Introduction

Advances in our understanding of the pathophysiology of chemotherapy-induced nausea and vomiting (CINV) have led to the development of effective classes of antiemetic agents, including 5-hydroxytryptamine-3 (5-HT₃) receptor antagonists, neurokinin-1 (NK₁) receptor antagonists, and corticosteroids. Acute emesis associated with either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) is preventable in 50% to 75% and 75% to 90% of patients, respectively. In several patient reports, 12% to 19% experienced acute vomiting and 30% to 59% experienced acute nausea after HEC or MEC. In these studies, a significantly higher percentage of patients reported experiencing delayed vomiting and nausea (19% to 33% and 49% to 75%, respectively), which has important implications because duration vs severity of CINV has been shown to have the greatest impact on quality of life. Collectively, these findings indicate that despite the availability of effective antiemetic agents, control of acute and delayed CINV often is suboptimal.

Strategies for CINV prophylaxis should be based on multiple criteria, including the emetogenicity of the scheduled chemotherapy agent(s), side effect profile of the antiemetic regimen, direct and indirect costs of nausea and vomiting, patient preferences, and addressing barriers to patients purchasing or taking antiemetics. Treatment selection also can be complicated by interpatient variability, which affects response to certain classes of antiemetic agents. This article discusses progress in our understanding of the physiology of emesis, advances in antiemetic research, direct and indirect costs that may impact symptom management, and nonpharmacologic therapies that may serve as useful adjuncts to standard-of-care agents.

A Brief History of Emesis Physiology

Understanding of the physiology of vomiting has progressed since the 1950s, when the “vomiting center”...
(VC)—a cluster of neurons in the dorsolateral reticular formation near the nucleus tractus solitarius (NTS) of the brainstem medulla—and the nearby spongiform, circumventricular chemoreceptor trigger zone (CTZ) in the area postrema were identified. Dopamine was considered to be the major neurotransmitter involved in nausea and vomiting. The 1980s brought understanding that vomiting occurs because chemical messages from the bloodstream and the cerebrospinal fluid reach the VC via the CTZ and from neural signals from vagal afferent fibers, which terminate in the NTS and project to the VC. The NTS plays an important role in nausea by influencing taste, salivation, swallowing, coughing and gagging, gut motility and secretions, and state of arousal.

The current view is that interplay among peripheral and central mechanisms, neurotransmitters (e.g., serotonin, substance P, dopamine), and receptors (5-HT3, NK1) causes CINV (Figure). Additional neurotransmitters such as acetylcholine, serotonin, histamine, and GABA and other receptors including cannabinoid-2 are involved. The limbic region and cerebral cortex contribute emotional responses and memory to CINV, particularly in heightening anticipatory nausea. It is not surprising that multiple mechanisms are involved because vomiting is a highly conserved protective reflex in humans and some animals to prevent accidental ingestion of toxic substances—even intravenously administered emetogenic antineoplastic agents.

The periods of acute CINV (≤ 24 hours after treatment) and delayed CINV (24 to 120 hours after treatment) were initially defined in antiemetic studies with cisplatin chemotherapy. However, patterns of CINV have been shown to depend on the antineoplastic agent(s) administered, and delayed nausea may persist for longer than 5 days. A prevalent current view is that serotonin release and binding at 5-HT3 receptors in the gastrointestinal (GI) tract are most prominent during acute CINV, whereas substance P binding at NK1 receptors in the medulla is more prominent during delayed CINV. However, multiple overlapping neurotransmitters (e.g., serotonin, substance P, dopamine, prostaglandins), acting in the peripheral and central nervous systems, may be involved in acute and delayed CINV. Animal data suggest crosstalk between 5-HT3 and NK1 receptor signaling pathways may allow synergistic action between 5-HT3 and NK1 receptor antagonists in controlling CINV. The enteric nervous system plays a major role in nausea and vomiting. Enterochromaffin cells, which constitute

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Figure. – Physiology of vomiting. Enterochromaffin cells distributed throughout the GI epithelium release serotonin in response to significant insults such as cytotoxic chemotherapy. Serotonin crosses GI tissues to various serotonin receptors. Binding at afferent vagal 5-HT3 receptors conducts information regarding intestinal tension, osmolality, and chemical stimuli within the bowel to the brain. Substance P is present in the brain and periphery, but central binding to NK1 receptors in the chemoreceptor trigger zone and about the vomiting center is the second major afferent pathway responsible for vomiting. Chemical messages, including emetogenic chemotherapy, reach the vomiting center via the circulation or the cerebrospinal fluid. Efferent pathways (dashed lines) coordinate vomiting via respiratory, diaphragmatic, and abdominal muscles. Reprinted with permission from Signal Health Media.
a significant portion of the enteric nervous system, store more than 85% of the body’s serotonin and are distributed throughout the GI epithelium from the stomach to the colon. Microvillous borders of enterochromaffin cells project into the lamina propria and release serotonin in response to significant insults, such as emetogenic chemotherapy, increased stretch or tone, or viral infection. Serotonin crosses GI tissues and binds to various receptors that influence intestinal motility and secretion. Binding at vagal 5-HT₃ receptors conducts information regarding intestinal tension and osmotic and chemical stimuli within the bowel to the brain—particularly the NTS—and slows intestinal motility.

Cisplatin chemotherapy induces serotonin release from enterochromaffin cells in animals and humans. A rat model of delayed CINV substantiated significantly higher serotonin levels and ileal changes in animals 72 hours after intraperitoneal cisplatin, but not in untreated rats. Histopathologic changes included disrupted villi, dilated luminal crypts, and decreased goblet cells. Another rat study showed cisplatin administration led to gastric distension and delayed stomach emptying, persisting for up to 1 week. However, a study on animals pretreated with a selective 5-HT₃ antagonist demonstrated inhibited serotonin release and only mild intestinal mucosal changes.

Substance P binds to NK₁ receptors in the medullary NTS and area postrema and provokes vomiting from various emetogenic stimuli including chemotherapy. Substance P binding to receptors in the gut may play an accessory role in nausea and vomiting. Animal data confirm that NK₁ antagonists (aprepitant, fosaprepitant) penetrate and are retained in brain tissues for at least 48 hours.

**Evolving Antiemetic Research**

Conducted in the 1960s, the first antiemetic study in CINV involved 300 patients with advanced gastric cancer hospitalized to receive their first or second course of 5-fluorouracil (5-FU; 15 mg/kg/day for 5 days, then 7.5 mg/kg every other day for 4 doses). Patients were randomly assigned to receive placebo, prochlorperazine (5 mg or 1 of 2 other phenothiazines), trimethobenzamide (200 mg), or an anti-histamine (no longer available) 20 minutes before meals for the first 6 days of chemotherapy. Only prochlorperazine and one other phenothiazine were significantly superior to placebo. After administration of 5-FU alone—a drug now considered to have low (10% to 30%) emetogenic potential—the incidence of nausea and vomiting in placebo-treated patients was 80% and 44%, respectively, even though patients were told they were receiving a drug that would help their nausea. A placebo effect may have been countered by patients’ expectations of experiencing CINV.

In the 1970s, antiemetic studies were based on the premise that antidopaminergic drugs (phenothiazines, butyrophenones, and metoclopramide) would be effective in CINV prophylaxis. However, standard doses of these agents were ineffective, and higher doses increased adverse effects. For example, high-dose metoclopramide (2 mg/kg to 3 mg/kg) caused distressing oversedation and fatigue, headache, diarrhea, and extrapyramidal symptoms. Diphenhydramine or lorazepam was added to regimens to decrease extrapyramidal symptoms rather than enhance antiemetic efficacy.

**5-HT₃ Receptor Antagonists**

Receptor-selective antiemetic research led to the development of first-generation 5-HT₃ antagonists ondansetron, granisetron, and dolasetron and the second-generation 5-HT₃ antagonist palonosetron. A meta-analysis of 44 randomized studies involving 12,343 patients showed that granisetron and ondansetron were equally effective for HEC and MEC, high-dose ondansetron may be superior to low-dose ondansetron for cisplatin-based chemotherapy, 1 mg and 3 mg of granisetron were equivalent, and 3 mg of granisetron may be superior to 8 mg of ondansetron.

There may be inherent interpatient variability, which affects response to particular 5-HT₃ antagonists. Subtle differences may exist in the rate of metabolism, chemical structure, half-life, receptor affinity, surmountable vs insurmountable antagonism, dose-response curves, and GI serotonin reuptake transporter expression. Compared with ondansetron, granisetron, and dolasetron, palonosetron has a longer half-life, greater binding affinity, and superior efficacy (Table 1). Furthermore, patients who receive a first-generation 5-HT₃ antagonist vs palonosetron have been shown to experience a greater negative impact on daily activities from acute or delayed CINV.

In recommended doses, oral and intravenous 5-HT₃ antagonists are considered equivalent. Granisetron is also available in a transdermal patch, which is applied 24 to 48 hours before chemotherapy and remains on the skin for up to 7 days. The total patch dose is 34.3 mg, which delivers approximately 3.1 mg of the agent per day over the course of approximately 10 to 11 days. When the patch is removed, the remaining granisetron in the skin and subcutaneous tissue is absorbed into the circulation, extending the antiemetic effect for another 12 to 24 hours. Transdermal administration of granisetron may eliminate problems related to nonadherence or persistent CINV, as patients do not have to adhere to an oral regimen.

**Corticosteroids**

The inspiration to add dexamethasone to antiemetics is unknown but may relate to lower rates of CINV observed in patients receiving antineoplastic regimens including prednisone. The benefit of corticosteroids was established in a meta-analysis of randomized trials, including 5457 evaluable patients. The likelihood of no acute or delayed vomiting increased by 25% to 30% when dexamethasone was administered in conjunction with a 5-HT₃ antagonist or other antiemetic. Doses of 8 mg to 100 mg were given for acute CINV (most commonly 20 mg), and the mean overall dose for acute and delayed CINV was 56 mg. Corticosteroids may act at central and peripheral receptors, may decrease serotonin release, and may have other effects on the GI mucosa. Short-term corticosteroids are generally well tolerated but can cause insomnia, dyspepsia, hyperglycemia, agitation, increased appetite and weight gain, and acne.
**NK, Receptor Antagonists**

Oral aprepitant (or intravenous fosaprepitant) is the only available NK antagonist and is approved to prevent acute and delayed CINV from HEC and MEC. Recommended dosing is 3 days (125 mg, 80 mg, and 80 mg) with a 5-HT₃ receptor antagonist and dexamethasone. Large studies have confirmed that this 3-drug regimen improves control of acute and delayed CINV, particularly in women.

A recent randomized double-blind study of 2,247 patients receiving cisplatin-based chemotherapy compared a simplified antiemetic regimen of intravenous fosaprepitant (150 mg on day 1 only) vs 3 days of oral aprepitant (125 mg on day 1, 80 mg on days 2 and 3), both administered with ondansetron (32 mg) plus dexamethasone (12 mg on day 1, 8 mg for the subsequent 3 days). There were no differences in complete response (no vomiting or retching, no rescue antiemetics; 71.9% vs 72.3%) or in the proportion of patients without nausea (53% vs 50.9%) between the study arms. Approximately 10% of the patients in each group received rescue antiemetics.

**Older Antiemetics**

Drugs evaluated in older antiemetic studies are now recommended for breakthrough CINV, but contemporary data on their utility alone or in combination are limited. In one study, 232 patients received oral ondansetron (24 mg) and dexamethasone (20 mg) before MEC or HEC and then were randomly assigned to twice daily oral prochlorperazine (15 mg), ondansetron (8 mg), or dexamethasone (8 mg on days 2 through 5) for delayed CINV. The rate of adherence to study antiemetics was 80% to 85%, but almost half of patients still experienced delayed CINV, most commonly on day 3. Nausea was mild (< 2.0 cm on a 10-cm visual analog scale), and 75% of patients did not experience delayed emesis. There were no differences in the efficacy and side effect profiles of prochlorperazine, ondansetron, or dexamethasone.

Another small observational study (N = 96) reviewed the effectiveness of usual physician-prescribed antiemetics for breakthrough CINV after the use of guideline-recommended antiemetics for acute CINV from MEC or HEC. Twenty-eight percent of patients required an antiemetic for breakthrough nausea and/or vomiting. Most patients (24 of 27) received prochlorperazine, which reduced nausea by about 75% for 4 hours, with minimal side effects. The other 3 patients took a 5-HT₃ receptor antagonist for breakthrough nausea and reported similar results.

Olanzapine, an atypical antipsychotic agent, is used in palliative care to enhance appetite, decrease nausea, or both. Possible side effects include sedation, weight gain, hyperglycemia, and diabetes. The antiemetic properties of olanzapine are attributed to high binding affinity for dopamine (D₁-D₅), serotonin (5-HT₂A, 2C,3,6), histamine (H₁), muscarin, and alpha₁-adrenergic receptors.

Oral olanzapine (10 mg on the day of chemotherapy and for 3 days afterward) combined with palonosetron (15 mg on day 1 only) vs 3 days of oral aprepitant (125 mg on day 1, 80 mg on days 2 and 3), both administered with ondansetron (32 mg) plus dexamethasone (12 mg on day 1, 8 mg for the subsequent 3 days). There were no differences in complete response (no vomiting or retching, no rescue antiemetics; 71.9% vs 72.3%) or in the proportion of patients without nausea (53% vs 50.9%) between the study arms. Approximately 10% of the patients in each group received rescue antiemetics.

**Table 1. — Characteristics of Standard-of-Care Antiemetics**

<table>
<thead>
<tr>
<th>5-HT₃ Antagonists</th>
<th>NK, Antagonist</th>
<th>Corticosteroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron</td>
<td>Granisetron</td>
<td>Dolasetron</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>pKi</td>
<td>8.39</td>
<td>8.91</td>
</tr>
<tr>
<td>Common Adverse Effects</td>
<td>Headache Constriction Fatigue Diarrhea Dizziness Pruritus Urinary retention</td>
<td>Headache Asthenia Somnolence Constipation Diarrhea Fever Rash Elevated liver transaminase levels Taste changes</td>
</tr>
<tr>
<td>Serious Adverse Effects</td>
<td>HSR Anaphylaxis Bronchospasm EPS QT prolongation Torsades de pointes</td>
<td>Leukopenia Thrombocytopenia Anemia HSR QT prolongation</td>
</tr>
</tbody>
</table>

EPS = extrapyramidal symptoms; HSR = hypersensitivity reaction; 5-HT₃ = 5-hydroxytryptamine-3; NK₁ = neurokinin-1; pKi = log scale for binding efficiency

Data from references 35-40.
<table>
<thead>
<tr>
<th>Risk</th>
<th>Acute CINV</th>
<th>Delayed CINV</th>
<th>Cost/Cycle (US Dollars)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| High > 90% | 5-HT<sub>3</sub> antagonist:  
  • Palonosetron 0.25 mg IV (preferred)  OR  
  • Dolasetron 100 mg PO or 100 mg IV  OR  
  • Granisetron 2 mg PO qd or 1 mg PO bid or 1 mg IV or 0.1 mg/kg IV or 34.3 mg transdermal patch applied 24-48 hours before chemotherapy for 7 days  OR  
  • Ondansetron 16-24 mg PO or 8-24 mg (max 32 mg) IV or 0.15 mg/kg IV                                                                 | • Aprepitant 80 mg PO days 2 and 3  OR  
  • Aprepitant 80 mg PO days 2 and 3  OR  
  • No aprepitant                                                                 | $407  $71 or $50  $46  $360  $1.36 per 8-mg tablet | • Brand name drugs (eg, palonosetron [Aloxi<sup>®</sup>], dolasetron [Anzemet<sup>®</sup>], transdermal granisetron [Sancuso<sup>®</sup>], aprepitant [Emend<sup>®</sup>]) will have a high copay in insurance plans that have prescription coverage  
  • Copay tiers:  
    * Tier 1: generic – lowest (eg, $4/month)  
    * Tier 2: preferred brand name based on safety, efficacy, and cost – higher  
    * Tier 3: brand name (alternative tier 1 or 2 drug available) – highest (eg, $25-$35/month)  
  • Consider the number of prescription and OTC drugs patients take  
  • Patient assistance programs: ProStrakan (Sancuso<sup>®</sup> transdermal granisetron), Eisai, Inc. (Emend<sup>®</sup> aprepitant); others may be available  
  • Make sure:  
    * Patient has prescription for scheduled and/or rescue antiemetic(s) for delayed CINV  
    * Review directions for taking antiemetics at home; establish that patient understands the importance of adherence to prescribed antiemetics  
    * Explore possible reasons for nonadherence (costs, side effects of antiemetics, dislike of taking medications, etc)  
  • Implement a follow-up plan for timely assessment, interventions for delayed CINV  
    * Telephone, text message, e-mail days 2 and 3  
    * Simple patient diary |                                                                                                                                                                                                 |
| Moderate 30%<sup>–</sup> 90% | 5-HT<sub>1</sub> antagonist:  
  • Palonosetron 0.25 mg IV (preferred)  OR  
  • Dolasetron 100 mg PO or 100 mg IV  OR  
  • Granisetron 2 mg PO qd or 1 mg PO bid or 1 mg IV or 0.1 mg/kg IV or 34.3 mg transdermal patch applied 24-48 hours before chemotherapy for 7 days  OR  
  • Ondansetron 16-24 mg PO or 8-24 mg (max 32 mg) IV or 0.15 mg/kg IV                                                                 | • Dexamethasone 12 mg PO or IV  
  • Dexamethasone 8 mg days 2, 3, and 4                                                                 | See above |                                                                                                                                                                                                 |
| Low 10%<sup>–</sup> < 30% | 5-HT<sub>3</sub> receptor antagonist:  
  • Dexamethasone 12 mg PO or IV  
  • Metoclopramide  
  • Prochlorperazine  
  • ± Lorazepam  
  • ± H2 blocker or proton pump inhibitor                                                                 | • Dexamethasone 8 mg days 2 and 3                                                                 | $1.71 | Breakthrough CINV, add drug from another class*:  
  • Benzodiazepine: lorazepam  
  • Cannabinoid: dronabinol  
  • Dopamine antagonist; prochlorperazine, haloperidol, or metoclopramide  
  • Histamine blocker: promethazine or scopolamine  
  • Other: olanzapine  
  • 5-HT<sub>3</sub> receptor antagonist  
  • Steroid: dexamethasone |                                                                                                                                                                                                 |
| Minimal < 10% | No routine prophylaxis                                                                                                                |                                                                             | | * lorazepam 2 mg: $0.74 each; dronabinol (Marinol<sup>®</sup>) 10-mg capsule: $11.34 each; prochlorperazine 10 mg (5 mg x 2): $0.94; haloperidol 2 mg: $0.23; metoclopramide 10 mg: $0.19; olanzapine (Zyprexa<sup>®</sup> or Zyprax Zydis<sup>®</sup> [oral dissolvable tablets]) 10 mg: $12.66 each  
  bid = twice daily; CINV = chemotherapy-induced nausea and vomiting; H<sub>2</sub> = histamine 2; 5-HT<sub>3</sub> = 5-hydroxytryptamine-3; IV = intravenously;  
  NK<sub>1</sub> = neurokinin-1; OTC = over the counter; PO = orally; qd = once daily  
  Data from references 26-28,39,40. |
and dexamethasone has been shown to enhance control of both acute and delayed CINV associated with HEC or MEC.\textsuperscript{51} Olanzapine may also offer efficacy and cost savings, based on a recent adequately powered study of 214 evaluable chemotherapy-naive patients receiving HEC (cisplatin $\geq$ 70 mg/m$^2$ or cyclophosphamide 600 mg/m$^2$ to 1,000 mg/m$^2$ plus doxorubicin 50 mg/m$^2$ to 60 mg/m$^2$).\textsuperscript{52} Patients were randomly assigned to receive either olanzapine (10 mg orally), intravenous dexamethasone (20 mg), and intravenous palonosetron (0.25 mg) 1 day before chemotherapy and olanzapine (10 mg orally) on days 2 to 4 after chemotherapy or oral aprepitant (125 mg), intravenous palonosetron (0.25 mg), and intravenous dexamethasone (12 mg) on day 1 of chemotherapy, oral aprepitant (80 mg) on days 2 and 3, and intravenous dexamethasone (4 mg) twice daily on days 2 to 4. The olanzapine and aprepitant regimens were equivalent in controlling acute (97\% vs 87\%) and delayed (77\% vs 73\%) vomiting and acute nausea (87\% for both); however, olanzapine was superior in controlling delayed nausea (69\% vs 38\%).\textsuperscript{52}

**The Economic Burden of CINV: A Potential Barrier to Optimal Care**

Oncology providers must be aware of the direct and indirect costs of CINV management within the larger context of the total cost of cancer care (Table 2).\textsuperscript{20,28,39,49} Medical illness is a common reason for personal bankruptcy and occurs almost twice as frequently in cancer patients 1 year after their diagnosis as in the general population.\textsuperscript{53} Not only are 5-HT$_3$ and NK$_1$ receptor antagonists expensive, but insurance copays are much higher for oral brand vs generic drugs. Patients without insurance may be responsible for the entire cost of these agents. The cost of treatment may account for the administration of less-than-optimal antiemetics, particularly for MEC.

The cost of standard-of-care antiemetics may be outweighed by the cost to rescue patients after suboptimal CINV prophylaxis, which is typically not factored into care costs. One retrospective analysis of 19,139 patients found that the first cycle of HEC (16\%) or MEC (84\%) found 2,641 (13.8\%) had primary or secondary ICD-9 codes reflecting medical care for CINV within 30 days or before their next chemotherapy cycle.\textsuperscript{54} Nearly all CINV resources (ie, hospital visits) were utilized for the treatment of delayed cases, and the median time to care was 7 days. More patients required hospital inpatient (64\%), outpatient (26\%), or emergency department (10\%) care after HEC than MEC (18\% vs 13\%). The average expense was $5,299 (US) for patients who needed hospital care vs $731 who did not.\textsuperscript{54}

Another observational study found total direct (antiemetics, office visits, emergency department visits, hospitalizations) and indirect (missed work and lost productivity) costs associated with CINV in patients who received prophylaxis for acute CINV averaged nearly $780 from day 1 through day 5 after chemotherapy.\textsuperscript{2} Patient-reported direct costs were three times the physician estimates and were higher in patients with severe vs moderate or mild nausea ($802 vs $32 and $7 per patient, respectively). Indirect costs for currently employed patients who reported missing work were higher for patients with severe vs mild nausea with regard to missed work ($379.13 vs $8.19) and lost productivity ($456.41 vs $85.83).\textsuperscript{2}

**Nonpharmacologic Measures as Adjuncts to Antiemetics**

Nonpharmacologic adjunctive measures with antiemetics may add small, but incremental, benefit for nausea, with little to no expense. Acupressure to the P6 point (3 finger breadths above the first wrist crease and between the first 2 medial tendons) with manual pressure or acupressure bands (often used for sea sickness) has been most widely studied. It is convenient, easy to perform, inexpensive, and offers patients control to decrease nausea.\textsuperscript{55}

Ginger is another measure that may alleviate nausea, but there is conflicting evidence for the benefit of 1 g per day.\textsuperscript{56,57} However, there is no evidence of detrimental effects, and patients can purchase ginger tablets from health food stores and can determine its personal effectiveness.

**Conclusions**

Progress in our understanding of the physiology of CINV has advanced the antiemesis armamentarium appreciably, resulting in the development of newer antiemetic agents, which improve control of CINV with fewer side effects compared with older agents. However, patient reports of nausea and vomiting indicate that use of these agents is suboptimal. In some cases, selection of a suboptimal agent may be related to financial considerations. Although older antiemetics such as olanzapine and prochlorperazine offer economic alternatives in certain settings, use of these agents must be weighed against the potential cost of having to rescue patients due to suboptimal prophylaxis.

**References**


34. de Wit R, Aapro M, Blower PR. Is there a pharmacological basis for differences in 5-HT3-receptor antagonist efficacy in refractory patients? *Cancer Chemother Pharmacol*. 2005;56(3):231-238.


