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Pharmacological Management of Chemotherapy-Induced Nausea and Vomiting

Focus on Recent Developments

Rudolph M. Navari

Department of Medicine, Indiana University School of Medicine, South Bend and Walther Cancer Research Center, University of Notre Dame, South Bend, Indiana, USA

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life. The emetogenicity of the chemotherapeutic agents, repeated chemotherapy cycles and patient risk factors significantly influence CINV. Serotonin 5-HT_3 receptor antagonists plus dexamethasone have significantly improved the control of acute CINV, but delayed CINV remains a significant clinical problem.

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Two new agents, palonosetron and aprepitant, have recently been approved for the prevention of both acute and delayed CINV. Palonosetron is a second-generation 5-HT_3 receptor antagonist with a longer half-life and a higher binding affinity than first-generation 5-HT_3 receptor antagonists. Aprepitant is the first agent available in the new drug class of neurokinin-1 (NK-1) receptor antagonists. Casopitant is another NK-1 receptor antagonist, which is under review by the US FDA after recent completion of phase III clinical trials.

The introduction of these new agents has generated revised antiemetic guidelines for the prevention of CINV. Future studies may consider the use of palonosetron, aprepitant and casopitant with other antiemetic agents (e.g. olanzapine, gabapentin, cannabinoids) in moderately and highly emetogenic chemotherapy, as well as in the clinical settings of multiple-day chemotherapy and bone marrow transplantation.

Chemotherapy-induced nausea and vomiting (CINV) is a distressing and common adverse event associated with cancer treatment. Seventy to eighty percent of patients undergoing chemotherapy experience emesis, with 10–44% experiencing anticipatory emesis.[1] CINV results in significant morbidity and negatively effects patient quality of life (QOL).[2,3] CINV may result in non-adherence to or dose reductions in chemotherapy.[4]

Increased risk of CINV is associated with the type of chemotherapy administered (table I) and specific patient characteristics (table II).[5,6] CINV can result in weakness, weight loss, electrolyte imbalance, dehydration or anorexia, and is associated with a variety of complications, including fractures, oesophageal tears, decline in behavioural and mental status, and wound dehiscence.[1] Patients who are dehydrated, debilitated or malnourished, as well as those who have an electrolyte imbalance or those who have recently undergone surgery or radiation therapy, are at greater risk of experiencing serious complications from CINV.[1]

Despite the introduction of more effective antiemetic agents (serotonin 5-HT_3 and neurokinin-1 [NK-1] receptor antagonists), emesis and nausea remain a significant complication of chemotherapy. This article reviews the clinical agents available for the prevention and treatment of CINV. The use of these agents in various clinical settings is described using the recently established American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) guidelines. The literature cited in this article consists of the primary clinical trials used for the US FDA approval of the various agents as well as recent comprehensive reviews.

Table I. Emetic potential of chemotherapy agents[6]

Emetogenic potential	Definition	Typical agents
High	Emesis in nearly all patients	Cisplatin Dacarbazine Melphalan (high dose) Nitrogen mustard
Moderate	Emesis in >70% of patients	Anthracyclines Carboplatin Carmustine (high dose) Cyclophosphamide Ifosfamide Irinotecan Methotrexate (high dose) Oxaliplatin Topotecan
Low	Emesis in 10–70% of patients	Etoposide Fluorouracil Gemcitabine Mitoxantrone Taxanes Vinblastine Vinorelbine
Minimal	Emesis in <10% of patients	Bortezomib Hormones Vinca alkaloids Bleomycin

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Table II. Patient-related risk factors for emesis following chemotherapy[5,6]

Major factors
Female
Age <50 y
History of low prior chronic alcohol intake
History of previous chemotherapy-induced emesis
Minor factors
History of motion sickness
Emesis during past pregnancy

1. Chemotherapy-Induced Nausea and Vomiting (CINV)

1.1 Pathophysiology of Nausea and Vomiting

The sensation of nausea and act of vomiting are protective reflexes that rid the intestine and stomach of toxic substances. The experience of nausea is subjective and nausea may be considered a prodromal phase to the act of vomiting,[7] although significant nausea may occur without vomiting. Vomiting consists of a pre-ejection phase, retching and ejection, and is accompanied by shivering and salivation. Vomiting is triggered when afferent impulses from the cerebral cortex, chemoreceptor trigger zone (CTZ), pharynx and vagal afferent fibres of the gastrointestinal (GI) tract travel to the vomiting centre (VC), located in the medulla (figure 1). Efferent impulses then travel from the VC to the abdominal muscles, salivation centre, cranial nerves and respiratory centre, causing vomiting. It is thought that chemotherapeutic agents cause vomiting by activating neurotransmitter receptors located in the CTZ, GI tract and VC. Serotonin, dopamine and substance P receptors are the primary neuroreceptors involved in the emetic response.[1,7,8]

The mechanisms of emesis are not well defined, but investigations suggest that it may be primarily mediated through neurotransmitters in the GI tract and the CNS. Figure 1 shows how chemotherapy agents, or their metabolites in the blood or cerebrospinal fluid, may directly affect areas in the medulla oblongata or may stimulate the GI tract via the vagus nerve to send impulses to the medulla. A VC, termed the 'central pattern generator' by some authors,[9] appears to be located in the lateral reticular formation of the medulla, which coordinates the mechanism of nausea and vomiting. An additional important area, also located in the medulla, is the CTZ in the area postrema near the fourth ventricle.[9] It is strongly suspected that the nucleus tractus solitarius (NTS) neurons lying ventrally to the area postrema initiate emesis.[10] This medullary area is a convergence point for projections arising from the area postrema, and the vestibular and vagal afferents.[10] The NTS is a good candidate for the site of action of centrally acting antiemetics.

The main approach to the control of emesis has been to identify the active neurotransmitters and their receptors in the CNS and the GI tract that mediate the afferent inputs to the VC (figure 2). Agents that may block these

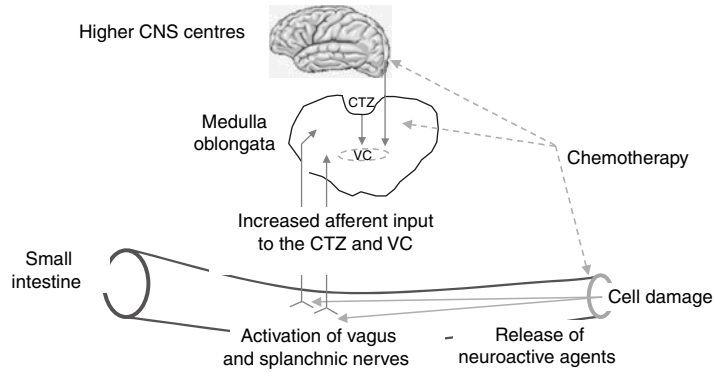

Fig. 1. Proposed pathways of chemotherapy-induced emesis. **CTZ** = chemoreceptor trigger zone; **VC** = vomiting centre.

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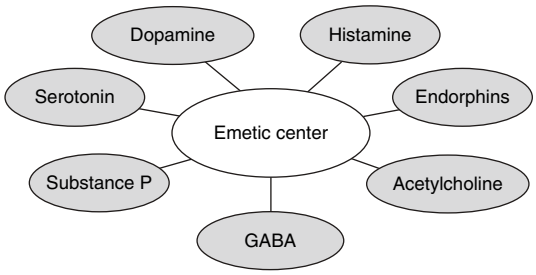

Fig. 2. Neurotransmitters involved in emesis.

neurotransmitter receptors in the CTZ, the VC or the GI tract may be useful in preventing or controlling emesis (table III).

1.2 Types of CINV

Five categories are used to classify CINV: acute, delayed, anticipatory, breakthrough and refractory. Nausea and vomiting may occur any time after the administration of chemotherapy, but the mechanisms appear different for CINV occurring in the first 24 hours after chemotherapy in contrast to that which occurs in the period of 1–5 days after chemotherapy. In order to differentiate these mechanisms, the term acute-onset CINV refers to nausea and/or vomiting occurring within 24 hours of chemotherapy administration.[5] The incidence of acute emesis reflects several treatment-related factors, including the environment in which chemotherapy is administered, the emetogenicity of the antiemetic therapy, the dosage of the emetogenic agents, and patient-related factors.[1,11]

Nausea and/or vomiting that develop more than 24 hours after chemotherapy administration is known as delayed emesis. Typically occurring with administration of carboplatin, doxorubicin or cyclophosphamide, delayed emesis is more common in those who experience acute emesis. Other predictive factors include the dose and the emtogenicity of the chemotherapeutic agent, patient sex and age, and protection against nausea and vomiting in previous cycles of chemotherapy.[3,11] For cisplatin, which has been most extensively studied, delayed emesis reaches peak intensity 2–3 days subsequent to chemotherapy administration and can last up to a week.[1,11,12]

If patients experience CINV, they may develop a conditioned response known as anticipatory nausea and/or vomiting, which occurs before the administration of chemotherapy in future chemotherapy cycles and is attributed to the adverse memory of earlier CINV. Incidence rates for this type of nausea and vomiting range from 10% to 45%, with nausea occurring more frequently.[1,13]

Vomiting that occurs within 5 days after prophylactic use of antiemetic agents or requires 'rescue' is called breakthrough emesis. Vomiting occurring after chemotherapy in subsequent chemotherapy cycles when antiemetic prophylaxis and/or rescue have failed in earlier cycles is known as refractory emesis.[1]

2. Antiemetic Agents

2.1 Dopamine Receptor Antagonists

Dopamine receptors are known to exist in the CTZ, and this is the main area of activity of the dopamine antagonists, such as the phenothiazines and the butyrophenones (droperidol, haloperidol). A high level of blockade of the dopamine receptors, however, results in extrapyramidal reactions, as well as disorientation and sedation, limiting the clinical use of these agents.

2.2 Serotonin 5-HT_3 Receptor Antagonists

Serotonin receptors, specifically the 5-HT_3 receptors, exist in the CNS and in the GI tract. The 5-HT_3 receptor antagonists, such as dolasetron, granisetron, ondansetron and tropisetron, appear to act through both the CNS and the GI tract via the vagus and splanchnic nerves. The main toxicities of these 5-HT_3 receptor antagonists consist only of a mild headache and occasional diarrhoea.

The effectiveness of the 5-HT_3 receptor antagonists in cisplatin-induced acute emesis[14-17] is believed to be due to a predominately peripheral site of action, the prevention of the stimulation of abdominal vagal afferent fibres by serotonin released from the enterochromaffin cells of the gut by cytotoxic agents. This has been well documented in animal ferret models.[18] 5-HT_3 receptor antagonists have been less effective in delayed cisplatin-induced emesis both in humans[19-24] and in ferret

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Table III. Antiemetic receptor antagonists

Dopamine receptor antagonists	Serotonin 5-HT_3 receptor antagonists	Dopamine/5-HT_3 receptor antagonists	Neurokinin-1 receptor antagonists
Phenothiazines	Azasetron	Metoclopramide	Aprepitant
Butyrophenones	Dolasetron		Fosaprepitant
	Granisetron		Casopitant
	Ondansetron		Vofopitant
	Ramosetron		CP-122 721
	Tropisetron		CJ-11 794
	Palonosetron		

models.[25] This may be due to the lack of central effect by the 5-HT_3 receptor antagonists, as demonstrated by the ineffectiveness of the 5-HT_3 receptor antagonists against the emesis induced by the centrally acting opioids (apomorphine, morphine) in experimental animals.[26]

The introduction of 5-HT_3 receptor antagonists for the prevention of CINV, as well as postoperative and radiotherapy-induced nausea and vomiting, has resulted in a major improvement in supportive care.[27-29] Treatment guidelines for the prevention of CINV recommended by a number of international groups[1,11-13] suggest the use of a 5-HT_3 receptor antagonist and dexamethasone prechemotherapy for the prevention of acute CINV, and the use of dexamethasone with or without a 5-HT_3 receptor antagonist following chemotherapy for the prevention of delayed nausea and vomiting.

Table IV shows the 5-HT_3 receptor antagonists currently in use. The first-generation 5-HT_3 receptor antagonists dolasetron, granisetron, ondansetron, tropisetron,[30] azasetron[31] and ramosetron[32] are equivalent in efficacy and toxicities when used in the recommended doses and compete only on a cost basis.[33] They have not been associated with major toxicities, with the most commonly reported adverse events being mild headache, constipation and occasionally mild diarrhoea.[14,15,28,34,35] A prolongation of cardiac conduction intervals has been reported for this class of compounds with dolasetron being more extensively studied than granisetron and ondansetron, but there have been no reported clinical cardiovascular adverse events.[35]

The first-generation 5-HT_3 receptor antagonists have not been as effective against delayed emesis as they are against acute CINV.[19-24] The available studies show that corticosteroids, alone or combined with either metoclopramide or a 5-HT_3 receptor antagonist in patients receiving cisplatin, reduce the incidence of delayed emesis, but it remains a significant problem.[29,36] The first-generation 5-HT_3 receptor antagonists do not add significant efficacy to that obtained by dexamethasone alone in the control of delayed emesis.[22] Hickok et al.[24] reported that the first-generation 5-HT_3 receptor antagonists used in the delayed period were no more effective than perchlorperazine in controlling nausea. A recent meta analysis[23] showed that there was neither clinical evidence nor considerations of cost effectiveness to justify using the first-generation 5-HT_3 antagonists beyond 24 hours after chemotherapy for the prevention of delayed emesis.

The second-generation 5-HT_3 receptor antagonist palonosetron has been approved for clinical use, and studies suggest that it may

Table IV. Serotonin 5-HT_3 receptor antagonists and dosage before chemotherapy[a]

Antiemetic	Route	Dosage
Azasetron	IV	10 mg
Dolasetron	IV	100 mg or 1.8 mg/kg
	PO	100 mg
Granisetron	IV	10 μg/kg or 1 mg
	PO	2 mg (or 1 mg twice daily)
Ondansetron	IV	8 mg or 0.15 mg/kg
	PO	24 mg
Ramosetron	IV	0.30 mg
Tropisetron	IV or PO	5 mg
Palonosetron	IV	0.25 mg

a The same doses are used for highly and moderately emetic chemotherapy.

IV = intravenous; **PO** = oral.

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have some efficacy in controlling delayed CINV compared with the first-generation 5-HT_3 receptor antagonists.

2.2.1 Palonosetron

Palonosetron is a 5-HT_3 receptor antagonist that has antiemetic activity at both central and GI sites. Compared with the older 5-HT_3 receptor antagonists, it has a higher binding affinity to the 5-HT_3 receptors, a higher potency, a significantly longer half-life (approximately 40 hours, four to five times longer than that of dolasetron, granisetron or ondansetron) and an excellent safety profile.[29] In two large studies[37,38] in patients receiving moderately emetogenic chemotherapy, complete response (no emesis, no rescue) was improved in the acute and the delayed period for the patients who received palonosetron 0.25 mg alone compared with either ondansetron alone (570 patients; acute: 81.0% vs 68.6%, $p = 0.008$; delayed: 74.1% vs 55.1%, $p < 0.001$)[38] or dolasetron alone (592 patients; acute: 63.0% vs 52.9%, $p = 0.049$; delayed: 54.0% vs 38.7%, $p = 0.004$).[37] Dexamethasone was given with the 5-HT_3 receptor antagonists to only a small number of patients (5%) in only one of these studies,[37] and it remains to be determined if the differences in complete response would persist if dexamethasone was used.

In another study, 650 patients receiving highly emetogenic chemotherapy (cisplatin ≥60 mg/m^2) received dexamethasone plus one of two doses of palonosetron (0.25 or 0.75 mg) or dexamethasone plus ondansetron (32 mg) pre-chemotherapy. Patients pre-treated with palonosetron (0.25 mg) plus dexamethasone had significantly higher complete response rates than those receiving ondansetron plus dexamethasone during the delayed and overall periods.[39]

In an analysis of the patients in these studies who received repeated cycles of chemotherapy, Cartmell et al.[40] reported that the complete response rates for both acute and delayed CINV were maintained with the single intravenous dose of palonosetron without concomitant corticosteroids.

On the basis of the above studies, palonosetron was approved by the FDA in July 2003, for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy; and for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Despite the use of both first- and second-generation 5-HT_3 receptor antagonists, the control of acute CINV, and especially delayed nausea and vomiting, is suboptimal with the agents listed in table IV. There is considerable opportunity for improvement with either the addition or substitution of new agents in current regimens.[29,36,41]

2.3 Dopamine-Serotonin Receptor Antagonists

Metoclopramide has antiemetic properties both in low doses as a dopamine antagonist and in high doses as a serotonin antagonist. The use of oral metoclopramide may be somewhat efficacious in relatively high doses (20 mg three times per day) in the delayed period, but may result in sedation and extrapyramidal side effects.[27,29,41]

2.4 Neurokinin-1 Receptor Antagonists

Substance P is a mammalian tachykinin that is found in vagal afferent neurons innervating the brainstem NTS, which sends impulses to the VC.[42] Substance P induces vomiting and binds to NK-1 receptors in the abdominal vagus, the NTS and the area postrema.[42] Compounds that block NK-1 receptors lessen emesis after cisplatin, ipecac, apomorphine and radiation therapy.[42] These observations have recently led to the development of NK-1 receptor antagonists and the study of the role they may play in controlling chemotherapy-induced nausea and emesis.

Studies in rhesus monkeys using positron emission tomography scans have demonstrated that the experimental NK-1 receptor antagonist vofopitant, when administered peripherally, had a distribution into brain regions consistent with specific binding to NK-1 receptors.[43] Injection of the NK-1 receptor antagonists CP-99 994 or aprepitant directly into the vicinity of the NTS

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neurons inhibited cisplatin-induced emesis in the ferret.[44] These results suggest that NK-1 receptor antagonists may exert their main antiemetic action by depressing the neural activity of the NTS neurons, with possibly some antiemetic effects from peripheral sites through a blockade of the NK-1 receptors located on the vagal terminals in the gut.[45-47]

Tattersall et al.[47] have reported that aprepitant and its water-soluble phosphoryl prodrug, fosaprepitant, inhibited acute and delayed cisplatin-induced emesis in a ferret animal model. A single dose of aprepitant prior to cisplatin decreased emesis during a 72-hour period and daily administration eliminated emesis during the entire 72-hour observation period. These animal studies provided the basis for the phase II and III clinical studies of NK-1 receptor antagonists.[48-60]

2.4.1 Aprepitant

The initial clinical studies using the NK-1 receptor antagonists[48-50] demonstrated that the addition of a NK-1 receptor antagonist (CP-122 721, CJ-11 794, fosaprepitant, aprepitant) to a 5-HT_3 receptor antagonist plus dexamethasone prior to cisplatin chemotherapy improved the control of acute emesis compared with the 5-HT_3 receptor antagonist plus dexamethasone, and improved the control of delayed emesis compared with placebo. In addition, as a single agent, fosaprepitant had a similar effect on cisplatin-induced acute emesis as ondansetron, but was superior in the control of delayed emesis.[51] Subsequent studies[52,53] showed that the combination of aprepitant plus dexamethasone was similar to a 5-HT_3 receptor antagonist plus dexamethasone in controlling acute emesis, was inferior in controlling acute emesis compared with triple therapy (aprepitant, 5-HT_3 receptor antagonist, dexamethasone) and confirmed the improvement of delayed emesis with the use of aprepitant compared with placebo.

In a dose administration study of oral aprepitant, which was the final capsule formulation, involving 563 chemotherapy-naive patients receiving cisplatin (≥70 mg/m^2), Chawla et al.[54] reported an improvement in the control of acute emesis when aprepitant was added to ondansetron plus dexamethasone and an improvement in the control of delayed emesis with the combination of aprepitant and dexamethasone compared with dexamethasone alone. Aprepitant 125 mg on day 1 followed by 80 mg on subsequent days appeared to be the regimen appropriate for further study.

In two randomized, double-blind, parallel, multicentre, controlled studies (520 patients in each study), patients received cisplatin (≥70 mg/m^2) and were randomized to receive 'standard therapy' of a 5-HT_3 receptor antagonist (ondansetron) plus dexamethasone pre-chemotherapy and dexamethasone post-chemotherapy (days 2–4) or 'standard therapy' plus aprepitant given prior to chemotherapy and aprepitant plus dexamethasone on days 2 and 3 post-chemotherapy.[55,56] The complete response (no emesis, no rescue) of the aprepitant group in both studies was significantly higher in the acute period (83–89%), the delayed period (68–75%) and overall (days 1–5) [62.7–72.7%] compared with that in the acute period (68–78%), the delayed period (47–56%) and overall (days 1–5) [43.3–52.3%] of the 'standard therapy'. The improvement in complete response with the addition of aprepitant was maintained over multiple cycles of chemotherapy.[57,61] Nausea was improved in the aprepitant group only in the delayed period in only one of the studies.[56]

The studies discussed in this section formed the basis for the approval of aprepitant by the FDA in March 2003. In combination with other antiemetics, aprepitant is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.[62,63]

In a follow-up study to the two randomized studies described previously, the aprepitant regimen was shown to have a higher complete response in patients receiving cisplatin not only to the 1-day ondansetron plus 4-day dexamethasone regimen in the previous trials, but also to a 4-day ondansetron plus 4-day dexamethasone regimen.[58]

All of the initial studies using aprepitant were performed with cisplatin chemotherapy. Recently, Warr et al.[59] presented a study on the use of

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aprepitant in 862 breast cancer patients receiving moderately emetogenic chemotherapy. An aprepitant regimen of aprepitant 125 mg, ondansetron 8 mg plus dexamethasone 12 mg pre-chemotherapy, then ondansetron (8 mg) 8 hours later on day 1, and aprepitant 80 mg/day on days 2 and 3 was compared with a 'standard' regimen of ondansetron 8 mg plus dexamethasone 20 mg pre-chemotherapy, then ondansetron 8 mg 8 hours later on day 1, and ondansetron 8 mg twice daily on days 2 and 3. There was a significant improvement in complete response (no emesis, no rescue) in the 24 hours after chemotherapy in the patients receiving aprepitant, but there was no significant improvement in complete response on days 2–5 in the post-chemotherapy period when aprepitant alone was compared with ondansetron alone. The overall (days 1–5) complete response was significantly improved for the aprepitant-containing regimen, most likely as a result of the improvement in the first 24 hours. The control of nausea was not improved with the use of aprepitant.

Aprepitant has been generally well tolerated with no reported serious adverse toxicities. Fatigue, asthenia and hiccups have occurred in higher frequency in treatment groups compared with control groups.[55,56]

2.4.2 Fosaprepitant

A medical need exists for chemotherapy patients to have the option of parenteral administration of prophylactic antiemetics. Patients who cannot tolerate orally administered medications because of active mucositis, difficulty in swallowing or poor function of the GI tract may require intravenous antiemetics prior to chemotherapy. Intravenous dexamethasone and intravenous 5-HT_3 receptor antagonists are available, but only an oral form of aprepitant is available. An intravenous alternative to the current oral formulation for aprepitant would allow more convenient dose administration in some clinical settings while maintaining efficacy and overall therapeutic margins.

The treatment of established CINV and the rescue of failed prophylaxis may be other potential uses for an intravenous form of an antiemetic, although few studies have been conducted for these situations.

Fosaprepitant is a water soluble phosphoryl prodrug for aprepitant, which, when administered intravenously, is converted to aprepitant within 30 minutes after administration via the action of ubiquitous phosphatases. The pharmacological effect of fosaprepitant is attributed to aprepitant. As a result of the rapid conversion of fosaprepitant to the active form (aprepitant) by phosphatase enzymes, it is expected to provide the same aprepitant exposure in terms of area under the concentration-time curve (AUC) and a correspondingly similar antiemetic effect.[64]

The tolerability of fosaprepitant has been evaluated in clinical trials with approximately 150 patients.[51,53] In these studies, fosaprepitant was administered as a single intravenous dose of 0.2–200 mg infused over 15–30 minutes, reconstituted in saline or polysorbate 80 to concentrations ranging from 1 to 25 mg/mL.

Fosaprepitant has also been administered in single daily doses of 25–100 mg on four consecutive days. The studies showed acceptable venous tolerability at 1 mg/mL infused over 15–30 minutes, but a concentration of 25 mg/mL at doses of 50 and 100 mg infused over 30 seconds, was associated with venous irritation. On the basis of these studies, it appears that the incidence of venous irritation depends on the total dose, the concentration and the rate of infusion.[65]

During the development of aprepitant, certain studies that assessed the tolerability of fosaprepitant also evaluated its efficacy in patients receiving chemotherapy. In a comparison of fosaprepitant versus ondansetron, each given as monotherapy prior to cisplatin, fosaprepitant was active against cisplatin-induced emesis, particularly in the delayed phase.[51] Moreover, an additional trial demonstrated the tolerability and efficacy of fosaprepitant as part of combination therapy with dexamethasone.[53] The clinical profile of fosaprepitant in these early studies suggested that fosaprepitant could be appropriate as an intravenous alternative to the aprepitant oral capsule.

In a study in healthy volunteers, fosaprepitant was well tolerated up to 150 mg (1 mg/mL) and fosaprepitant 115 mg was AUC bioequivalent to aprepitant 125 mg.[65] Fosaprepitant in the intravenous dose of 115 mg has recently been

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approved in the US (February 2008) and the EU (January 2008) as an alternative to oral aprepitant 125 mg on day 1 of a 3-day regimen, with oral aprepitant 80 mg administered on days 2 and 3. Further studies are in progress to determine the efficacy, safety and tolerability of a single dose of intravenous fosaprepitant necessary to replace the 3-day oral regimen.[64]

2.4.3 Casopitant

Casopitant is a novel substituted piperazine derivative, which has potential for the treatment of conditions mediated by tachykinins, including substance P and other neurokinins. Casopitant competitively binds to the NK-1 receptor, thereby inhibiting NK-1 receptor binding of substance P and blocking the activity of the receptor.[60] Casopitant and its mesylate salt are being developed for the potential treatment of CINV, postoperative nausea and vomiting (PONV), anxiety, depression and insomnia. Phase II and phase III clinical trials have been completed for CINV[66-69] and PONV,[70] and applications to the FDA for these indications were made in 2008.

Two phase III clinical trials with intravenous and oral casopitant have been completed. The first was designed to demonstrate that casopitant, when used in addition to dexamethasone plus ondansetron, is more effective in the prevention of vomiting than dexamethasone plus ondansetron alone in patients with solid malignant tumours receiving cisplatin-based highly emetogenic chemotherapy.[69] Patients (n = 810) received either oral casopitant 150 mg, intravenous ondansetron 32 mg plus oral dexamethasone 8 mg on day 1 and then oral dexamethasone 8 mg twice daily on days 2–4, or intravenous casopitant 90 mg, intravenous ondansetron 32 mg plus oral dexamethasone 8 mg on day 1 and then oral casopitant 50 mg on days 2–3 plus oral dexamethasone 8 mg once daily on days 2–4. Treatment was continued for up to six cycles. A control group received intravenous ondansetron 32 mg plus oral dexamethasone 20 mg on day 1 and then oral dexamethasone 8 mg twice daily on days 2–4. Table V summarizes the complete response for the casopitant regimens compared with the control regimen. Casopitant significantly improved the complete response and this was maintained over six cycles.

The second of these phase III clinical trials was designed to establish whether casopitant, when used in addition to dexamethasone plus ondansetron, is more effective in the prevention of vomiting than dexamethasone plus ondansetron alone in patients receiving non-cisplatin-based moderately emetogenic chemotherapy.[68] 1933 patients with solid malignant tumours were enrolled, mostly breast cancer (96%), with the primary endpoint again being complete response

Table V. Complete response (no vomiting, no nausea) in phase III trials of casopitant added to ondansetron and dexamethasone for the prevention of chemotherapy-induced nausea and vomiting (CINV)

CINV	Complete Response (%)					
	Strausz et al.[69][a]			Grunberg et al.[68][b]		
	Control[c]	Casopitant 150 mg PO day 1[c] [p-value][d]	Casopitant 90 mg IV day 1, 50 mg PO days 2, 3[c] [p-value][d]	Control[e]	Casopitant 150 mg PO[e] [p-value]	Casopitant 150 mg PO day 1, 50 mg PO days 2, 3[e] [p-Value]
Overall (0–120 h)	66	86 [<0.0001]	80 [<0.0004]	59	73 [<0.0001]	73 [<0.0001]
Acute (0–24 h)	88	95 [<0.0044]	94 [<0.0165]	85	88 [<0.1586]	89 [<0.0545]
Delayed (24–120 h)				59	73 [<0.0001]	73 [0.0001]

a In patients receiving cisplatin.

b In patients receiving anthrcycline and cyclophosphamide.

c IV ondansetron 32 mg on day 1 plus PO dexamethasone 8 mg on day 1 and 8 mg twice daily on days 2–4.

d p-Values are vs control.

e PO ondansetron 8 mg twice daily on days 1–3 plus IV dexamethasone 8 mg on day 1.

IV = intravenous; **PO** = oral.

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in the first 120 hours post-chemotherapy. Patients received casopitant in a schedule of oral casopitant 150 mg on day 1 and 50 mg/day on days 2 and 3, or intravenous casopitant 90 mg on day 1, followed by 2 days of oral casopitant 50 mg/day, or oral casopitant 150 mg on day 1. Treatment was continued for up to four cycles. Patients also received oral ondansetron 8 mg twice daily on days 1–3 plus intravenous dexamethasone 8 mg on day 1. In the first 120 hours of the first treatment cycle for the intravenous/oral casopitant group, the complete response rate was 74% compared with 59% for controls ($p < 0.0001$). Table V summarizes the complete response for the two oral casopitant regimens compared with the control regimen. Casopitant significantly improved the complete response and this was maintained over four cycles.

A third phase III clinical trial has been initiated to establish the efficacy of a single intravenous dose of casopitant, administered in combination with ondansetron and dexamethasone, in preventing CINV in 700 patients with colorectal cancer receiving the moderately emetogenic chemotherapy oxaliplatin. The primary endpoint of this trial is the measurement of vomiting and the use of rescue medication during cycle 1 (not defined). This study was expected to be completed in April 2009.[71]

In the phase II and phase III studies reported, there have been no reported serious adverse events related to casopitant, and the reported common adverse events (neutropenia, constipation, alopecia and fatigue) occurred with comparable frequency across control and treatment groups.[60]

2.5 Corticosteroids

Corticosteroids have been shown in a number of studies to be effective antiemetics in the prevention of CINV.[22,72-77] When used in combination with the 5-HT_3 receptor antagonists[72-74] and in combination with the NK-1 receptor antagonists,[62] the control of CINV is markedly enhanced compared with the use of the 5-HT_3 receptor antagonists or the NK-1 antagonists alone.

The mechanism of action of the antiemetic effects of the corticosteroids is unknown. There are no data that suggest an active receptor of a site of action.

The most widely used corticosteroid antiemetic is dexamethasone with studies showing the optimal pre-chemotherapy dosages.[76,77] Although dexamethasone is effective for both acute and delayed emesis, the optimal dose for the control of delayed emesis has not been determined.

2.6 Olanzapine

Olanzapine is an FDA-approved antipsychotic that blocks multiple neurotransmitters: dopamine at D_1, D_2, D_3 and D_4 brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3 and 5-HT_6 receptors, catecholamines at α_1-adrenergic receptors, acetylcholine at muscarinic receptors and histamine at H_1 receptors.[78,79] Common adverse effects are sedation and weight gain,[80,81] as well as an association with the onset of diabetes mellitus.[82] The activity of olanzapine at multiple receptors, particularly at the D_2 and 5-HT_3 receptors, which appear to be involved in nausea and emesis, suggests that it may have significant antiemetic properties.

A phase I study demonstrated that olanzapine could be safely used for the prevention of delayed emesis in cancer patients receiving their first cycle of chemotherapy consisting of cyclophosphamide, doxorubicin, cisplatin and/or irinotecan.[83] Using the maximum tolerated dose of olanzapine in the phase I trial, a phase II trial was performed for the prevention of CINV in patients receiving their first course of either highly emetogenic or moderately emetogenic chemotherapy. When olanzapine was added to granisetron plus dexamethasone in the acute period and added to dexamethasone in the delayed period, there was a very high complete response (no emesis, no rescue) and excellent control of nausea. The study concluded that olanzapine is safe and highly effective in controlling acute and delayed CINV in patients receiving highly or moderately emetogenic chemotherapy.[84]

An additional phase II study was performed to determine the control of acute and delayed

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CINV in patients receiving moderately or highly emetogenic chemotherapy with the combined use of palonosetron, olanzapine plus dexamethasone with the dexamethasone given on day 1 only. Forty chemotherapy-naive patients received an antiemetic regimen of dexamethasone, palonosetron plus olanzapine on day 1. Patients continued olanzapine for days 2–4 following chemotherapy administration. Patients recorded daily episodes of emesis, daily symptoms utilizing the M.D. Anderson Symptom Inventory[85] and the utilization of rescue therapy. For the first cycle of chemotherapy, the complete response (no emesis, no rescue) for the acute period (24 hours post-chemotherapy) was 100%, the delayed period (days 2–5 post-chemotherapy) 75% and the overall period (0–120 hours post-chemotherapy) 75% in eight patients receiving highly emetogenic chemotherapy, and was 97%, 75% and 72% in 32 patients receiving moderately emetogenic chemotherapy. No nausea for patients in the acute period was 100%, the delayed period 50% and the overall period 50% in eight patients receiving highly emetogenic chemotherapy, and was 100%, 78% and 78% in 32 patients receiving moderately emetogenic chemotherapy. The complete response and control of nausea in subsequent cycles of chemotherapy were not significantly different from cycle one. Olanzapine combined with a single dose of dexamethasone and a single dose of palonosetron was very effective in controlling acute and delayed CINV in patients receiving both highly and moderately emetogenic chemotherapy.[86]

2.7 Gabapentin

A report by Guttuso et al.[87] in a small number of patients receiving adjuvant chemotherapy (doxorubicin plus cyclophosphamide) for breast cancer suggested that the anti-epileptic gabapentin may reduce delayed nausea. Further studies will be necessary to determine the efficacy of this agent.

2.8 Cannabinoids

Two oral formulations of cannabinoids, dronabinol and nabilone, have been approved by the FDA for use in CINV refractory to conventional antiemetic therapy.[88] The NCCN has suggested the use of cannabinoids for breakthrough treatment.[1] Cannabinoid CB_1 receptors are present in the area postrema, NTS and dorsal motor nucleus, which are key sites within the brainstem for emetogenic control.[89] Recent evidence suggests that CB_2 receptors are present on brainstem neurons and may have a role in mediating the cannabinoids effects on emesis.[89,90]

There have been no comparative studies of dronabinol and nabilone with the 5-HT_3 receptor antagonists and the NK-1 receptor antagonists in the prevention of CINV. The role of the cannabinoids in the prevention of CINV remains to be established.[88]

3. Clinical Management of CINV

3.1 Principles in the Management of CINV

During 2006–8, updated antiemetic guidelines were published by the NCCN and ASCO.[1,11,13] The updates were based, in part, on the Multinational Association Supportive Care in Cancer Antiemetic Guideline Update Meeting held in Perugia, Italy, in 2004. Representatives from nine cancer organizations (including ASCO and NCCN) participated using a literature update and consensus statements to create organization-specific guidelines.[12] NCCN guidelines are based on clinical consensus, with recommendations reflecting uniform agreement based on lower-level evidence such as clinical experience, unless specifically stated.[1]

3.2 Single-Day Chemotherapy

For patients receiving highly emetogenic chemotherapy, current evidence suggests the following:[1,11,13]

- Pre-chemotherapy: any of the 5-HT_3 receptor antagonists with dexamethasone plus aprepitant. Fosaprepitant may be administered intravenously as an alternative to oral aprepitant on day 1.
- Post-chemotherapy: aprepitant on days 2 and 3, and dexamethasone on days 2–4. Antiemetic guidelines[1,11,13] have recommended the use of

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aprepitant for patients receiving highly emetogenic chemotherapy.

For patients receiving moderately emetogenic chemotherapy, current evidence suggests the following:[1,11,13]

- Pre-chemotherapy: any of the 5-HT_3 receptor antagonists plus dexamethasone.
- Post-chemotherapy: dexamethasone or a first-generation oral 5-HT_3 receptor antagonist on days 2–4.

It should be noted that all four of the 5-HT_3 receptor antagonists available in the US are approved for the prevention of acute CINV, and palonosetron is the only 5-HT_3 receptor antagonist approved for the control of delayed CINV (in patients receiving moderately emetogenic chemotherapy). However, the recent antiemesis guidelines[1,11,13] state that at appropriate dosages, all of the 5-HT_3 antagonists are interchangeable without preference for any agent. The use of aprepitant in patients receiving moderately emetogenic chemotherapy will await review of recently presented data.[59] The guidelines also suggest consideration of the use of aprepitant for patients receiving the combination of cyclophosphamide and doxorubicin.[1,11,13]

Antiemetic guidelines of the recent past[91] as well as more recent guidelines[1,11,13] have included the available oral first-generation 5-HT_3 receptor antagonists as optional therapy for the prevention of delayed emesis, but the level of evidence supporting this practice is low.[23,24,29]

For patients receiving low emetogenic chemotherapy, a single agent in the form of a 5-HT_3 receptor antagonist, dexamethasone or a phenothiazine, depending on the clinical situation, should be used pre-chemotherapy, and an antiemetic following chemotherapy should be given only as needed.

3.3 Multiple-Day Chemotherapy

Although there have been significant improvements in the prevention of CINV in patients receiving single-day highly and moderately emetogenic chemotherapy, there has been limited progress in the prevention of CINV in patients receiving multiple-day chemotherapy or high-dose chemotherapy with stem cell transplant. The current recommendation for these patient groups is to give a first-generation 5-HT_3 receptor antagonist plus dexamethasone daily during each day of chemotherapy.[92] This regimen appears to be at least partially effective in controlling acute CINV, but is not very effective in controlling delayed CINV. The complete response in most studies of 5 days of cisplatin and in various high-dose chemotherapy regimens is 30–70% with the majority of studies reporting a complete response of ≤50%.[92]

The new antiemetic agents palonosetron, aprepitant, casopitant and olanzapine have shown effectiveness in controlling both acute and delayed CINV in patients receiving single-day moderately and highly emetogenic chemotherapy. With the exception of the use of palonosetron in one report of patients receiving 5 days of cisplatin,[93] these agents have not been studied in patients receiving multiple-day or high-dose chemotherapy.

3.4 Rescue Therapy

Intravenous phenothiazines, metoclopramide or dexamethasone may be effective in the treatment of established nausea and vomiting. A 5-HT_3 receptor antagonist may also be effective unless a patient presents with nausea and vomiting, which developed following the use of a 5-HT_3 receptor antagonist as prophylaxis for chemotherapy- or radiotherapy-induced emesis. It is very unlikely that established nausea and vomiting will respond to an agent in the same drug class after unsuccessful prophylaxis with an agent with the same mechanism of action. However, in patients receiving moderately emetogenic chemotherapy and who received ondansetron plus dexamethasone prior to chemotherapy plus dexamethasone after chemotherapy, Fabi et al.[94] used ondansetron as a rescue medication with oral ondansetron being more effective than intramuscular ondansetron.

It is important to note that aprepitant has been approved as an additive agent to a 5-HT_3 receptor antagonist plus dexamethasone for the prevention of CINV. It has not been studied

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in and should not be used to treat established nausea and vomiting.

3.5 Refractory Therapy

Vomiting occurring after chemotherapy in subsequent chemotherapy cycles when antiemetic prophylaxis and/or rescue therapy have failed in earlier cycles is known as refractory emesis.[1] A number of studies have shown that palonosetron[40] and aprepitant[57] are effective in preventing CINV over multiple cycles of chemotherapy, but there have been few formal studies in treating refractory CINV. Most practitioners will change the pre- and post-chemotherapy antiemetics in order to attempt to control refractory nausea and vomiting.

4. Summary and Conclusions

The first-generation 5-HT_3 receptor antagonists (dolasetron, granisetron, ondansetron, tropisetron, ramosetron and azasetron) have significant and similar efficacy in the prevention of acute CINV for patients receiving moderately and highly emetogenic chemotherapy. However, these agents do not appear to have significant efficacy in the prevention of delayed CINV and these 5-HT_3 receptor antagonists compete primarily on a cost basis.

Recent studies suggest that the use of palonosetron alone improves the complete response rate of acute and delayed emesis when compared with the use of the first-generation 5-HT_3 receptor antagonists alone in patients receiving moderately emetogenic chemotherapy and, in combination with dexamethasone, is effective in controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy. The complete response rates for palonosetron appear to be maintained over repeated cycles of chemotherapy for patients receiving either moderately or highly emetogenic chemotherapy. The effect of palonosetron on the control of acute and delayed CINV in combination with dexamethasone in patients receiving moderately emetogenic chemotherapy and in combination with other antiemetics will be the subject of further studies.

For patients receiving moderately or highly emetogenic chemotherapy, dexamethasone significantly improves acute CINV when added to the 5-HT_3 receptor antagonists, and it is moderately effective in the prevention of delayed CINV when used alone or in combination with other agents.

Aprepitant significantly improves the control of acute CINV when added to a 5-HT_3 receptor antagonist plus dexamethasone for patients receiving highly emetogenic chemotherapy. Aprepitant alone does not appear to control acute emesis as well as the 5-HT_3 receptor antagonists, nor in combination with dexamethasone, compared with the 5-HT_3 agents plus dexamethasone.[52] Aprepitant also improves the control of delayed CINV for patients receiving highly emetogenic chemotherapy compared with placebo, and in combination with dexamethasone when compared with dexamethasone alone. The efficacy of aprepitant appears to be maintained over repeated cycles of cisplatin chemotherapy.

Studies on the use of aprepitant in patients receiving moderately emetogenic chemotherapy suggest that the addition of aprepitant to ondansetron plus dexamethasone improved the complete response in the 24 hours post-chemotherapy, but there was no difference in complete response in days 2–5 post-chemotherapy when aprepitant alone was compared with ondansetron alone. Aprepitant did not improve nausea in the study. The appropriate use of aprepitant in patients receiving moderately emetogenic chemotherapy will be determined by future studies.

Intravenous fosaprepitant 115 mg has been recently approved as an alternative to oral aprepitant 125 mg on day 1 of a 3-day regimen, with oral aprepitant 80 mg administered on days 2 and 3. Further studies are in progress to determine the doses of fosaprepitant necessary to replace the 3-day oral regimen.

There are no published studies on the use of aprepitant alone compared with aprepitant plus dexamethasone for the prevention of delayed CINV. Such a comparison would determine whether dexamethasone might be withheld for patients who cannot tolerate corticosteroids.

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Recently completed phase III trials of casopitant have demonstrated that there is a significant improvement in the prevention of CINV with the addition of casopitant to dexamethasone plus ondansetron compared with ondansetron plus dexamethasone alone in patients receiving cisplatin or non-cisplatin chemotherapy. Casopitant can be administered orally or intravenously, and the specific dosages for use will await the FDA review of the recently reported phase III trials.

The control of nausea in patients receiving moderately and highly emetogenic chemotherapy remains a significant problem. The current 5-HT_3 receptor antagonists, while very effective in controlling emesis in a large percentage of patients in the initial 24 hours post-chemotherapy, nevertheless fail to adequately control nausea in a significant number of patients, and the recent palonosetron studies provided only marginal improvement. Pre-chemotherapy triple therapy (a 5-HT_3 receptor antagonist plus dexamethasone plus aprepitant) may control acute nausea better than a 5-HT_3 receptor antagonist plus dexamethasone,[50,52] and three studies[50,52,54] have suggested that daily dose administration of aprepitant for 5 days may improve the control of delayed nausea. Delayed nausea was improved by the addition of aprepitant to dexamethasone in one of the studies using 3-day administration,[56] but there was no improvement in nausea when the 3-day aprepitant administration was added to ondansetron plus dexamethasone in patients receiving moderately emetogenic chemotherapy.[59]

The addition of casopitant to ondansetron plus dexamethasone improved no significant nausea compared with ondansetron plus dexamethasone alone in patients receiving cisplatin chemotherapy in the recently reported phase III trial. No information on nausea control was reported in the phase III trial of the use of casopitant in breast cancer patients receiving moderately emetogenic chemotherapy.

A recent phase II study using olanzapine in combination with granisetron plus dexamethasone showed promise in controlling acute and delayed nausea in patients receiving moderately and highly emetogenic chemotherapy.[84]

On the basis of their mechanism of action, cannabinoids may be useful in the control of chemotherapy-induced nausea, but there are currently no trials that define the use of the available agents.

The introduction of the second-generation 5-HT_3 receptor antagonist palonosetron and the NK-1 receptor antagonists aprepitant and fosaprepitant have significantly improved the control of CINV. This will allow more patients to experience more normal functioning during chemotherapy with fewer toxicities. The overall cost of care as well as job absences should also be reduced.

5. Future Developments

Clinicians and other healthcare professionals who are involved in administering chemotherapy should be aware that studies have strongly suggested that patients experience more acute and delayed CINV than is perceived by practitioners,[95] and patients often do not receive adequate prophylaxis.[41,96] In addition, it is essential to emphasize that the current and new agents have been used as prophylaxis for acute and delayed CINV, and have not been studied for use in established CINV.[29,41]

Oncology practitioners now have a number of new antiemetics for use in preventing acute and delayed CINV. Future studies will determine how these agents are best used, and what combinations of new and older agents will be the most beneficial for patients.

Some questions that have arisen concerning palonosetron include: how does it differ in mechanism of action from the current 5-HT_3 receptor antagonists? Does the higher binding affinity, the longer half-life or the high potency account for the differences, or does palonosetron affect other serotonin receptors in a different way or in a different location? What are the effects of palonosetron on nausea in combination with dexamethasone or in combination with aprepitant? Future research may answer some of these questions.

Palonosetron is the only 5-HT_3 receptor antagonist with an indication for the control of

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delayed CINV, which suggests it may be more effective than first-generation 5-HT_3 receptor antagonists in patients receiving multiple-day and high-dose chemotherapy. The use of palonosetron on an every other day or daily administration schedule during the period of the multiple-day chemotherapy may be a reasonable approach in patients receiving multiple-day or high-dose chemotherapy. The use of palonosetron may treat both acute and delayed CINV and in combination with dexamethasone may result in a relatively high complete response. A specific administration schedule will require future studies.

Aprepitant is approved as an additive agent to a 5-HT_3 receptor antagonist plus dexamethasone in controlling acute and delayed CINV in patients receiving single-day chemotherapy. It is given for 3 days beginning on the day of chemotherapy. For patients receiving multiple-day or high-dose chemotherapy, a consideration for clinical implementation and for a potential clinical trial would be to add aprepitant to a 5-HT_3 receptor antagonist plus dexamethasone for the first 3 days of chemotherapy and then repeat the 3-day aprepitant regimen on the final day of chemotherapy. This approach may improve both the acute and delayed CINV during and after the multiple-day chemotherapy regimen.

On the basis of the results of the phase II and phase III clinical trials, it appears that casopitant will be efficacious when used in conjunction with ondansetron plus dexamethasone in the prevention of CINV for patients receiving either highly or moderately emetogenic chemotherapy. It is anticipated that the current data will be used for FDA review and potential approval of casopitant. Further awaited data from the phase III clinical trials should provide more information on the effectiveness of oral and intravenous dose administration, as well as any adverse events. On the basis of the information available, no serious adverse events are expected that would preclude drug approval.

It is anticipated that casopitant will have similar utility to that of aprepitant (and its prodrug fosaprepitant) and if approved by the FDA, casopitant would become the second distinct NK-1 receptor antagonist available for the prevention of CINV. The indications and potential adverse events for casopitant are likely to be similar to those of aprepitant. In its current formulation, aprepitant can be taken with or without food. Trials need to be conducted to establish whether the absorption of casopitant will be affected by food intake. On the basis of the clinical data available, casopitant currently does not appear to offer any clinical advantage over aprepitant. Although aprepitant has been highly effective in controlling emesis, it has not been effective in controlling nausea. A detailed review of the data from phase III clinical trials with casopitant will determine whether casopitant is an effective antinausea agent, and would thus have an advantage over aprepitant.

Olanzapine has been shown to be an effective agent in controlling CINV in patients receiving single-day chemotherapy when added to a 5-HT_3 receptor antagonist plus dexamethasone. The addition of olanzapine to a 5-HT_3 receptor antagonist plus dexamethasone during each day of multiple-day chemotherapy and for 3 days after the completion of the chemotherapy may significantly improve the complete response. This would be a consideration for clinical implementation and for a potential clinical trial.

Future studies of aprepitant and the new NK-1 drug class will explore their use in moderately emetogenic chemotherapy as well as in specific clinical situations, such as bone marrow transplantation and multiple-day chemotherapy regimens. Such studies will also determine the most effective use of these agents, both alone and in combination with other antiemetics. Palonosetron, aprepitant, casopitant and olanzapine have not been studied in radiotherapy-induced nausea and vomiting. Future studies may address whether these new agents would be effective in patients who experience nausea and vomiting during radiotherapy. Finally, future studies on the use of agents such as olanzapine,[69] gabapentin[70] and cannabinoids as antiemetics, agents having been initially used for other clinical indications, may not only provide additional options for the control of acute and delayed CINV, but may also provide new information on the mechanism of CINV.

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References

1. NCCN Clinical Practice Guidelines in Oncology; v0.2.2006: Antiemesis. National Comprehensive Cancer Network (NCCN) [online]. Available from URL: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. [Accessed 2006 Nov 22]
2. Cohen L, de Moor CA, Eisenberg P, et al. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 2007; 15 (5): 497-503
3. Bloechl-Daum B, Deuson RR, Mavros P, et al. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 2006; 24: 4472-8
4. Gralla RJ, de Wit R, Herrstedt J, et al. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5-HT_3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of combined data from two phase III randomized clinical trials. Cancer 2005; 104: 864-8
5. Schwartzberg L. Chemotherapy-induced nausea and vomiting: state of the art in 2006. J Support Oncol 2006; 4 (2) Suppl. 1: 3-8
6. Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-an update. Support Care Cancer 2005; 13: 80-4
7. Guyton AC. Physiology of gastrointestinal disorders. In: Guyton AC, Hall JE, editors. Textbook of medical physiology. Philadelphia (PA): Elsevier Saunders, 2006
8. Baker PD, Morzorati SL, Ellett ML. The pathophysiology of chemotherapy-induced nausea and vomiting. Gastroenterol Nurs 2005; 28: 469-80
9. Koga T, Fukuda H. Neurons in the nucleus of the solitary tract mediating inputs from vagal afferents and the area postrema in the pattern generator in the emetic act in dogs. Neurosci Res 1992; 14: 366-79
10. Yates BJ, Grelot L, Kerman IA, et al. Organization of the vestibular inputs to nucleus tractus solitarius and adjacent structures in cat brain stem. Am J Physiol 1994; 267: R974-83
11. Navari RM. Review of updated antiemetic guidelines for chemotherapy-induced nausea and vomiting. Commun Oncol 2007; 4 (1 Suppl.): 3-11S
12. Roila F, Hesketh PJ, Herrstedt J. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. Ann Oncol 2006; 17: 20-8
13. Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006; 24: 2932-47
14. Hesketh PJ, Navari RM, Grote T, et al. Double blind randomized comparison of the antiemetic efficacy of intravenous dolasetron and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. J Clin Oncol 1996; 14: 2242-9
15. Navari RM, Gandara D, Hesketh P, et al. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. J Clin Oncol 1995; 13: 1242-8
16. Navari RM, Kaplan HG, Gralla RJ, et al. Efficacy and safety of granisetron, a selective, 5-hydroxytryptamine receptor antagonist, for the prevention of nausea and vomiting induced by high dose cisplatin. J Clin Oncol 1994; 12: 2204-10
17. Perez EA. Review of the preclinical pharmacology and comparative efficacy of 5-hydroxytryptamine-3 receptor antagonists for chemotherapy-induced emesis. J Clin Oncol 1995; 13: 1036-43
18. Sanger GJ. The involvement of the 5-HT_3 receptors in visceral function. In: Hamon M, editor. Central and peripheral 5-HT_3 receptors. London: Academic Press, 1992: 207-55
19. Roila F, Warr D, Clark-Snow R, et al. Delayed emesis: moderately emetogenic chemotherapy. Support Care Cancer 2005; 13 (2): 104-8
20. Latreille J, Pater J, Johnston D, et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. J Clin Oncol 1998; 16: 1174-8
21. Navari RM, Madajcwicz S, Anderson N, et al. Oral ondansetron for the control of cisplatin-induced delayed emesis: a large, multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. J Clin Oncol 1995; 13: 2408-16
22. The Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. N Engl J Med 2000; 342: 1554-9
23. Geling O, Eichler H. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24. hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. J Clin Oncol 2005; 23: 1289-94
24. Hickok JT, Roscoe JA, Morrow GR, et al. 5-HT_3 receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomized controlled trial. Lancet Oncol 2005; 6: 765-72
25. Rudd JA, Naylor RJ. Effects of 5-HT_3 receptor antagonists on models of acute and delayed emesis induced by cisplatin in the ferret. Neuropharmacology 1994; 33: 1607-8
26. Andrews PLR. 5-HT_3 receptor antagonists and antiemesis. In: King FD, Jons BJ, Sanger GJ, editors. 5-Hydroxytryptamine-3 receptor antagonists. Boca Raton (FL): CRC Press, 1994: 255-317
27. Hesketh PJ. New treatment options for chemotherapy-induced nausea and vomiting. Support Care Cancer 2004; 12: 550-4
28. Mantovani G, Maccio A, Aslexandro B, et al. Comparison of granisetron versus ondansetron versus tropisetron in the prophylaxis of acute nausea and vomiting induced by cisplatin for the treatment of head and neck cancer; a randomized controlled trial. Cancer 1996; 77: 941-8

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29. Navari RM. Pathogenesis-based treatment of chemotherapy-induced nausea and vomiting: two new agents. J Support Oncol 2003; 1: 89-103
30. Simpson K, Spencer CM, McClellan KJ. Topisetron: an update of its use in the prevention of chemotherapy-induced nausea and vomiting. Drugs 2000; 59: 1297-315
31. Kimura E, Niimi E, Watanabe A, et al. Study on clinical effect of a continuous intravenous infusion of azasetron against nausea and vomiting induced by anticancer drugs including CDDP. Gan To Kagaku Ryoho 1996; 23: 477-81
32. Taguchi T, Tsukamoto F, Watanabe T, et al. Usefulness of ramosetron hydrochloride on nausea and vomiting in CMF or CEF therapy for breast cancer. Gan To Kagaku Ryoho 1999; 26: 1163-70
33. Hesketh PJ. Comparative review of 5-HT_3 receptor antagonists in the treatment of acute chemotherapy-induced nausea and vomiting. Cancer Invest 2000; 18: 163-73
34. Perez EA, Navari RM, Kaplan HG, et al. Efficacy and safety of different doses of granisetron for the prophylaxis of cisplatin-induced emesis. Support Care Cancer 1997; 5: 31-7
35. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine-3 receptor antagonists. Ann Pharmacother 2003; 37: 1276-86
36. Hickok JT, Roscoe JA, Morrow GR, et al. Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5 hydroxytryptamine-3 antiemetics. Cancer 2003; 97: 2880-6
37. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT_3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. Cancer 2003; 98: 2473-82
38. Gralla R, Lichinitser M, Van Der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 2003; 14: 1570-7
39. Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 2006; 17: 1441-9
40. Cartmell AD, Ferguson S, Yanagihara R, et al. Protection against chemotherapy-induced nausea and vomiting is maintained over multiple cycles of moderately or highly emetogenic chemotherapy by palonosetron, a potent 5-HT_3 receptor antagonist [abstract]. Proc Am Soc Clin Oncol 2003 May 31-Jun 3; Chicago (IL), 3041
41. Kris MG. Why do we need another antiemetic? J Clin Oncol 2003; 21: 4077-80
42. Diemunsch P, Grelot L. Potential of substance P antagonists as antiemetics. Drugs 2000; 60: 533-46
43. Fasth KJ, Bergstrom M, Kilpatrick G. Brain uptake and receptor binding of two C11 labeled selective high affinity NK-1 antagonists, GR 203040 and GR 205171. J Labeled Comp Radiopharm 1997; 40: 665-7
44. Tattersall FD, Rycroft W, Francis B, et al. Tachykinin NK-1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharmacology 1996; 35: 1121-9
45. Minami M, Endo T, Kikuchi K, et al. Antiemetic effects of sendide, a peptide tachykinin NK-1 receptor antagonist, in the ferret. Eur J Pharmacol 1998; 363: 49-55
46. Minami M, Endo T, Yokoda H, et al. Effects of CP-99,994, a tachykinin NK-1 receptor antagonist, on abdominal afferent vagal activity in ferrets: evidence for involvement of NK-1 and 5-HT_3 receptors. Eur J Pharmacol 2001; 428: 215-20
47. Tattersall FD, Rycroft W, Cumberbatch M, et al. The novel NK-1 receptor antagonist MK-869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 2000; 39: 652-63
48. Kris MG, Radford JE, Pizzo BA, et al. Use of a NK-1 receptor antagonist to prevent delayed emesis after cisplatin [letter]. J Natl Cancer Inst 1997; 89: 817-8
49. Hesketh PJ, Gralla RJ, Webb RT, et al. Randomized phase II study of the neurokinin-1 receptor antagonist CJ-11,974 in the control of cisplatin-induced emesis. J Clin Oncol 1999; 17: 338-43
50. Navari RM, Reinhardt RR, Gralla RJ, et al. Reduction of cisplatin-induced emesis by a selective neurokin-1 receptor antagonist. N Engl J Med 1999; 340: 190-5
51. Cocquyt V, Van Belle S, Reinhardt RR, et al. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. Eur J Cancer 2001; 37: 835-42
52. Campos D, Pereira JR, Reinhardt RR, et al. Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001; 19: 1759-67
53. Van Belle S, Liechinitser M, Navari RM, et al. Prevention of cisplatin- induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. Cancer 2002; 94: 3032-41
54. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK-1 antagonist Aprepitant for chemotherapy-induced nausea and vomiting. Cancer 2003; 97: 2290-300
55. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind placebo-controlled trial in patients receiving high-dose cisplatin: the Aprepitant protocol 052 study group. J Clin Oncol 2003; 21: 4112-9
56. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Cancer 2003; 97: 3090-8
57. De Wit R, Herrstedt J, Rapoport BL, et al. Addition of the oral NK-1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003; 21: 4105-11

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58. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. Ann Oncol 2006; 17 (6): 1000-6
59. Warr DG, Hesketh PJ, Gralla RJ, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. J Clin Oncol 2005; 23: 2822-30
60. Navari RM. Casopitant, a neurokinin-1 receptor antagonist with anti-emetic and antinausea activities. Curr Opin Investig Drugs 2008; 9: 774-85
61. De Wit R, Herrstedt J, Rapoport B, et al. The oral NK-1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. Eur J Cancer 2004; 40: 403-10
62. Navari RM. Aprepitant: a neurokinin-1 receptor antagonist for the treatment of chemotherapy-induced nausea and vomiting. Expert Rev Anticancer Ther 2004; 4 (5): 715-24
63. Dando TM, Perry CM. Aprepitant: a review of its use in the prevention of chemotherapy-induced nausea and vomiting. Drugs 2004; 64: 777-94
64. Navari RM. Fosaprepitant (MK-0517): a neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. Expert Opin Investig Drugs 2007; 16: 1977-85
65. Lasseter KC, Gambale J, Jin B, et al. Tolerability of fosaprepitant and bioequivalency to aprepitant in healthy subjects. J Clin Pharmacol 2007; 47: 834-40
66. Arpornwirat W. Multicenter randomized, double-blind, ondansetron (ond)-controlled, dose-ranging, parallel group trial of the neurokinin-1 receptor antagonist (NK1 RA) casopitant mesylate for chemotherapy-induced nausea/vomiting (CINV) in patients (pts) receiving moderately emetogenic chemotherapy (MEC) [abstract]. Proc Am Soc Clin Oncol 2006 Jun 2-6; Atlanta (GA), 8512
67. Rolski J. Randomized phase II trial of the neurokinin-1 receptor antagonist (NK1 RA) casopitant mesylate with ondansetron (ond)/dexamethasone (dex) for chemotherapy-induced nausea/vomiting (CINV) in patients (pts) receiving highly emetogenic chemotherapy (HEC) [abstract]. Proc Am Soc Clin Oncol 2006 Jun 2-6; Atlanta (GA), 8513
68. Grunberg SM, Aziz Z, Shaharyar A, et al. Phase III results of a novel oral neurokinin-1 (NK-1) receptor antagonist, casopitant: single oral and 3-day oral dosing regimens for chemotherapy-induced nausea and vomiting (CINV) in patients (pts) receiving moderately emetogenic chemotherapy (MEC) [abstract]. Proc Am Soc Clin Oncol 2008 May30-Jun 3; Chicago (IL), 9540
69. Strausz J, Rolski J, Aziz Z, et al. Phase III results for the novel neurokinin-1 (NK-1) receptor antagonist, casopitant: 3-Day IV/oral dosing regimen for chemotherapy-induced nausea and vomiting (CINV) in patients (Pts) receiving highly emetogenic chemotherapy (HEC) [abstract]. Proc Am Soc Clin Oncol 2008 May 30-Jun 3; Chicago (IL), 20585
70. GlaxoSmithKline. Post-operative nausea and vomiting study in female patients [ClinicalTrials.gov identifier NCT00274690]. US National Institutes of Health, Clinical Trials.gov [online]. Available from URL http://www.clinicaltrials.gov [Accessed 2008 May 13]
71. GlaxoSmithKline. Study of iv casopitant for the prevention of chemotherapy-induced nausea and vomiting [Clinical Trials.gov identifier NCT00601172]. US National Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2008 May 13]
72. Hesketh PJ, Harvey WH, Harker WG, et al. A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 1994; 12: 596-600
73. The Italian Group for Antiemetic Research. Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. N Engl J Med 1995; 332: 1-5
74. Latreille J, Stewart D, Laberge F, et al. Dexamethasone improves the efficacy of granisetron in the first 24h following high-dose cisplatin chemotherapy. Support Care Cancer 1995; 3: 307-12
75. Ioannidis JP, Hesketh PJ, Lau J. Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. J Clin Oncol 2000; 18: 3409-22
76. The Italian Group for Antiemetic Research. Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. J Clin Oncol 1998; 16: 2937-42
77. The Italian Group for Antiemetic Research. Randomized, double-blind, dose-finding study of dexamethasone in preventing acute emesis induced by anthracyclines, carboplatin, or cyclophosphamide [published erratum appears in J Clin Oncol 2004; 22: 2038]. J Clin Oncol 2004; 22: 725-9
78. Bymaster FP, Calligaro D, Falcone J, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996; 14: 87-96
79. Bymaster FP, Falcone JF, Bauzon D, et al. Potent antagonism of 5-HT_3 and 5-HT_6 receptors by olanzapine. Eur J Pharmacol 2001; 430: 341-9
80. Allison DB, Casey DE. Antipsychotic-associated weight gain: a review of the literature. J Clin Psychiatry 2001; 62: 22-31
81. Hale AS. Olanzapine. Br J Hosp Med 1997; 58: 443-5
82. Goldstein LE, Sporn J, Brown S, et al. New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999; 40: 438-43
83. Passik SD, Navari RM, Loehrer PJ, et al. A phase I trial of olanzapine (Zyprexa) for the prevention of delayed emesis in cancer patients receiving chemotherapy. Cancer Invest 2004; 22: 383-8
84. Navari RM, Einhorn LH, Loehrer PJ, et al. A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting. Support Care Cancer 2005; 13: 529-341634-46
85. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory Cancer 2000; 89: 1634-46
86. Navari RM, Einhorn LH, Loehrer PJ, et al. A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting. Support Care Cancer 2007; 15: 1285-91

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87. Guttuso T, Roscoe J, Griggs J. Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. Lancet 2003; 361: 1703-5
88. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 2005; 310: 329-32
89. Martin BR, Wiley JL. Mechanism of action of cannabinoids: how it may lead to treatment of cachexia, emesis, and pain. J Support Oncol 2004; 2: 305-16
90. Slatin MD. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: beyond prevention of acute emesis. J Support Oncol 2007; 5 (3 Suppl.): 1-9S
91. Koeller JM, Aapro MS, Gralla RJ, et al. Antiemetic guidelines: creating a more practical treatment approach. Support Care Cancer 2002; 10: 517-8
92. Navari RM. Prevention of emesis from multiple-day chemotherapy regimens. J Natl Compr Canc Netw 2007; 5: 51-9
93. Einhorn LH, Brames ML, Dreicer R, et al. Palonosetron plus dexamethasone for the prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. Support Care Cancer 2007; 15: 1293-300
94. Fabi A, Ciccarese M, Metro G, et al. Oral ondansetron is highly active as rescue antiemetic treatment for moderately emetogenic chemotherapy: results of a randomized phase II study. Support Care Cancer 2008; 16: 1375-80
95. Grunberg SM, Deuson R, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics: perception versus reality. Cancer 2004; 100: 2261-8
96. Fabi A, Barduagni M, Lauro S, et al. Is delayed chemotherapy-induced emesis well managed in oncological clinical practice? An observational study. Support Care Cancer 2003; 11: 156-61

Correspondence: Dr *Rudolph M. Navari*, 1234 Notre Dame Avenue, South Bend, IN 46617, USA.
E-mail: navari.1@nd.edu

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