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# Emerging Treatments in Chemotherapy-Induced Nausea and Vomiting

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**Abstract:** Chemotherapy-induced nausea and vomiting (CINV) is a concern for many cancer patients. It can have an enormous impact on quality of life. CINV occurring in the first 24 hours after treatment is considered acute, and CINV occurring on days 2 through 5 after treatment is considered delayed. Anticipatory nausea and depression can also occur when patients are reminded of their chemotherapy treatment. CINV can lead to weight changes, fatigue, and the need for additional medications. Even mild to moderate CINV can increase health care utilization and costs, as well as delay treatment. Nausea and vomiting are separate events, although their mechanisms are entwined. Drugs that stop vomiting do not necessarily treat nausea. Control of CINV allows patients to complete treatment and to minimize use of health care resources and additional medications. Current antiemesis agents, such as 5-hydroxytryptamine-3 (5-HT3) antagonists and neurokinin-1 (NK-1) antagonists, have markedly decreased hospitalization for chemotherapy and have nearly eliminated acute emesis. The second-generation 5-HT3 receptor palonosetron has a unique pharmacology that makes it especially effective at preventing delayed emesis.

Supported through an educational grant from Eisai Inc.

PIM Postgraduate Institute for Medicine

## Target Audience

This activity has been designed for oncologists, hematologists, and oncology nurses who treat cancer patients who receive chemotherapy.

## Statement of Need/Program Overview

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of chemotherapy. The most important factor in determining whether CINV will occur is the chemotherapy itself. Risk is higher in women and younger patients. CINV can have an enormous impact on quality of life and can lead to fatigue, weight gain, and an inability to conduct activities of daily living. Patients with CINV may require additional medications or even a change in their chemotherapy regimen. CINV prevention is the primary principle of emesis control, as outlined by the major antiemetic guidelines. Nausea and vomiting are related but separate events, as suggested by agents that treat one more effectively than the other. Physicians must be familiar with the different treatment strategies best for acute nausea, delayed nausea, acute vomiting, and delayed vomiting.

## Educational Objectives

After completing this activity, the participant should be better able to:

- Identify patients at greater risk of chemotherapy-induced nausea and vomiting (CINV)
- Recognize the impact of CINV on general patient functioning
- Utilize treatment strategies for acute versus delayed CINV and for nausea versus vomiting
- Distinguish among the various 5-hydroxytryptamine-3 (5-HT3) antagonists

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# Mechanisms of Chemotherapy-Induced Nausea and Vomiting and Antiemetic Agents

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The emesis reflex has evolved to defend against ingested toxins, and it is widespread in the animal kingdom.[1] Since chemotherapeutic agents are toxins, emesis is a common side effect of anticancer therapies; nausea and vomiting are especially pronounced with DNA alkylating agents, such as cyclophosphamide, cisplatin, and carmustine.

The emetic response has several key stages.[2-5] In the first stage, chemotherapy administration damages enterochromaffin cells in the gastrointestinal (GI) tract, causing a release of serotonin. The serotonin then binds to 5-hydroxytryptamine-3 (5-HT3) receptors on the vagal afferents, triggering sensory inputs that project from the GI tract to the emetic center in the brain stem. The area postrema in the chemoreceptor trigger zone (CTZ) is also activated by the vagal afferents. Chemoreceptors in the area postrema are found outside the blood-brain barrier, and can also be directly activated by the blood-borne chemotherapeutic agents. These receptors are activated by several transmitters, including serotonin, dopamine, and substance P (SP). The final stage of emetic activation occurs at the emetic center. Importantly, the emetic center is not an anatomically distinct center, but rather a network of loosely organized neurons throughout the medulla oblongata that is activated sequentially during emesis.[3] The emetic center receives signals through afferents from the GI tract, higher cortical centers, vestibular centers, and the area postrema (Figure 1). Consolidation of these signals at the emetic center and a subsequent output through vagal efferents to the abdominal muscles, diaphragm, and stomach results in the emetic response. The emetic response involves several transmitters, 3 of which have been the focus of drug development: dopamine, serotonin, and SP.

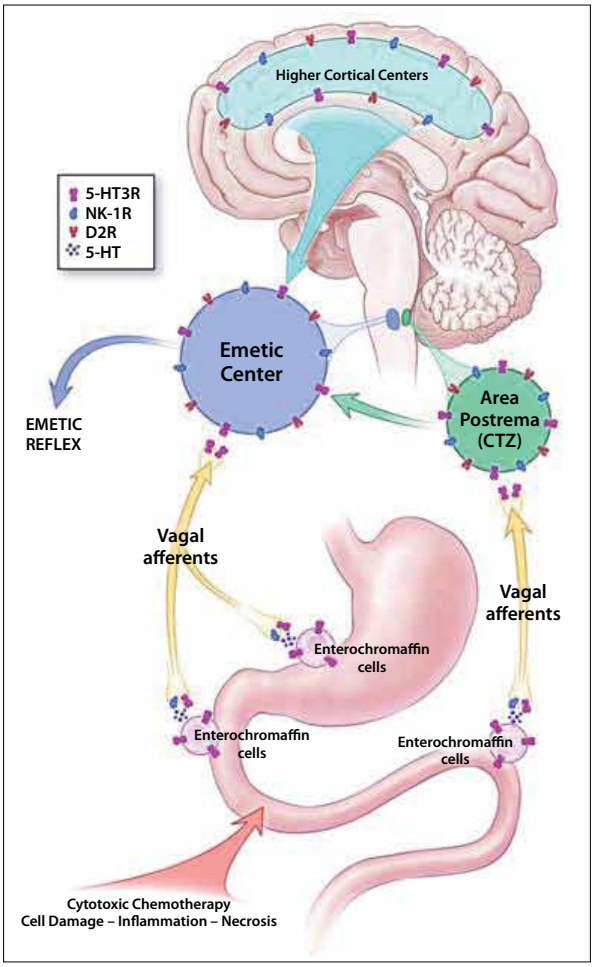


**Figure 1.** Activation of the emetic response by chemotherapy.[5] The gastrointestinal tract can be damaged by cytotoxic chemotherapy, triggering the release of serotonin from enterochromaffin cells that then initiates a sensory input through abdominal vagal afferents. Chemoreceptors in the area postrema are also activated by different transmitters, including serotonin, dopamine, and substance P. Signal consolidation occurs at the dorsal vagal complex composed of the emetic center, area postrema, and vagal afferent terminals. Signaling output through vagal efferents to the abdominal muscles, diaphragm, and stomach results in the emetic response. CTZ=chemoreceptor trigger zone; 5-HT3=5-hydroxytryptamine-3 receptor; NK-1R=neurokinin-1 receptor.

## Deconstructing Chemotherapy-Induced Nausea and Vomiting

Emesis encompasses both nausea and vomiting, which are different events.[5-7] Nausea is a subjective or unpleasant sensation reported by the patient that cannot be objectively

measured. From a physiologic perspective, nausea involves a loss of gastric tone and peristalsis, along with contraction of the duodenum, which refluxes some of the intestinal contents back into the stomach. Nausea is an autonomic nervous response that is often accompanied by other autonomic responses like salivation, tachycardia, and perspiration. Vomiting, on the other hand, can be measured objectively, as it is an expulsion of the GI contents from the mouth. Vomiting is a reflex motor response during which the diaphragm distends and the abdominal muscles contract, in a process coordinated by the autonomic nervous system. Nausea and vomiting are different but related events that happen after chemotherapy. Drugs that prevent vomiting can also help with nausea; however, nausea can occur without vomiting.

The mechanisms of nausea and vomiting are entwined. Nausea has proven to be more difficult to treat than vomiting and remains a significant clinical challenge. Nausea's distinct pathophysiology is not understood, even though some hypotheses exist about its mechanisms. In both people and animals, nausea can be induced by the same stimuli that can cause vomiting. Nausea usually requires less stimulation than vomiting, and it is sometimes considered a warning sign of vomiting to come. It seems, however, that nausea and vomiting are associated with different physiologic responses, as suggested by the observation that drugs that stop vomiting do not necessarily treat nausea. Some empirical evidence suggests that the hypothalamic pituitary adrenal (HPA) axis is involved in both nausea and vomiting.[8] Nausea is associated with low plasma cortisol levels and high vasopressin; both come from the HPA axis.

Importantly, when patients receive chemotherapy, the time course of CINV has an acute phase and a delayed phase.[1,6] On the first day of a patient's chemotherapy, a very intense acute phase of nausea and vomiting can occur. This acute phase of vomiting is thought to be primarily due to damage of the enterochromaffin cells, which release serotonin and SP and activate the signals for emesis through vagal afferents. Following the first day after chemotherapy, nausea and vomiting decrease. However, patients often experience a second wave of emesis on days 2 through 5. The mediators involved in this delayed emesis are not known, although they are thought to be products of cellular breakdown, along with inflammatory mediators that occur after damage to the gut. Typically, serotonin 5-HT3 receptor antagonists are used for treatment of emesis in the acute phase, and neurokinin-1 (NK-1) receptor antagonists and glucocorticoid drugs are used for the treatment of both the acute and chronic phases.

## Early Treatment of CINV

Since the 1990s, CINV treatment has included the use of corticosteroids. The most commonly used corticosteroid has been dexamethasone. Dexamethasone acts through multiple mechanisms that are not well understood.[1] One hypothesis suggests that it may increase the low cortisol levels associated with nausea and vomiting. Additionally, corticosteroids are known to be anti-inflammatory, since they block prostaglandins and release endorphins, which can make patients feel better. Corticosteroids are still part of current CINV therapy[9,10]; they are not typically used by themselves, but their efficacy is additive when they are combined with other antiemetics.[1]

Early treatments of CINV also used dopamine $D_2$ receptor antagonists, with metoclopramide being the most common.[11] Metoclopramide is thought to act on the periphery,[12] the CTZ, and the emetic center.[13,14] Also, metoclopramide is a weak 5-HT3 receptor antagonist,[15,16] which has led to some postulation that this activity may account for some of antiemetic effects seen with metoclopramide.

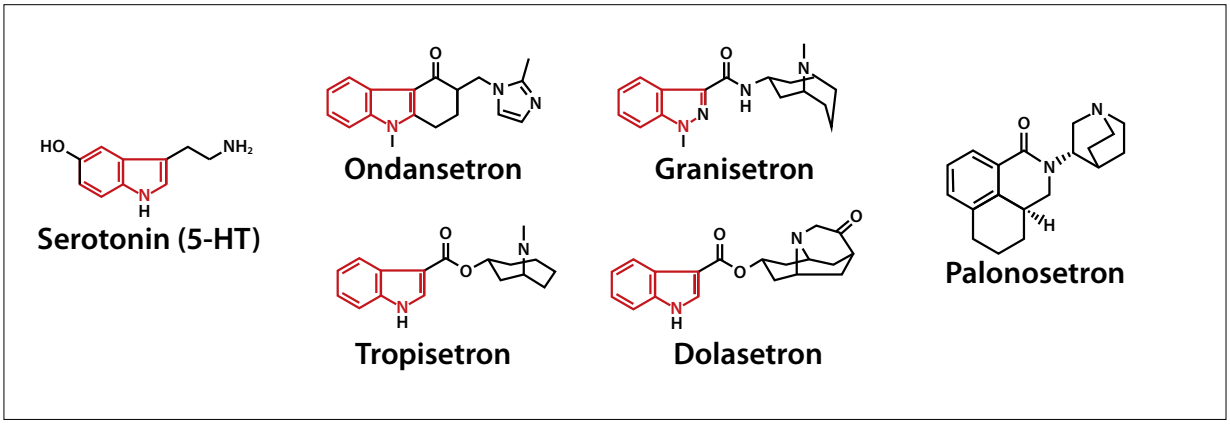


**Figure 2.** Chemical structures of serotonin and 5-hydroxytryptamine-3 (5-HT3) receptor antagonists. First-generation antagonists incorporate a 3-substituted indole structure (in red) that resembles serotonin. Palonosetron's structure contains a fused tricyclic ring system attached to a quinuclidine moiety.

## Newer Treatments for CINV

A breakthrough in the management of CINV occurred in 1991, when ondansetron came to the market. Ondansetron is a 5-HT3 receptor antagonist that prevents the stimulation of vagal afferents by serotonin released from enterochromaffin cells and the subsequent signaling to the emetic center in the brain stem.[17] The chemical structure of ondansetron resembles the structure of serotonin (Figure 2). Several other 5-HT3 receptor antagonists were introduced to the market throughout the 1990s, including granisetron, tropisetron, and dolasetron. These agents all have structures that are similar to serotonin, and they work by binding to the serotonin side of the 5-HT3 receptor, blocking its actions on the vagal afferents. The use of ondansetron and other first-generation antagonists constituted a major advancement in the treatment of acute CINV.

NK-1 receptor antagonists were the next class of drugs that came on the market for CINV treatment.[18-20] Aprepitant was approved in 2003, and was also a significant advance in the treatment of CINV. NK-1 receptor antagonists are thought to work in higher cortical centers and in the dorsal vagal complex in the brain stem.

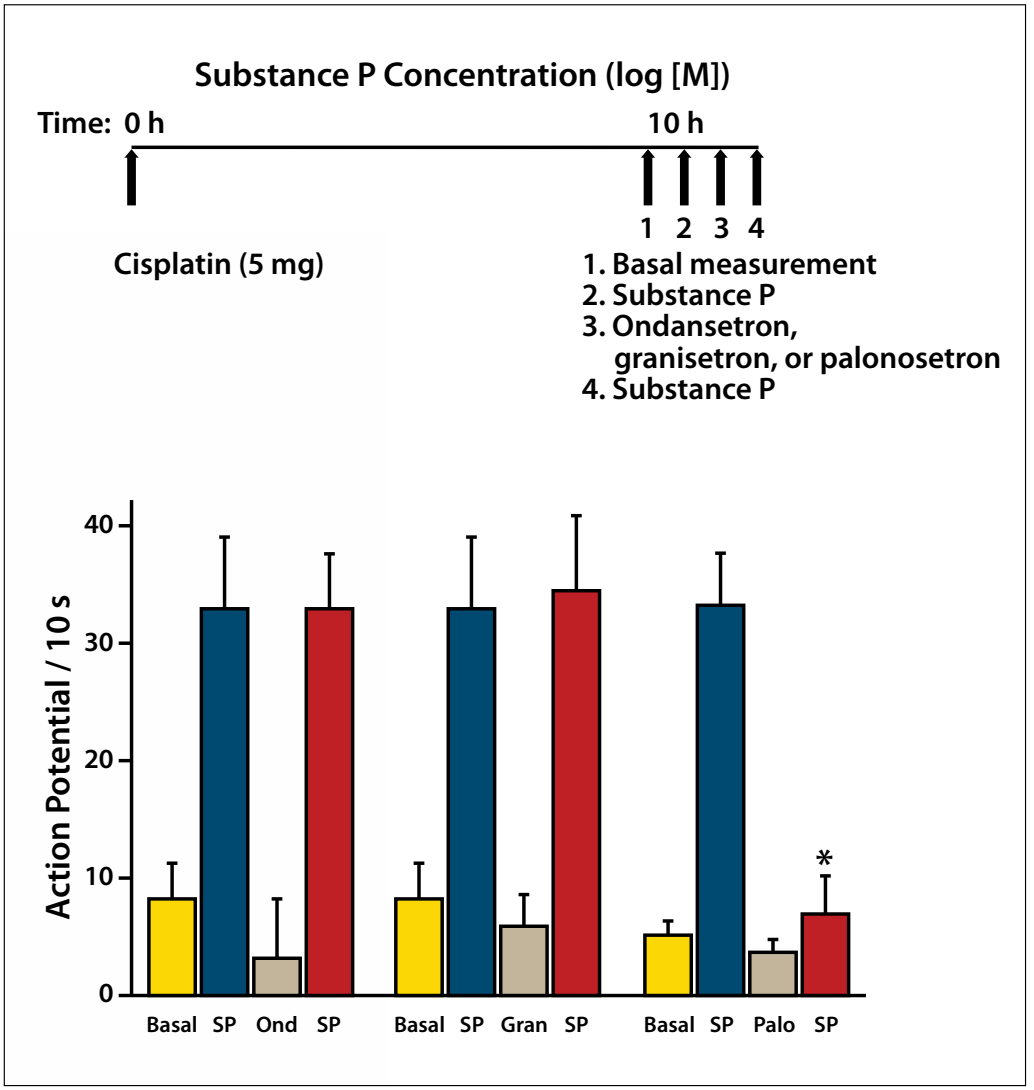


**Figure 3.** Effects of 5-hydroxytryptamine-3 receptor antagonists on the cisplatin-induced neuronal response to substance P.[30] Upper panel: experimental protocol. Cisplatin was given, and 10 hours later, 4 different measurements were made at intervals of 10–30 minutes: (1) basal measurement, (2) response to substance P, (3) effect on baseline of ondansetron, granisetron, or palonosetron; and (4) response to substance P following ondansetron, granisetron, or palonosetron administration. Lower panel: Set of 4 measurements for each antagonist as described in the upper panel; palonosetron (Palo) but not ondansetron (Ond) or granisetron (Gran) exhibited inhibition of the cisplatin-induced substance P (SP) response. Results are the average of at least 12 independent neuronal measurements from at least 7 rats (*$P$<.001 compared to substance P). Error bars correspond to ± standard errors of the mean.

Brain penetration is essential to the activity of NK-1 antagonists,[21] as their primary site of action is thought to be mediated centrally rather than at the level of the gut. In contrast to the first-generation 5-HT3 receptor antagonists, NK-1 receptor antagonists work to prevent both acute and delayed emesis.

Besides aprepitant, 2 other NK-1 receptor antagonists are currently in clinical development: netupitant and rolapitant. These agents are in late-stage clinical trials, so they may be available in the next few years.

### *The Unique Pharmacology and Clinical Profile of Palonosetron*

Palonosetron is a second-generation 5-HT3 receptor antagonist with a unique pharmacology that has been consistently superior at preventing delayed emesis compared to other 5-HT3 receptor antagonists.[22-24] Palonosetron is the only 5-HT3 receptor antagonist that is labeled for both acute and delayed emesis; the other 5-HT3 receptor antagonists are labeled only for acute emesis.

Palonosetron exhibits a higher binding affinity and a longer plasma half-life than other agents in its class. The binding of palonosetron is 30-fold and 100-fold more potent than granisetron and ondansetron, respectively.[25] Further, palonosetron has a plasma half-life of approximately 40 hours; the half-life of granisetron and ondansetron is 5-fold to 10-fold shorter.[26] However, differences in binding affinity and plasma half-life do not explain palonosetron's uniqueness in the clinic. If its effects on delayed emesis were due to palonosetron being a more potent compound, giving more of the weaker drug would have the same effect. Similarly, if its efficacy were the result of longer half-life alone, a drug with a shorter half-life that was administered more frequently would be equally efficacious. However, ondansetron could not mimic palonosetron's efficacy when given at higher doses and beyond 24 hours after chemotherapy.[27]

Our research group considered the question of why palonosetron is uniquely efficacious for delayed emesis. Ondansetron, granisetron, tropisetron, and dolasetron incorporate a 3-substituted indole structure resembling serotonin. Palonosetron, on the other hand, is structurally distinct; it contains a fused tricyclic ring system attached to a quinuclidine moiety (Figure 2). This distinct structure suggested that it might bind and act differently at the receptor relative to the other 5-HT3 receptor antagonists.

A direct comparison of palonosetron, ondansetron and granisetron showed that palonosetron binds to a site on the 5-HT3 receptor that is different from serotonin (allosteric binding). In addition, binding of palonosetron exhibited positive cooperativity, meaning that when one palonosetron molecule binds, it increases the affinity of the receptor for a second palonosetron molecule. These traits were unique to palonosetron and were not seen with ondansetron or granisetron, which exhibited simple bimolecular binding.[28] Additional comparison studies indicated that the 5-HT3 receptor could be internalized

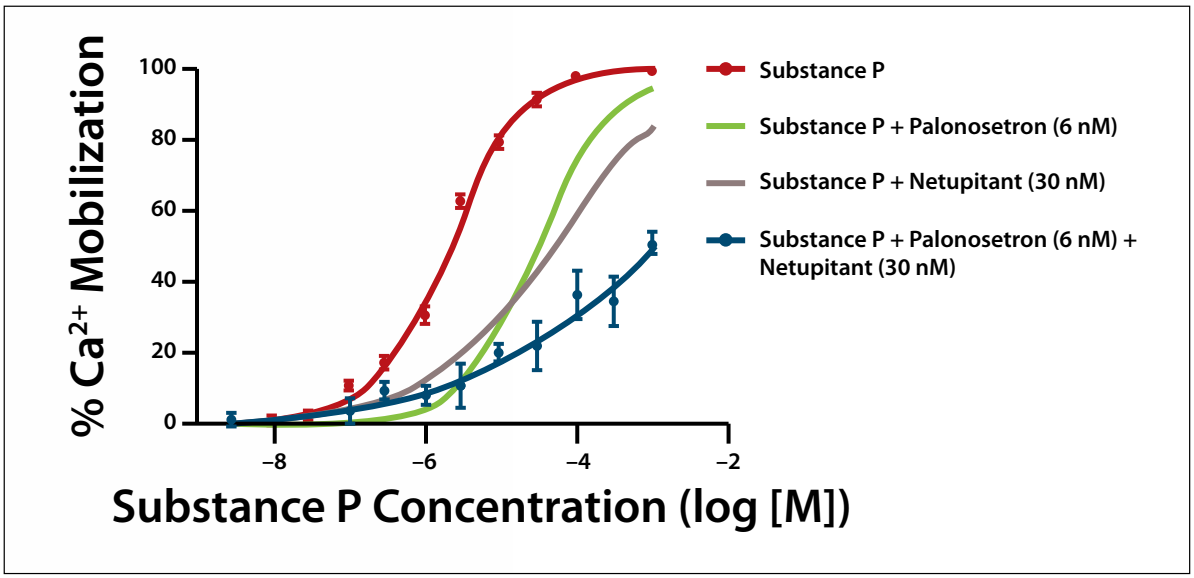


**Figure 4.** Effect on substance P response in NG108-15 cells when using palonosetron alone, netupitant alone, and palonosetron plus netupitant.[33] Cells were pre-incubated with netupitant, palonosetron, or a combination of palonosetron plus netupitant. After antagonist(s) removal, cells were incubated at 37°C for 1 hour with various substance P concentrations, followed by measurement of calcium-ion mobilization. Concentrations of netupitant and palonosetron were the concentrations at which maximal inhibition of the substance P response was observed when each antagonist was used alone. In cases where maximal activity was not reached even at a substance P concentration of 1 mM, the EC50 measurements represent the substance P concentration required to obtain 50% of the control response rather than 50% of maximal activity. Error bars correspond to ± standard errors of the mean.

into the cell by palonosetron but not by ondansetron or granisetron.[29] When palonosetron binds, it downregulates and internalizes the 5-HT3 receptor, resulting in persistent long-term inhibition of receptor function.

One surprise finding was that palonosetron could also suppress NK-1 receptor function.[30] Research focused on NK-1 receptors because they are associated with delayed emesis. Since palonosetron helps prevent delayed emesis, it was thought to possibly have activity at the NK-1 receptor. However, palonosetron does not bind to the NK-1 receptor.[25] Evidence of crosstalk between the NK-1 receptor and the 5-HT3 receptor was published in the early 2000s, showing that activity at the 5-HT3 receptor could influence the NK-1 receptor function and vice versa.[31,32]

Given the efficacy of palonosetron on delayed emesis and its ability to internalize the 5-HT3 receptor, the question that emerged was whether palonosetron could indirectly block the NK-1 signaling pathway. Rats were used to test if palonosetron, ondansetron, or granisetron could block NK-1 receptor responses in nodose ganglia, the ganglia associated with the vagal afferents discussed above. The rats were given cisplatin, and 10 hours later, the neuronal response to SP was measured. The rats were then given an intravenous dose of ondansetron, granisetron, or palonosetron. The antagonists were allowed to wash away, and the neuronal response to SP was measured again.[30] Palonosetron, but not ondansetron or granisetron, inhibited the NK-1 agonist response as measured through SP. The results showed that exposure to palonosetron inhibited the NK-1 agonist response in vivo (Figure 3).

More recent studies showed that when palonosetron and an NK-1 receptor antagonist were administered together, they could inhibit the SP response with a synergistic effect.[33] The SP response was measured in NG108-15 cells, which are known to express both 5-HT3 and NK-1 receptors. SP increased calcium ion mobilization with an EC50 of 2 µM. When cells were pretreated with palonosetron, calcium ion mobilization decreased 15-fold (the EC50 was 30 µM). In contrast, when cells were pretreated with either ondansetron or granisetron, the SP response remained the same (the EC50 was 2 µM). When cells were pretreated with netupitant, an NK-1 receptor blocker, the EC50 decreased from 2 µM to

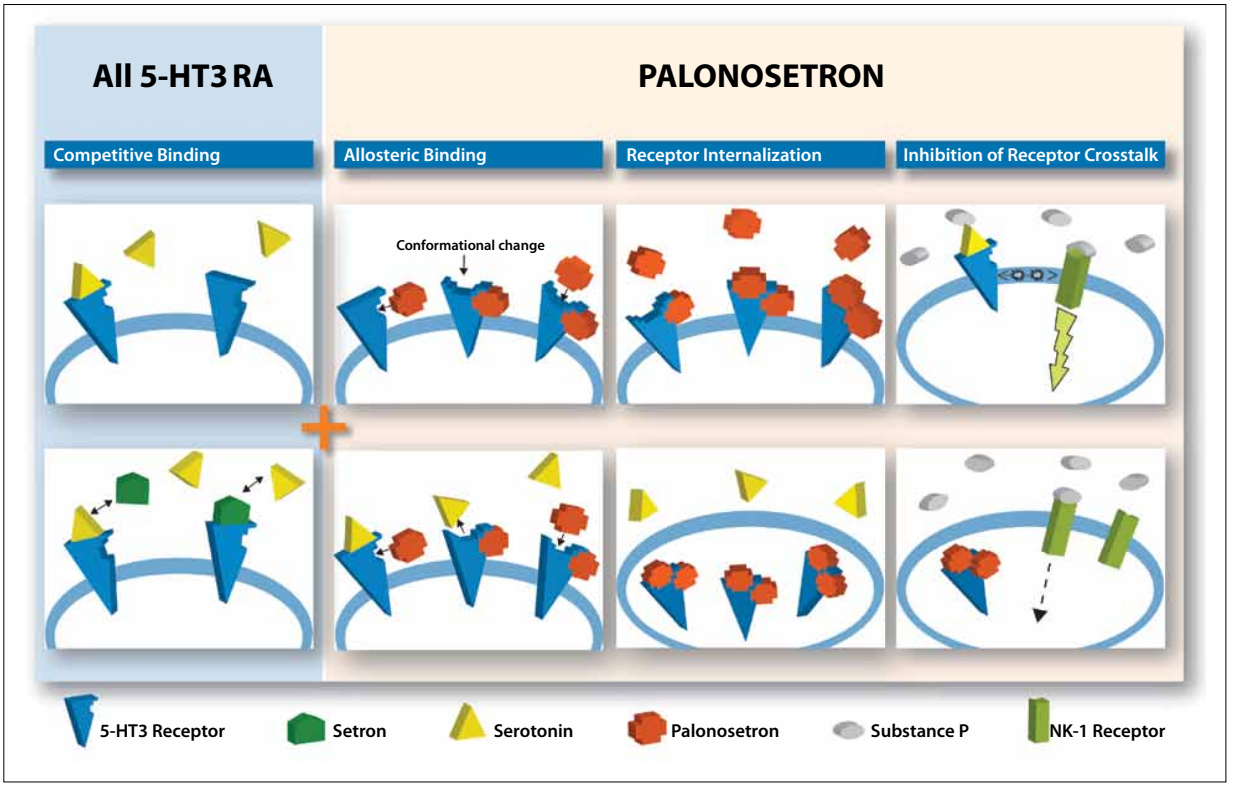


**Figure 5.** Summary of pharmacologic differentiation of palonosetron versus other 5-hydroxytryptamine-3 receptor antagonists (5-HT3 RA).[34] All 5-HT3 receptor antagonists compete with serotonin and exhibit competitive binding.[35] Palonosetron, in addition to competing with serotonin, exhibits allosteric binding and positive cooperativity.[28] Allosteric binding induces a conformational change that brings about an increased binding affinity between palonosetron and the 5-HT3 receptor. Increased binding affinity is possibly the result of at least 1 additional palonosetron molecule binding to the same receptor. Palonosetron also triggers 5-HT3 receptor internalization[29] and inhibits 5-HT3/neurokinin-1 (NK-1) receptor crosstalk.[30] These pharmacologic differences help explain the ability of palonosetron, unique among 5-HT3 receptor antagonists, to inhibit delayed emesis.

40 μM. When cells were pretreated with both netupitant and palonosetron, a synergistic inhibition of the SP response was observed (the EC50 was 970 μM). In short, combining palonosetron with an NK-1 antagonist exhibited a larger effect on the SP response in these cells than simply adding the effects of the 2 drugs (Figure 4).

In summary, palonosetron exhibits allosteric binding and positive cooperativity, and triggers 5-HT3 receptor internalization resulting in persistent inhibition of 5-HT3 receptor function. Palonosetron also inhibits cisplatin-induced NK-1 signaling, possibly as a result of 5-HT3 receptor internalization influencing crosstalk with the NK-1 receptor (Figure 5). The molecular pharmacology results provide a rationale to explain why palonosetron has activity in both the acute and delayed settings. More recent evidence using NG108-15 cells indicates that palonosetron could act synergistically with the NK-1 receptor antagonist (Figure 4), which suggests that combination therapy could lead to an even better clinical response.

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# Overview of Chemotherapy-Induced Nausea and Vomiting

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Traditionally, CINV has been the most-feared toxicity of chemotherapy for cancer patients.[1] The magnitude is less than it was 30 years ago, but the problem still exists. Before modern antiemetics, highly emetogenic chemotherapy would cause vomiting on the first day of therapy in virtually all patients, and moderately emetogenic chemotherapy would cause vomiting in at least half of patients. For the more emetogenic agents, vomiting would persist into the delayed period in a significant number of patients. Delayed vomiting may even have affected more patients than acute vomiting.

Modern antiemetics have markedly decreased the incidence and severity of CINV. Vomiting has been decreased by as much as 80–90% for the most emetogenic chemotherapy.[2] However, some vomiting is still present in a significant number of patients. At least 25–50% of patients still have at least some nausea and vomiting.[3] From the patient's viewpoint, even 1 or 2 episodes of vomiting and even a few hours of nausea are unacceptable. We must emphasize that the patient's viewpoint is the most important viewpoint in supportive care. Until we reach the goal of complete control of CINV, we must keep trying to understand the natural history, mechanisms, and treatment of this problem.

## Individual Risk Factors for CINV

The most important factor in determining if CINV will occur is the chemotherapy itself. Not all chemotherapies have the same propensity to induce nausea and vomiting (Table 1). Highly emetogenic agents, such as cisplatin, would induce vomiting in virtually all patients if no antiemetics were given. However, other chemotherapeutic agents are associated with minimal or no CINV. It is important to understand the level of risk for the chemotherapeutic regimen that is being used to design an antiemetic regimen that matches the emetogenicity of the chemotherapy itself.

There are patient characteristics that modulate the emetic response. Knowing these characteristics enables us to understand which patients may require extra attention to obtain good control of nausea and vomiting. Younger patients are more likely to vomit than older patients, given the same chemotherapy.[4] An inverse relationship exists between emetogenic potential and age (excluding newborns). More problems with nausea and vomiting will tend to occur with patients who are adolescents or in their 20s or 30s than with patients in their 60s, 70s, or 80s. We need to be more vigilant and perhaps more aggressive in our antiemetic management of younger patients. Given the same chemotherapy, women will vomit more than men.[5,6] The reason for this difference is unknown, but it has been consistently found. Therefore, for example, CINV would be more likely among breast cancer patients, who tend to be younger women, than among patients with head and neck cancer, who are often older men. Patients with a history of heavy alcohol use are less likely to have nausea and vomiting with chemotherapy.[7,8] The mechanism of this phenomenon is unknown, although it is unlikely to be a direct effect of alcohol or chronic exposure to alcohol. Alcohol itself does not induce protection from vomiting, and acute intoxication would not help the patient. However, a tendency toward alcoholism may reflect important differences in neurotransmitter receptor pathways between different patients.

**Table 1.** Emetic Risk of Common Chemotherapy Agents

| | |
|---|---|
| **High Risk**<br>>90% of patients | Cisplatin<br>Dacarbazine<br>Nitrogen mustard<br>Cyclophosphamide/Doxorubicin |
| **Moderate Risk**<br>>30% of patients | Doxorubicin<br>Carboplatin<br>Cyclophosphamide |
| **Low Risk**<br>>10% of patients | Paclitaxel<br>Etoposide |
| **Minimal Risk**<br><10% of patients | Chlorambucil<br>Vinorelbine |

## Types of CINV: Acute, Delayed, Anticipatory, and Refractory

CINV tends to be divided into different categories, with the 2 main ones being acute and delayed nausea and

vomiting. Acute nausea and vomiting occurs within the first 24 hours after chemotherapy. Delayed nausea and vomiting occurs after that first 24 hours, from 24 to 120 hours. The dividing line between the 2 categories is a line of convenience and not an exact dividing line. Delayed nausea and vomiting can begin as early as 16 hours after chemotherapy is administered. Acute nausea and vomiting tends to appear 2–6 hours after the most emetogenic chemotherapies are administered.

Delayed nausea and vomiting is more common with chemotherapies classified as high-moderate or highly emetogenic. The use of antiemetics is usually not required in patients receiving minimal or low emetogenic chemotherapy. Because acute vomiting and delayed vomiting have different remedies, they must be distinguished. They both involve multiple neurotransmitter and neurotransmitter receptor pathways, the serotonin pathways, the neurokinin pathways, steroid-related pathways, and dopaminergic pathways. However, the relative contribution of different pathways to different phases of nausea and vomiting may change. For example, during the acute period, the serotonergic pathways tend to be the key pathways, and the neurokinin pathways have a lesser role. During later periods, neurokinin pathways have a greater role, and serotonin pathways tend to have a lesser role.

Anticipatory vomiting is a very different but related phenomenon. Whereas acute vomiting and delayed vomiting result from the direct chemical effects of chemotherapies on the body, anticipatory vomiting is a learned response. When a person has a bad experience with chemotherapy, then the thought of chemotherapy, the sight of the hospital, or any reminder may activate this learned response. In essence, it is an almost Pavlovian reflex in which a nonphysical stimulus will lead to a certain predictable response. Anticipatory vomiting is misnamed, as it is a learned response that could occur at any time before, during, or after chemotherapy. If a patient who had a previous bad response to chemotherapy receives a second cycle of chemotherapy and has persistent nausea and vomiting that is not responding to standard emetic agents, one must consider that a learned response might be part of that reaction.

Agents such as benzodiazepines are effective against learned responses. When a learned response has taken hold, it may be best to add a benzodiazepine rather than another antidopaminergic, antiserotonergic, or NK-1–blocking agent. The best way to prevent a learned response is not to learn it at all. In any area of supportive care, prevention is much more effective than treatment.

Nausea and vomiting are considered breakthrough or refractory when they have not responded to standard antiemetic agents. A learned response should be considered as an additional factor. Other causes of nausea and vomiting rather than the chemotherapy should also be considered. A patient receiving chemotherapy can still experience nausea and vomiting unrelated to treatment from causes such as bowel obstruction, brain metastases, gastroenteritis, or electrolyte abnormalities, all of which would need to be addressed in different ways.

Patients with refractory CINV might benefit from rotation of antiemetics. The best rotation strategy is to move to a family of antiemetic agents that have not been tried previously. For example, if a patient had already received an antiserotonergic agent, a corticosteroid, and an NK-1–blocking agent, then an antidopaminergic agent might be given to see if it would be more effective.

## Managing Adverse Events Associated With Treatments for CINV

Most antiemetics have very good toxicity profiles. However, it is important to keep in mind that antiserotonergic agents can be associated with headache or constipation. If a patient develops those conditions during chemotherapy, a change in dose or agent may be required.

The NK-1 antagonists available up to now have been well tolerated. One exception is that the intravenous administration required with some agents, such as fosaprepitant, may irritate the vein and cause pain upon infusion. These concerns may lead to the use of oral forms instead of intravenous forms. Also, these agents may affect the metabolism of numerous other medications because they affect the CYP3A4 cytochrome P450 metabolic pathway. Dose adjustments or avoidance of other agents may be required to prevent drug-drug interactions.

## On Nausea and Vomiting

Although the phrase *nausea and vomiting* has traditionally been used to refer to one phenomenon, we now appreciate that nausea and vomiting are related but different. Some of the agents that have been used historically are better at blocking nausea while others are better at blocking vomiting. The neurologic pathways that lead to nausea are not as well understood as those that lead to vomiting. As we obtain a better understanding of those pathways, we will develop more targeted antinausea treatments with increased efficacy.

Nausea may be more closely related to anorexia/cachexia than to vomiting. Relevant pathways and strategies may be found by comparing data from antiemetic studies with data from the anorexia/cachexia literature. This is an ever-developing field of research, and it has led to ever-increasing benefits for our patients.[9-11] We are not done yet.

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# Impact of Chemotherapy-Induced Nausea and Vomiting


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CINV has an enormous impact on patient quality of life and on the ability of patients to continue daily activities (Figure 1).[1] Research has focused on the differential effects of acute and delayed nausea, which have a similar impact on daily life. Overall, patients report that delayed nausea and vomiting play a larger role in adverse quality of life than acute nausea and vomiting. This role is largely due to the duration of time and the psychologic impact of having nausea that is protracted over a number of days.

In previous years, when emesis was a major component of chemotherapy toxicity, it was clearly impacting quality of life for patients. Interestingly, the impact of delayed nausea is often more difficult for health care practitioners to appreciate. In fact, the differential effect of moderately emetogenic chemotherapy has been assessed based on both health care provider predictions and patient reports.[2-6] These studies have demonstrated that health care providers tend to assess the impact of acute and delayed nausea relatively similarly, but patients state that delayed nausea has a much greater impact on several different factors. Health care providers tend to see nausea as part of a package that is being treated. Patients tend to assess the impact of nausea and/or vomiting on each individual activity throughout their day.

Studies have tried to evaluate the impact of CINV on general patient functioning through a number of different surveys.[7] The Functional Living Index for Emesis (FLIE) scale examines how nausea and vomiting affect the ability of patients to conduct activities in their daily lives, such as taking care of themselves, eating a meal, going to work, taking medication, or conducting household tasks.[8,9] Nausea induced by chemotherapy has a major impact on the ability of patients to conduct all of these activities.[10] In addition, any additional medications needed to prevent or treat delayed nausea can have side effects that impact quality of life.

## Impact of CINV on Physical Health

CINV affects the physical health of patients in a number of ways. Interestingly, patients can lose or gain weight during chemotherapy due to CINV. Some patients are unable to eat during the period of CINV, while others will continue to eat in an effort to reduce the effects of delayed nausea. Therefore, gaining weight is an unpleasant consequence of chemotherapy for many patients. Patients with chronic nausea often have concomitant gastritis or reflux symptoms, which must be treated with additional medication. The nausea medications that patients take may lead to the development of constipation or other neurologic side effects, such as dystonic reaction, which can be caused by drugs like prochlorperazine. CINV significantly impacts physical health and over time can lead to fatigue. Fatigue is one of the most recognized side effects of chemotherapy.

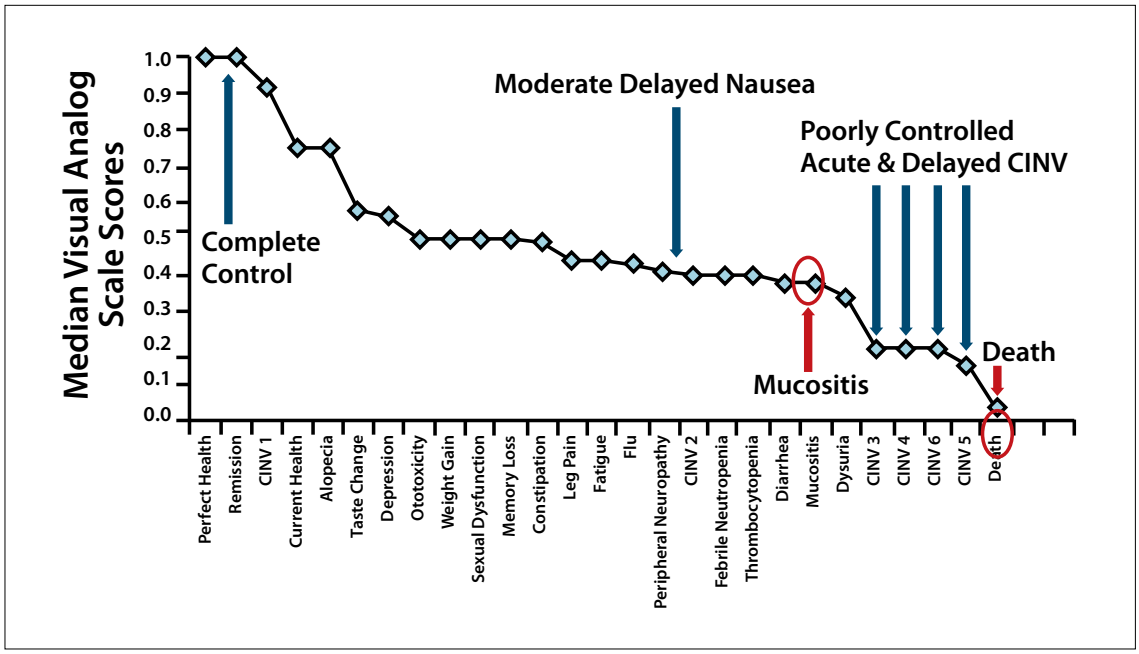


**Figure 1.** The impact of chemotherapy-induced nausea and vomiting (CINV) on quality of life. Adapted from Sun CC et al. *Support Care Cancer*. 2005;13:219-227.[1]

CINV contributes significantly to the sensation of fatigue both from the side effects of the medications used for treatment and from the long-term effects of having protracted nausea. Patients with delayed nausea from chemotherapy have amplified fatigue from these effects. Fatigue is the most predominant symptom in patients who are receiving moderately emetogenic chemotherapy.

## Impact of CINV on Mental Health

The impact of CINV on mental health should not be overlooked. Mental health is always a challenge for health care providers. Patients who are receiving chemotherapy are already anxious. Their treatment has sufficient impact on the conduct of their daily lives so that they experience anxiety, depression, and catastrophizing. CINV can increase the patient's sense of hopelessness and depression because of its impact on daily life. Some of the medications used to treat CINV may further cause depression. Health care providers must address the mental health aspects of CINV as well as the physical consequences of chemotherapy.

Anticipatory nausea is one mental health aspect of CINV. Patients who have significant nausea and emesis will then be nauseated before they come in for the next visit. One example is a young patient with early stage breast cancer who had no trouble with weekly paclitaxel, and then she started receiving doxorubicin/cyclophosphamide. By the start of her third cycle, she had emesis when she looked at her water bottle. In her subconscious mind, although not her conscious mind, she associated the water bottle with the CINV and the protracted nausea that she had experienced in her previous cycle.

Similarly, patients may go to the grocery store and need to leave because CINV is associated with smells or other stimuli. Both the physical and mental health consequences of CINV are protracted and may last longer than the actual experience of CINV. Patients who have delayed nausea may have more fatigue and take longer to recover from their chemotherapy than patients who have less toxicity from their chemotherapy. Similarly, patients with delayed nausea will have protracted issues with gastritis and nausea from other types of treatments, such as local radiation therapy.

## CINV and Health Care Resource Utilization

The utilization of health care resources in patients with a variety of different toxicities from chemotherapy has been examined.[11-13] Clearly, CINV is a large culprit. Health care utilization costs increase significantly in patients who have even mild to moderate CINV. However, as the intensity of CINV increases, the cost rises significantly. The costs include outpatient medications and loss of work hours, along with inpatient resources. Patients with significant CINV are seen more frequently. These patients call the clinic more often, leading to greater cost in terms of use of health care providers. Patients with significant CINV are sometimes treated in urgent care centers or in the hospital because of the continued consequences of CINV. Obviously, costs increase for patients with continued CINV who require hydration or intravenous antiemetics. Thankfully,

marked improvement in the agents used to prevent CINV have made the use of hydration or intravenous antiemetics much less frequent than in previous decades. In addition, unanticipated consequences can arise from CINV. For example, I treated a young patient with breast cancer who was receiving carboplatin-based chemotherapy and had significant emesis in the first 24 hours. She developed GI bleeding that was associated with her emesis.

Preventing and treating CINV is important because we want our patients to get through treatment, particularly in the early-stage setting. In that setting, the goal is to treat patients for a brief interval and then send them back to their daily lives with toxicity that is minimal or resolves quickly. However, in the advanced setting, survival or progression-free survival is discussed from diagnosis, and the caveat is quality of life. We want patients to live as long as possible, but with the best quality of life. If a patient is feeling nauseated half of the time when receiving treatment and is unable to conduct activities of daily living, then we have not succeeded in our goal.

In early-stage disease, more so than in late-stage disease, we count on our patients being able to show improvement and outcomes at the doses and schedules prescribed, which is critical to the success of many treatments. The efficacy of treatment is affected when patients with significant CINV stop chemotherapy early or delay their next cycle of chemotherapy. For example, doxorubicin and cyclophosphamide are commonly used in combination in patients with early-stage breast cancer, and significant CINV will shorten the duration of this regimen. Clearly, toxicity is causing patients to drop their last cycle of chemotherapy. Additionally, patients need to maintain their activities of daily living during treatment, and CINV is one of the biggest toxicities impacting the ability of patients to function on a daily basis after receiving chemotherapy.

## Cost of CINV-Associated Health Care

Health care resources are impacted by CINV. Delayed nausea causes patients to visit the emergency room, the hospital, or infusion centers for additional therapy. Patients with acute CINV need to stay in infusion centers longer to manage their CINV. Delayed nausea probably has an even bigger impact on health care resource utilization than acute nausea. These patients may need to be seen and evaluated. Patients with delayed nausea use their health care providers, including triage nurses, advanced practice nurses, and physicians, to manage additional medications. The cost of health care associated with CINV includes additional visits to the emergency room and other treatment settings that markedly escalate health care costs.[11] These costs include visit time, the use of health care personnel, and the high cost of additional rescue medication.

### *Pharmacoeconomics of CINV Treatments*

The pharmacoeconomics of CINV treatments are interesting. If the newer drugs to prevent nausea and emesis were very expensive, then we would be increasing the cost of health care for our patients who are receiving moderately or highly emetogenic chemotherapy. In fact, in most cases, the reverse is true. Assessing pharmacoeconomics is complicated, and often includes modeling with consideration of quality of life, expenditure in the health care sector, and medication use. In general, if CINV is controlled, then patients complete their treatments, their disease outcome is better, they use fewer health care resources, and they use fewer additional expensive medications. In fact, as is true in many aspects of medical care, a higher upfront expenditure actually ends up with a positive ratio on cost expenditure and outcome in treatment of cancer.

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# Discussion: Emerging Treatments in CINV

Steven M. Grunberg, MD, and Hope S. Rugo, MD

**Steven M. Grunberg, MD** Dr. Rugo, you mentioned the pharmacoeconomic impact of patients returning to the emergency room due to delayed nausea and vomiting. You touched on the decreased time in the infusion room during treatment, but before the introduction of serotonergic agents, virtually all solid tumor chemotherapy was given on an inpatient basis. My own feeling is that 2 advances were especially important in this area. One was the development of implantable access devices. The other was the development of effective antiemetics. These advances changed solid tumor chemotherapy from an inpatient procedure to an outpatient procedure. In previous decades, nearly all patients spent at least 1 day in the hospital to receive each cycle of chemotherapy. Routine hospitalization no longer occurs, and the cost savings must be huge. What are your thoughts on that?

**Hope S. Rugo, MD** That is an important point. For example, when we were treating patients in the 1980s with cisplatin regimens, patients were hospitalized, and their ability to be discharged was dependent on their ability to keep food and liquids down. Patients would stay in the hospital for additional days because of delayed nausea and vomiting. This was not just the nausea we see now, but really significant emesis as well.

There has been an almost complete turnaround. Certainly we are concerned about ongoing nausea and its occurrence in the delayed setting, but in the past, this toxicity impacted not just cost, but also quality of life in a significant way. Even when these patients were discharged, we did not have any medications that targeted delayed nausea at all. The patients had ongoing nausea and sometimes vomiting that would significantly delay treatment and affect their ability to receive additional treatment. So, a very dramatic shift has occurred in terms of expected costs, just based on the availability of newer antiemetics.

**Steven M. Grunberg, MD** As we have begun to concentrate more on patient-reported outcomes, we have to depend more on reports from patients after they leave the hospital. When the patient was in the hospital, we could see what was going on. You mentioned the studies that looked at the impressions of doctors and nurses versus the reality for the patients, and how the doctors and nurses could much more accurately predict early effects as compared to late effects that occur when the patients are out of sight. Literature is starting to develop on this point as well. Work by Salsman and colleagues at Northwestern University, who study communications and patient-reported outcomes, discussed barriers to good antiemetic management.[1] Disconnects exist between what we think is going on and what our patients say is going on. Their research found that patients may hesitate to voluntarily report toxicities for fear that clinicians would reduce their treatment or simply because patients may want to give the answer that their physicians want to hear. However, doctors and nurses may tend to assume that they are hearing everything that happens to the patient accurately.

**Hope S. Rugo, MD** That is very important to note. We see this in a number of different areas of toxicity. Patients will not report back during the intervening period between chemotherapy cycles for a couple of reasons: they do not want to sound like complainers, and they do not want to potentially affect their ability to receive care. Unreported symptoms can affect treatment compliance and other areas of health, including mental health. We tend to significantly under-evaluate the effects on mental health, which can guide how side effects are managed through the treatment cycles.

How are you incorporating the newer antiemetics into management? As we begin to use the newer drugs, the older drugs may be underused. How would you manage a patient who has delayed nausea despite the best drugs?

**Steven M. Grunberg, MD** Some areas certainly need further work. Recent antiemetic regimens are shortened but maintain the same efficacy through the later period by using a longer-acting 5-HT3 antagonist or a higher dose of an NK-1 antagonist earlier. This at least decreases the compliance problem. However, you are right that we do not always have too many other places to go. Corticosteroids are perhaps underused, at least for some delayed problems. A role for rotation to some of the older families of antiemetics may still exist. These areas are certainly challenging to us.

**Hope S. Rugo, MD** I want to highlight the importance of corticosteroids as an addition to other treatments. Extending corticosteroids out for several days is an often

underutilized strategy, particularly in patients with significant delayed nausea.

**Steven M. Grunberg, MD** I was recently at a conference on the treatment of breast cancer in countries that have fewer resources than the United States. One of the points that came up was that a corticosteroid can be quite effective for many types of chemotherapy. Corticosteroids are inexpensive and often available in places where some of the newest agents may not be. This is something we should keep in mind.

**Hope S. Rugo, MD** Guidelines are an interesting area. There are guideline tables that tell us whether agents are classified as moderately or highly emetogenic. As a breast cancer oncologist, I am always interested to see that doxorubicin/cyclophosphamide is still classified as moderately emetogenic, when it is not. I see patients who are being treated at a variety of different centers and are having issues with CINV. Often, they are not receiving the treatments outlined in the guidelines. It is unclear how we can better disseminate these guidelines throughout the community and overcome the barriers to implementation. One barrier may be based on cost in regard to health care provider organizations, but other barriers exist as well.

**Steven M. Grunberg, MD** Yes. One thing to remember about the guidelines and the emetogenic classification of agents is that the emetogenic classification systems were specifically designed to rate agents when they are used as a single agent in a single dose. When combinations are used, changes occur in the emetogenicity of the combination. We do not have a good way to determine what that will be. As you point out with cyclophosphamide and anthracycline, although they are both moderately emetogenic agents, together they act more like a highly emetogenic stimulus. That cannot be underestimated.

Getting clinicians to follow the guidelines has been a continuing challenge. A number of strategies have been tried, and the educational strategies have not been very effective. Dr. Stuebe wrote an editorial in the *New England Journal of Medicine* about how we learn.[2] She pointed out that, while we might say in our heads that we learn from level 1 evidence from randomized, controlled clinical trials, in our hearts we learn from level 4 evidence and anecdotes. A bad experience with your own patient is going to have a more lasting impact than a 2,000-patient randomized trial of people you have never met. We react to how our own patients do.[3]

One approach is to encourage clinicians to follow-up on their patients. It could be through a phone call from the office a few days after chemotherapy or by using a tool such as the Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool, which is a single questionnaire for 4-day recall. Patients can complete it after they have received chemotherapy, when everything is still fresh in their mind, and bring it back to their next office visit. This type of information has been found to be an effective stimulus in improving treatment and encouraging the upgrading of management strategies when necessary.

**Hope S. Rugo, MD** That is a very interesting comment about how we incorporate new areas into our treatment policies. Of course, understanding the cost is complex because, as you mentioned, educational programs may have cost containment, but they do not actually impact practice. Cost may have more impact in global economics, and that may be difficult for physicians to see overall in their daily lives.

Sometimes we do not know how to deal with the side effects of antiemetics. When patients have toxicities like constipation or headache, we are not sure how to handle it. The ability to give aprepitant intravenously has made a big difference for patients who could not get pills down because they experienced nausea after therapy. But, in some patients, 5-HT3 receptor antagonists, such as palonosetron, are not tolerated well. One question is how to manage that toxicity.

**Steven M. Grunberg, MD** Drugs such as ondansetron and granisetron, which are older drugs that were used over a wide range of doses, are often being used at higher doses than necessary. In those cases, the dose can be de-escalated, which will have a major impact. As you mentioned, fosaprepitant has improved compliance, but it may irritate the vein. In that case, a central line may be needed.

**Hope S. Rugo, MD** How would you manage a patient receiving palonosetron who develops headaches and constipation?

**Steven M. Grunberg, MD** Because only 1 dose of palonosetron is approved, it might sometimes be necessary to change to a different agent.

**Hope S. Rugo, MD** Education about these toxicities makes a big difference. For example, patients who know that constipation is an issue can start preventive medicines to try to reduce that constipation, which otherwise can really increase the impact of CINV in the first few days. We make sure that patients know how to manage the headache. This preventive approach has led to the majority of our patients doing better than they had in the past. In my experience, patients who receive a single dose beforehand and then manage side effects afterwards

may respond better than those who continuously have to take medication. For example, if a patient receives a short-acting 5-HT3 antagonist, he or she may not want to keep taking it because of the side effects. However, if the patient receives a long-acting drug and the side effects occur afterwards, the patient has much better compliance and better tolerance.

**Steven M. Grunberg, MD** You are exactly right when we talk about supportive care agents being used for prevention rather than treatment. If we anticipate the side effect of the supportive care agent, we can try to prevent it. None of us would think twice about the idea that a patient receiving opiates might need stool softeners to prevent constipation. Not every patient receiving a 5-HT3 antagonist will have constipation, but if a patient is known to have had that problem, then prophylactic use of stool softeners is completely reasonable. The steroids are some of the most challenging agents in this area, since they can have numerous side effects. Almost all of their side effects are treatable if you anticipate and recognize them.

**Hope S. Rugo, MD** Is there anything that you are looking forward to on the horizon, such as new drugs or studies that are ongoing that may impact your practice?

**Steven M. Grunberg, MD** I am looking forward to a better understanding of the problem of nausea, which will lead to better treatments. That is really a bigger problem than vomiting is for our patients at this point.

**Hope S. Rugo, MD** I am also looking forward to that. An area that will be really interesting is the new agents that offer advantages. We have seen this incremental improvement in CINV. The biggest improvement has been the near elimination of emesis, particularly in the acute period. We need to understand who is at risk, which has been an elusive endpoint. We need to understand the pharmacogenomics and maybe the psyche of CINV. The agents have a tremendous and varied impact on individuals.

**Steven M. Grunberg, MD** Exactly. Everything we have learned about targeted therapy and about individual differences in pharmacogenomics and pharmacogenetics for treatment modalities is also going to apply to supportive care. Some of that work is starting to appear. Patients with different expression of their cytochrome P450 systems may have different sensitivity to antiemetics.[4] The 5-HT3 receptor itself can be mutated.[5] We are all getting used to thinking of mutations to epidermal growth factor receptor tyrosine kinases, but mutations to 5-HT3 receptor subunits also exist, and these can change sensitivity to antiemetics. Overall, when you put together individual genes, eventually you end up with complete human beings. Ethnic differences exist in sensitivity to antiemetics and emetogenic agents.[6] As we begin to understand genetic variations in different populations, we will identify more directions for future targeted research.

**Hope S. Rugo, MD** It is exciting that this research is taking off because it is being performed in an ethnically diverse population. We have been observing these differences for a long time. The study has been quite difficult because of the complexity of pharmacogenomics. It is very exciting that we are making progress now. It is also exciting that we now have drugs that have completely changed our ability to manage CINV and deliver chemotherapy to our patients.

***Acknowledgment***

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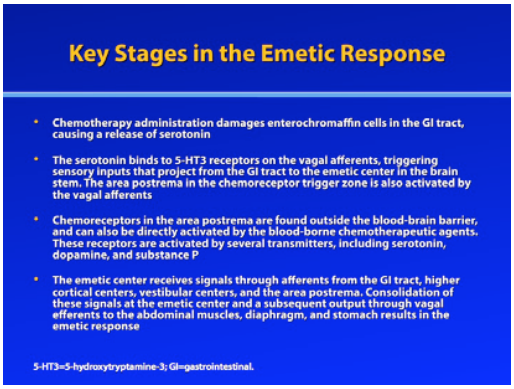


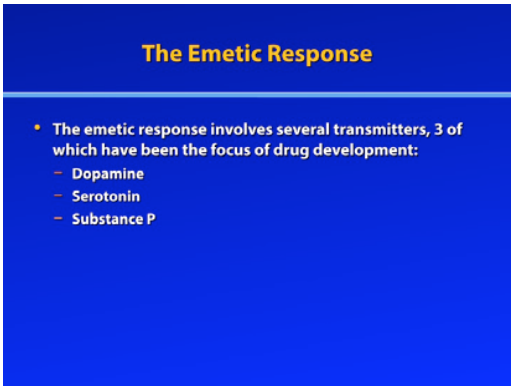


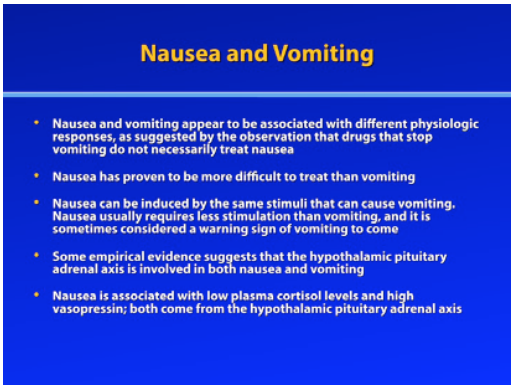


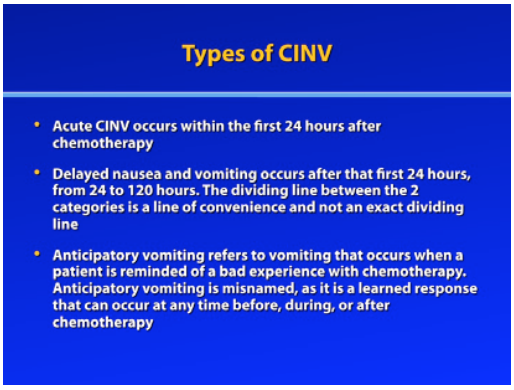


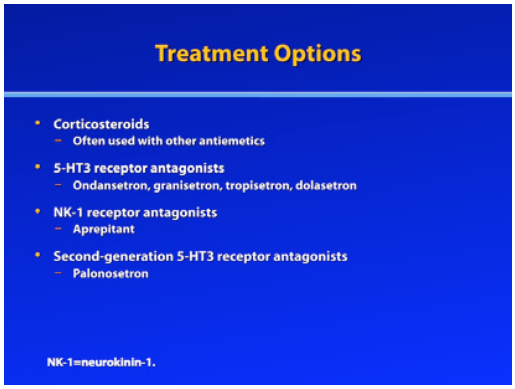


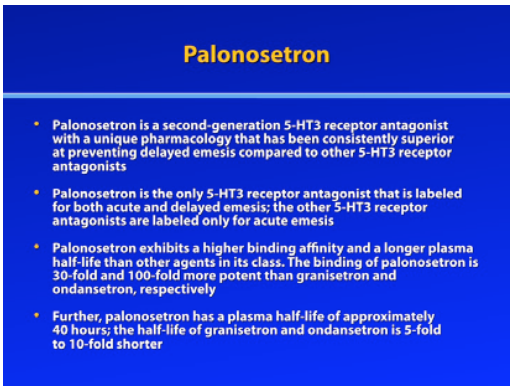

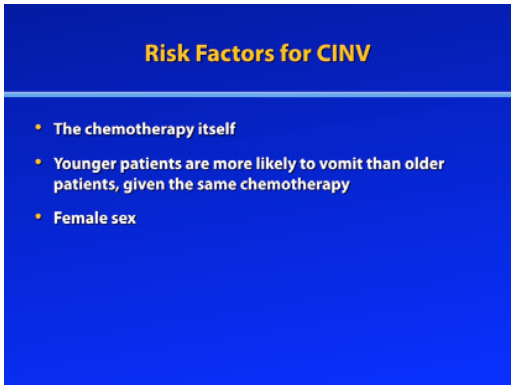


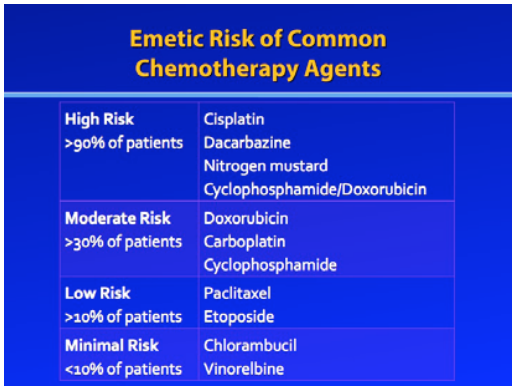


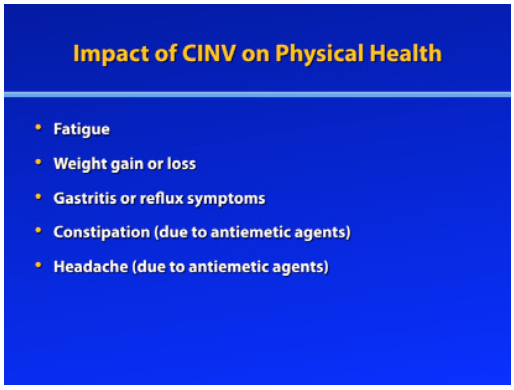


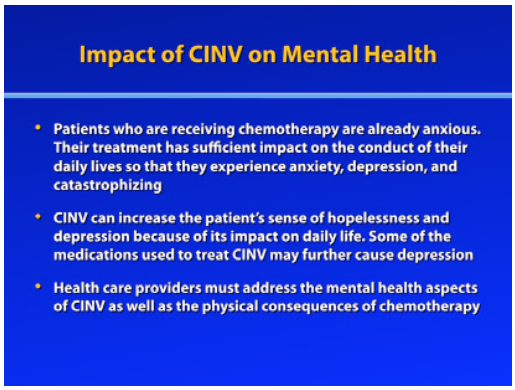


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# Emerging Treatments in Chemotherapy-Induced Nausea and Vomiting

**CME Post-Test:** *Circle the correct answer for each question below.*

1. In the first stage of the emetic response, chemotherapy administration:

   a. Damages enterochromaffin cells in the gastrointestinal tract, causing a release of serotonin
   b. Increases calcium ion mobilization
   c. Induces signals through afferents from the gastrointestinal tract, higher cortical centers, and vestibular centers
   d. Penetrates the area postrema

2. Which agents are thought to work in higher cortical centers and in the dorsal vagal complex in the brain stem?

   a. Corticosteroids
   b. Dopamine $D_2$ receptor antagonists
   c. 5-HT3 receptor antagonists
   d. NK-1 receptor antagonists

3. Which 5-HT3 receptor antagonist is the only one that is labeled for both acute and delayed emesis?

   a. Granisetron
   b. Ondansetron
   c. Palonosetron
   d. Tropisetron

4. Modern antiemetics have decreased vomiting associated with the most emetogenic chemotherapy by as much as:

   a. 45–55%
   b. 50–60%
   c. 65–75%
   d. 80–90%

5. Which agent is associated with a high risk of CINV?

   a. Cisplatin
   b. Doxorubicin
   c. Etoposide
   d. Paclitaxel

6. Which agent is associated with a minimal risk of CINV?

   a. Cyclophosphamide
   b. Dacarbazine
   c. Etoposide
   d. Vinorelbine

7. Patients with a history of heavy alcohol use are less likely to experience nausea and vomiting with chemotherapy.

   a. True
   b. False

8. During the acute phase of CINV, which are the key pathways?

   a. Dopaminergic pathways
   b. Neurokinin pathways
   c. Neurotransmitter receptor pathways
   d. Serotonergic pathways

9. What is the most common symptom in patients who are receiving moderately emetogenic chemotherapy?

   a. Fatigue
   b. Nausea
   c. Weight loss
   d. Vomiting

10. According to patients, which CINV event has the greatest impact on quality of life factors?

    a. Acute nausea
    b. Acute vomiting
    c. Delayed nausea
    d. Delayed vomiting

Project ID: 9133

# Evaluation Form: Emerging Treatments in Chemotherapy-Induced Nausea and Vomiting

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

**Please rate your level of agreement by circling the appropriate rating:**
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**Learning Objectives**
After participating in this activity, I am now better able to:

| | |
|---|---|
| 1. Identify patients at greater risk of chemotherapy-induced nausea and vomiting (CINV) | 1 2 3 4 5 |
| 2. Recognize the impact of CINV on general patient functioning | 1 2 3 4 5 |
| 3. Utilize treatment strategies for acute versus delayed CINV and for nausea versus vomiting | 1 2 3 4 5 |
| 4. Distinguish among the various 5-hydroxytryptamine-3 (5-HT3) antagonists | 1 2 3 4 5 |

**Based upon your participation in this activity, choose the statement(s) that apply:**
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

**What strategies/changes do you plan to implement into your practice?** _____

_____

**How confident are you that you will be able to make this change?**
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

**What barriers do you see to making a change in your practice?** _____

_____

**Please rate your level of agreement by circling the appropriate rating:**
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**The content presented:**

| | |
|---|---|
| Enhanced my current knowledge base | 1 2 3 4 5 |
| Addressed my most pressing questions | 1 2 3 4 5 |
| Promoted improvements or quality in health care | 1 2 3 4 5 |
| Was scientifically rigorous and evidence-based | 1 2 3 4 5 |
| Avoided commercial bias or influence | 1 2 3 4 5 |
| Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc) | 1 2 3 4 5 |
| My opportunity for learning assessment was appropriate to the activity | 1 2 3 4 5 |

**Handout materials were useful:** ❒ Yes ❒ No ❒ No handouts for this activity

**Would you be willing to participate in a post-activity follow-up survey?** ❒ Yes ❒ No

**Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:**

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 9133**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

## Post-test Answer Key

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |

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❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.