doses. The most common adverse events include mild headache, transient elevation of hepatic aminotransferase levels, and constipation. Single-dose daily schedules are similar in efficacy to multiple-dose daily schedules, and at the approved doses, the oral formulation is therapeutically equivalent to the intravenous route of administration.<sup>13,57</sup> Clinical trials with the older 5-HT<sub>3</sub> antagonists (e.g., granisetron, ondansetron), have shown much lower efficacy for the delayed type of chemotherapy-induced nausea and vomiting as compared with the acute type. These agents appear to have little activity when used to prevent delayed emesis induced by cisplatin and only modest activity when used to prevent delayed emesis induced by moderately emetogenic chemotherapy.<sup>58</sup>

In 2003, a new 5-HT<sub>3</sub> antagonist, palonosetron, was approved by the Food and Drug Administra-

**Table 2. Doses and Schedules of Antiemetic Agents with a High Therapeutic Index.\***

Drug	Dose	
	Before Chemotherapy (day 1)	After Chemotherapy
Dolasetron (Anzemet, Sanofi-Aventis)	Intravenous dose: 100 mg or 1.8mg/kg of body weight; oral dose: 100 mg	Oral dose: 100 mg on days 2 and 3 for MEC with potential for delayed emesis
Granisetron (Kytril, Roche)	Intravenous dose: 1 mg or 0.01 mg/kg; oral dose: 2 mg	Oral dose: 1 mg twice daily on days 2 and 3 for MEC with potential for delayed emesis
Ondansetron (Zofran, GlaxoSmithKline)	Intravenous dose: 8 mg or 0.15 mg/kg; oral dose: 24 mg for HEC, 8 mg twice daily for MEC	Oral dose: 8 mg twice daily on days 2 and 3 for MEC with potential for delayed emesis
Palonosetron (Aloxi, MGI Pharma)	Intravenous dose: 0.25 mg	
Tropisetron (Navoban, Novartis)	Intravenous dose: 5 mg; oral dose: 5 mg	Oral dose: 5 mg on days 2 and 3 for MEC with potential for delayed emesis
Dexamethasone		
With aprepitant or fosaprepitant	Intravenous dose: 12 mg; oral dose: 12 mg	Oral dose: 8 mg on days 2–4 for HEC, 8 mg on days 2 and 3 for MEC with potential for delayed emesis
Without aprepitant or fosaprepitant	Intravenous dose: 20 mg for HEC, 8 mg for MEC; oral dose: 20 mg for HEC, 8 mg for MEC	Oral dose: 8 mg twice daily on days 2–4 for HEC, 8 mg on days 2 and 3 for MEC with potential for delayed emesis
Fosaprepitant (Emend [for injection], Merck)	Intravenous dose: 115 mg	Oral dose: 80 mg on days 2 and 3
Aprepitant (Emend [capsules], Merck)	Oral dose: 125 mg	Oral dose: 80 mg on days 2 and 3

\* HEC denotes highly emetogenic chemotherapy, and MEC moderately emetogenic chemotherapy.

tion (FDA). It differs from the older 5-HT<sub>3</sub> antagonists in its prolonged half-life (approximately 40 hours) and its substantially greater binding affinity for the 5-HT<sub>3</sub> receptor.<sup>59</sup> Three randomized, prospective trials have compared the use of a single intravenous dose of palonosetron before chemotherapy with the use of an older 5-HT<sub>3</sub> antagonist. Two trials involving patients receiving moderately emetogenic chemotherapy compared palonosetron with either ondansetron<sup>60</sup> or dolasetron.<sup>61</sup> In a third trial, with patients receiving highly emetogenic chemotherapy, palonosetron was compared with ondansetron.<sup>62</sup> All three trials were designed as noninferiority trials and met their primary end point of complete response (no vomiting and no rescue medication required). Palonosetron was superior to the comparators for some secondary end points in the trials conducted with moderately emetogenic chemotherapy.<sup>60,61</sup> These studies indicate that palonosetron is a potent 5-HT<sub>3</sub> antagonist that compares favorably with the older 5-HT<sub>3</sub> antagonists in terms of effectiveness and safety. Should palonosetron be considered the preferred 5-HT<sub>3</sub> antagonist? The answer awaits completion of prospective trials designed to demonstrate the superiority of palonosetron when used according to evidence-based guidelines

incorporating other appropriate classes of antiemetics and multiple doses of the shorter-acting agents.

#### *Neurokinin-1–Receptor Antagonists*

The neurokinin-1–receptor antagonists represent the newest class of antiemetic agents that are effective for the prevention of chemotherapy-induced nausea and vomiting. Aprepitant (Emend, Merck), approved by the FDA in 2003 in an oral formulation, was the first available agent in this class.

Two prospective phase 3 trials conducted with highly emetogenic chemotherapy led to the approval of aprepitant.<sup>63,64</sup> Both trials, of identical design, compared the three-drug combination of ondansetron, dexamethasone, and aprepitant, all administered before chemotherapy, with ondansetron and dexamethasone alone. In the investigational-treatment group, aprepitant was continued along with dexamethasone. In the standard-treatment group, dexamethasone alone was continued. Significantly better control of emesis was noted during the 5-day study period in both trials in the group that received aprepitant. The magnitude of the benefit (an approximate 50% reduction in the risk of emesis or need for rescue medications) established aprepitant as an important component

**Table 3. Doses and Schedules of Antiemetic Agents with a Low Therapeutic Index.**

Drug	Dose	
	Before Chemotherapy (day 1)	After Chemotherapy
Metoclopramide (Reglan, Baxter and Alaven)	Intravenous dose: 1–2 mg/kg of body weight*	Intravenous dose: 1–2 mg/kg 2 hr after chemotherapy; oral dose: 0.5 mg/kg every 6 hr on days 2–4
Prochlorperazine (Compazine, GlaxoSmithKline)	Intravenous dose: 5–10 mg; oral dose: 5–10 mg	Oral dose: 5–10 mg every 6 hr as needed
Dronabinol (Marinol, Solvay)	Oral dose: 5 mg/m <sup>2</sup> of body-surface area	Oral dose: 5 mg/m <sup>2</sup> every 2–4 hr as needed
Nabilone (Cesamet, Valeant)	Oral dose: 1–2 mg	Oral dose: 1–2 mg twice daily or as needed
Olanzapine (Zyprexa, Eli Lilly)	Oral dose: 5 mg daily for 2 days preceding chemotherapy; 10 mg on day 1	Oral dose: 10 mg on days 2–4

\* This dose is for use only in patients who cannot tolerate or do not have a response to 5-HT<sub>3</sub>-receptor antagonists, dexamethasone, and aprepitant, given the risk of adverse neurologic events with this higher dose of metoclopramide.

of antiemetic management strategies for highly emetogenic chemotherapy. A subsequent phase 3 trial had an identical design, with the exception that the standard-treatment group received a daily dose of ondansetron as well as dexamethasone on days 2 through 4 after treatment with highly emetogenic chemotherapy.<sup>65</sup> Superior control of emesis was again observed in the aprepitant group during the 5-day study period.

A single phase 3 trial evaluated the use of aprepitant with moderately emetogenic chemotherapy in 866 patients with breast cancer (99% of whom were women).<sup>66</sup> The patients were scheduled for treatment with an anthracycline and cyclophosphamide and received either a combination of aprepitant, ondansetron, and dexamethasone given before chemotherapy on day 1, followed by aprepitant alone on days 2 and 3, or a combination of ondansetron and dexamethasone on day 1, followed by ondansetron alone on days 2 and 3. There was a significantly higher rate of complete response (no vomiting or need for antiemetic rescue) during the 5-day study period in the aprepitant group than in the control group (51% vs. 42%).

Three of the phase 3 trials also assessed the outcome over multiple cycles of treatment.<sup>63,64,66</sup> In each trial, better sustained antiemetic protection was observed in the aprepitant group than in the control group.<sup>67,68</sup> The most common adverse effects were fatigue or asthenia, hiccups, and dyspepsia.

Aprepitant has a complex metabolism. In vitro studies using human liver microsomes have shown that aprepitant is metabolized primarily through the cytochrome P-450 3A4 pathway, with minor metabolism by cytochrome P-450 1A2 and cyto-

chrome P-450 2C9.<sup>69</sup> Aprepitant is also a moderate inhibitor and inducer of the cytochrome P-450 3A4 pathway. This information is relevant when it is administered with corticosteroids, which are also metabolized through the cytochrome P-450 3A4 pathway. Coadministration of aprepitant and dexamethasone increases the plasma concentrations of dexamethasone.<sup>70</sup> A substantial number of antineoplastic agents are metabolized through the cytochrome P-450 3A4 pathway, raising the possibility of increased toxicity when these agents are administered with aprepitant. To date, no evidence of a clinically important interaction between aprepitant and any antineoplastic agent has been noted.<sup>63,64,71,72</sup> Aprepitant is also a weak inducer of the cytochrome P-450 2C9 pathway, through which warfarin and other medications are metabolized. Indeed, it has been reported that the international normalized ratio decreased by 15% in patients receiving warfarin and aprepitant concurrently.<sup>73</sup> In early 2008, regulatory approval was granted in the European Union and the United States for an intravenously administered neurokinin-1-receptor antagonist. Fosaprepitant (Emend, Merck) is a water-soluble phosphoryl prodrug for aprepitant that is converted to aprepitant within 30 minutes after intravenous administration.

#### Corticosteroids

Corticosteroids were first shown to be effective antiemetic agents more than 25 years ago.<sup>74</sup> They can be effective when administered as a single agent in patients receiving chemotherapy of low emetic potential. Corticosteroids are most beneficial, however, when used in combination with other antiemetic agents. This has been well demonstrated when corticosteroids have been used in

combination with the 5-HT<sub>3</sub>-receptor antagonists.<sup>75-77</sup> Corticosteroids are effective for both acute and delayed emesis.<sup>78</sup> Relatively little is known about the site or mechanism of action of corticosteroids as compared with the 5-HT<sub>3</sub> antagonists and neurokinin-1 antagonists. Many types of corticosteroids have been used as antiemetic agents. The widest experience has been reported with dexamethasone and methylprednisolone. Dose-ranging studies have been performed with highly and moderately emetogenic chemotherapy to determine the optimal prechemotherapy dose of dexamethasone (Table 2)<sup>79,80</sup>; however, dose-ranging data for delayed emesis are lacking. When corticosteroids are administered with the moderate cytochrome P-450 3A4 inhibitor aprepitant, doses should be reduced by approximately 50% (Table 2). The only exception would be cases in which corticosteroids constitute part of the antineoplastic regimen. In those instances, therapeutic corticosteroid doses should not be attenuated.

#### AGENTS WITH A LOW THERAPEUTIC INDEX

A number of agents, including metoclopramide, butyrophenones, phenothiazines, cannabinoids, and olanzapine, are included among antiemetic agents with a lower therapeutic index (Table 3). These drugs are generally characterized by lower efficacy and a greater potential for adverse effects, as compared with the agents with a high therapeutic index. In addition, the clinical database supporting their use is less robust. The phenothiazines constitute the oldest and most widely used agents in this category. They are appropriate for use as primary prophylaxis in patients receiving chemotherapy with a low emetogenic potential or for use as a salvage agent for patients in whom breakthrough emesis is developing. Metoclopramide, at standard doses, and the butyrophenones, like the phenothiazines, are also dopaminergic D<sub>2</sub> antagonists and have a similar spectrum of use.<sup>81,82</sup> The efficacy of metoclopramide improves with increasing doses, probably because of its capacity to inhibit 5-HT<sub>3</sub> receptors at higher blood concentrations.<sup>83</sup> The synthetic cannabinoids nabilone and dronabinol have also been shown to have antiemetic efficacy, especially for chemotherapy with low-to-moderate emetic potential<sup>53</sup>; adverse effects such as postural hypotension and dysphoria limit their usefulness. Olanzapine, which antagonizes several neurotransmitter receptors, including dopamine and 5-HT receptors, has been shown in two

phase 2 trials to be effective in preventing both acute and delayed chemotherapy-induced nausea and vomiting.<sup>84,85</sup> Information on the comparative efficacy of this agent with other antiemetics or on its use in combination with aprepitant is not available.

Benzodiazepines are another class of agents that may be helpful in some situations. Although benzodiazepines have modest antiemetic efficacy, their antianxiety properties can be useful in some settings.<sup>86,87</sup> The most commonly used agent in the class is lorazepam, which is helpful in the prevention and treatment of anticipatory emesis and as an adjunct to other antiemetic agents when first-line agents fail.

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#### MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

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The introduction of 5-HT<sub>3</sub> antagonists approximately 20 years ago led to an unprecedented increase in clinical trials evaluating chemotherapy-induced nausea and vomiting. This was an important stimulus behind efforts to standardize the methods for evaluating new approaches to treating the problem.<sup>88</sup> As a consequence, a relative abundance of data from well-designed, methodologically sound clinical trials is available to guide treatment decisions for acute and, to a lesser extent, delayed nausea and vomiting arising from intravenously administered chemotherapy. A number of professional oncology groups have analyzed the data and developed evidence-based treatment recommendations. Four groups (the Multinational Association of Supportive Care in Cancer, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the European Society for Medical Oncology) have recently published updated antiemetic guidelines.<sup>13,57,89,90</sup> There is broad agreement among these groups on most key issues. The treatment recommendations that follow reflect a composite of the consensus recommendations of these groups.

#### SINGLE-DAY CHEMOTHERAPY

Chemotherapy used in the treatment of most non-hematologic and some hematologic cancers is most frequently administered intravenously over the course of a single day. This is also the setting in which clinical data on the use of antiemetic agents are most abundant. The fundamental principle that should guide decisions about antiemetic treatment is that complete prevention of nausea and vomit-



ing is the ultimate objective, and it is best accomplished with the use of appropriate, evidence-based preventive treatment. The choice of regimen is guided by two considerations: the emetogenic potential of the chemotherapy and whether there is a substantial risk of delayed nausea and vomiting. There is level 1 evidence<sup>91</sup> — defined as evidence from at least one well-designed, randomized trial with a low false positive (alpha level) error rate — to support specific treatment recommendations in several single-day chemotherapy settings (Table 4).

#### *High Emetic Risk*

The combination of a 5-HT<sub>3</sub> antagonist, dexamethasone, and aprepitant is recommended before the administration of chemotherapy that is associated with a high risk of emesis (Table 4). Abundant clinical data support this combination for patients receiving cisplatin-based chemotherapy.<sup>13,57</sup> Very limited data are available to support the use of this regimen with other agents that are associated with a high emetic risk; however, professional oncology groups consistently recommend the use of this regimen with all agents for which the risk of emesis is high. Delayed emesis develops in approximately 90% of patients treated with cisplatin in the absence of appropriate prophylaxis.<sup>15</sup> Patients receiving chemotherapy with high emetogenic potential should receive a combination of aprepitant on days 2 and 3 and dexamethasone on days 2 to 4 (Table 4). As with acute emesis, this recommendation is primarily based on data with cisplatin.

#### *Moderate Emetic Risk*

In patients receiving treatment with an anthracycline and cyclophosphamide, a combination of a 5-HT<sub>3</sub> antagonist, dexamethasone, and aprepitant is recommended before chemotherapy (Table 4).<sup>13,57,89,90</sup> Because this chemotherapeutic regimen has a moderate potential for delayed emesis, aprepitant should also be administered on days 2 and 3. With other chemotherapeutic regimens that have moderate emetogenic potential, a combination of a 5-HT<sub>3</sub> antagonist and dexamethasone is recommended before chemotherapy, with a 5-HT<sub>3</sub> antagonist or dexamethasone given alone on days 2 and 3.<sup>13,57,89,90</sup> For many chemotherapeutic agents that are associated with a moderate risk of emesis, like those associated with a high risk, there is limited knowledge of the potential for delayed emesis. Nevertheless, prophylactic treatment is recommended.

#### *Low Emetic Risk*

A single dose of dexamethasone before chemotherapy is recommended for agents associated with a low risk of emesis (Table 4).<sup>13,57,89,90</sup> A single dose of a dopaminergic antagonist is another reasonable preventive option.<sup>89</sup> No routine prophylaxis for delayed emesis is indicated. Although guidelines from oncology groups are in agreement with this recommendation, it is not based on prospective clinical trial data.

#### *Minimal Emetic Risk*

No routine prophylaxis for acute or delayed emesis is warranted for chemotherapeutic agents that are associated with a minimal risk of emesis.

#### **OTHER CHEMOTHERAPY SETTINGS**

A number of other settings may lead to nausea and vomiting in patients receiving chemotherapeutic agents. Some regimens are administered on multiple, consecutive days. Often, the most emetogenic agents are given on day 1, and for these regimens, single-day antiemetic treatment will suffice. In other instances, such as consecutive-day administration of cisplatin or high-dose regimens used in hematopoietic stem-cell transplantation, different approaches are required. Limited prospective data suggest that daily administration of a 5-HT<sub>3</sub> antagonist and dexamethasone for highly emetogenic, multiple-day chemotherapeutic regimens is most appropriate.<sup>92</sup> The role of aprepitant in such situations has not been defined.

In recent years, there has been increasing use of orally administered antineoplastic agents. Most such agents are dispensed on multiple-day schedules. Although classification of the emetic potential of orally administered antineoplastic agents has been proposed,<sup>93</sup> almost no prospective data are available to guide the use of antiemetic agents in such cases. Thus, treatment remains largely empirical.

Anticipatory emesis also presents a unique challenge. Believed to represent a conditioned reflex in response to poor prior control of emesis, it has become less common because control of chemotherapy-induced nausea and vomiting has improved, starting with the initial cycle of chemotherapy. Behavioral therapy with systematic desensitization, together with benzodiazepines, may be helpful in treating anticipatory emesis, should it occur.<sup>94</sup>

Few prospective data are available to guide treatment decisions when so-called breakthrough

**Table 4. Recommended Antiemetic Treatment for Single-Day, Intravenously Administered Chemotherapy.**

Emetogenic Level	Risk of Emesis %	Antiemetic Regimen	
		Before Chemotherapy (day 1)	After Chemotherapy
1	<10 (minimal)	None	None
2	10–30 (low)	Dexamethasone or prochlorperazine	None
3	31–90 (moderate)		
	For anthracycline plus cyclophosphamide	5-HT <sub>3</sub> -receptor antagonist, dexamethasone, and aprepitant*	Aprepitant on days 2 and 3 or dexamethasone on days 2 and 3*
	For other regimens	5-HT <sub>3</sub> -receptor antagonist and dexamethasone†	5-HT <sub>3</sub> -receptor antagonist or dexamethasone on days 2 and 3
4	>90 (high)	5-HT <sub>3</sub> -receptor antagonist, dexamethasone, and aprepitant*	Dexamethasone on days 2–4 and aprepitant on days 2 and 3*

\* The recommendations for aprepitant are supported by level 1 evidence (data from at least one high-quality randomized trial).<sup>91</sup>

† The recommendation for 5-HT<sub>3</sub>-receptor antagonist and dexamethasone administered on day 1 with emetogenic level 3 chemotherapy is supported by level 1 evidence.

emesis develops, even after oncology group guidelines have been followed. Lack of standardized methods for evaluating breakthrough emesis has hindered the performance of prospective trials. Treatment is largely empirical, with phenothiazines and benzodiazepines often used. There is some evidence that the addition of a dopamine-receptor antagonist may improve antiemetic control in subsequent cycles.<sup>95,96</sup>

Finally, as strategies to prevent vomiting have become more successful, the problem of nausea has become the major remaining challenge. Control of nausea has consistently lagged behind control of emesis, even with the introduction of newer antiemetic agents.<sup>2</sup> This problem is illustrated in a phase 3 trial evaluating the role of aprepitant in patients receiving chemotherapy with an anthracycline combined with cyclophosphamide.<sup>66</sup> The proportion of patients in the aprepitant group who had no vomiting differed significantly from the proportion in the control group (76% vs. 59%). Despite this difference in vomiting, similar proportions of patients used antiemetic rescue medications, implying similar rates of nausea in the two groups. This possibility is supported by results of the nausea assessments. On the basis of scores on visual analogue scales, the rates of both

overall and clinically significant nausea were similar in the two groups. New antiemetic treatment strategies are going to be needed to improve the control of nausea.

#### SUMMARY

Over the past two decades, more effective and better-tolerated pharmacologic agents have been developed to prevent chemotherapy-induced nausea and vomiting. Selective 5-HT<sub>3</sub> antagonists, neurokinin-1 antagonists, and corticosteroids are at present the most effective therapeutic agents. Despite the progress, uncontrolled vomiting and inadequately controlled nausea remain major problems in a minority of patients. Nonetheless, complete prevention of chemotherapy-induced nausea and vomiting should be a realistic goal for most patients receiving emetogenic chemotherapy.

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