Controlling Emesis: Evolving Challenges, Novel Strategies

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Abstract Control of nausea and vomiting following chemotherapy, radiation therapy, and surgery has significantly improved in recent years due to the development of novel, effective, and better-tolerated antiemetic therapies. However, the incidence and severity of emesis are often underestimated by the medical community and remain among the most distressing outcomes following treatment. Inadequately controlled nausea and vomiting can negatively impact several aspects of emetogenic therapy, including quality of life, cost of therapy, compliance, and possibly treatment outcomes. To address these concerns, antiemetic therapy continues to evolve along several avenues, such as the development and use of novel 5-hydroxytryptamine and neurokinin-1 receptor antagonists, refinement of antiemetic therapeutic guidelines, identification of additional risk factors for acute and delayed nausea and vomiting, and additional research toward the role of nonpharmacologic complementary therapies. In addition to improved treatment options, the development of alternative oral drug delivery systems, including orally dissolving tablets and film strips, should further improve the overall convenience of antiemetic therapy.

Nausea and vomiting following the administration of chemotherapy, radiation therapy, or surgery remain significant and distressing complications associated with these therapies.[1,2] Continued research over the past 25 years has led to steady progress in the management of emesis among patients in these treatment settings, particularly with the development of 5-hydroxytryptamine (5-HT_3) and neurokinin-1 (NK_1) receptor antagonists and the improved use of corticosteroids.[3–8]

Despite these noteworthy achievements, several therapeutic challenges and unaddressed needs continue to impact the control of emesis. Episodes of chemotherapy-induced and radiation-induced nausea and vomiting (CINV and RINV, respectively) remain frequent among patients undergoing any of these treatment modalities, often occurring in up to 80% of cases.[1,9–11] Among them, CINV is typically the most severe, and clinical evidence indicates that optimal management of this complication has not been achieved.[12,13]

Management of Nausea and Vomiting Remains an Evolving Challenge

A retrospective analysis by Roscoe and colleagues concluded that following the introduction of 5-HT_3 receptor antagonists, the incidence of post-treatment nausea increased despite a decreased frequency of post-treatment vomiting.[12] In addition, two meta-analyses have reported that 5-HT_3 receptor antagonists given alone or in combination with corticosteroids have not been effective for treating delayed CINV.[13,14]

Although at first glance these findings initially suggest that 5-HT_3 agents are not effective, recent clinical data indicate that inadequate management of emesis may be at least partly attributable to healthcare professionals minimizing the degree to which patients will experience nausea and vomiting following treatment. The Anti-Nausea Chemotherapy Registration (ANCHOR) study by Grunberg and colleagues was designed to prospectively assess the frequency and impact of nausea and vomiting among patients receiving moderately or highly emetogenic chemotherapy (MEC or HEC, respectively).[15,16] Doctors and nurses from 14 oncology practices estimated the expected frequency of nausea and vomiting following chemotherapy, which was compared with recorded episodes of acute (24 hours post chemotherapy) and delayed (2–5 days post chemotherapy) nausea and vomiting in patients undergoing MEC (n = 231) or HEC (n = 67).[15] Functional Living Index–Emesis (FLIE) questionnaires were also completed at baseline and on day 6 after therapy to measure changes in quality of life.[15,16]

The results of the ANCHOR study demonstrated that CINV, particularly delayed CINV,

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occurs more frequently than expected by healthcare professionals. Among MEC patients, doctors and nurses accurately predicted that acute vomiting would occur in 13% of patients. However, the incidence of acute nausea was underestimated, with a predicted incidence of 24% and an observed incidence of 37%. Delayed CINV was underestimated to an even greater degree; although delayed nausea and vomiting were predicted to occur in 24% and 15% of patients, respectively, the diaries of MEC patient revealed delayed nausea and vomiting incidences of 52% and 28%, respectively.[15] Although the prevalence of acute emesis was similar between HEC and MEC patients (12% and 13%, respectively), HEC patients were significantly more likely to report delayed emesis ($P < 0.05$) and reported more frequent and severe delayed nausea episodes than MEC patients.[16] Among all patients who experienced delayed nausea or vomiting (n = 173), 23% reported an impact of CINV on their overall quality of life. Based on these results, the investigators concluded that the incidence of CINV is underestimated by healthcare professionals and negatively impacts quality of life, even when it is not experienced during the first 24 hours following treatment.[15,16]

Although evidence is less conclusive for RINV and postoperative nausea and vomiting (PONV), it is generally believed that the magnitude of both of these complications is similarly underestimated.[17–19] In one observational study of RINV, one-third of surveyed radiotherapy patients experienced nausea and vomiting. However, 85% of these patients were not prescribed antiemetics.[20] Another study by the Italian Group for Antiemetic Research in Radiotherapy (IGARR) similarly reported that 40% of radiotherapy patients experienced nausea and vomiting. However, only 14% of these patients were prescribed antiemetics. In addition, antiemetics were more frequently prescribed with the goal of managing existing episodes rather than for the prophylaxis of potential symptoms.[21]

Evidence shows that the incidence of PONV is also higher than expected. Results from a study by Carroll and colleagues examining PONV among patients (n = 143) released from outpatient surgery centers demonstrated that many patients continued to experience PONV following discharge.[18] Although the initial incidence of PONV recorded in the postanesthesia care unit (PACU) was 36%, this incidence rose to 78% when patients who reported PONV via telephone within 48 hours following discharge were included.[18]

Similar results were seen in a prospective study by Apfel and colleagues evaluating survey data from more than 2,000 adult patients who received elective surgery under general anesthesia.[19] Although the incidences of nausea and vomiting in the PACU were 20% and 3%, respectively, these rates increased to 44% and 12% when expanded over a 48-hour period. Additionally, the incidence of nausea and vomiting 48 hours after anesthesia was 37%, compared with the 15% predicted by the investigators.[19]

In addition to their higher-than-expected incidences, CINV, RINV, and PONV remain highly distressing complications for patients. Among patients receiving chemotherapy or surgery, CINV and PONV are consistently reported as the most unpleasant aspects associated with treatment.[22–26] Even one or two emetic episodes are sufficient to deteriorate quality of life and disrupt physical and cognitive function in these patients.[27] In a prospective study by Rusthoven and colleagues assessing health-related quality-of-life questionnaires from patients receiving emetogenic chemotherapy, patients who experienced episodes of CINV reported significantly greater deterioration across several functional quality-of-life categories than those without CINV ($P < 0.05$).[28] PONV is also frequently associated with significant morbidity and can lead to several complications, including dehydration, electrolyte imbalance, suture tension and dehiscence, venous hypertension/bleeding, esophageal rupture, and life-threatening airway compromise.[29–32] Emetic episodes can also lead to delays in recovery room discharges, particularly for outpatient surgeries. These delays often result in delayed procedures at surgical centers due to the increased recovery time associated with PONV.[29,33–35]

Although RINV is generally considered less severe than CINV or PONV, patients receiving fractionated radiotherapy (up to 40 fractions over 6–8 weeks) often experience prolonged episodes of emesis, which can adversely impact their quality of life.[1,17,36]

Ultimately, suboptimal management of nausea and vomiting has multiple consequences. In addition to its impact on quality of life, uncontrolled emesis frequently leads to reduced treatment compliance, as patients often delay or refuse a potentially curative therapy.[1,27,29,37–40] There is also a substantial socioeconomic burden associated with nausea and vomiting that affects patients, their employers, and the healthcare industry overall.[33,41,42] Similarly, CINV has also been shown to lower employee productivity and increase overall healthcare costs due to prolonged inpatient hospitalization and home nursing expenses.[42] Healthcare costs for patients who experience CINV and PONV have been reported to be up to $184 and $415 per person, respectively.[33,41]

Due to the persistence and significance of these treatment challenges, there is an unmet need for the development of more effective and tolerable antiemetic therapies. Moreover, the role of the delivery system used to administer these drugs is often overlooked. Although the vast majority of antiemetic drugs are administered orally or intravenously, there are inherent limitations associated with both delivery methods in this treatment setting.[43–49]

This article will focus primarily on currently available antiemetic therapies—including risk factors and currently recommended treatment guidelines—for CINV, RINV, and PONV. In addition, novel antiemetic therapies and the evolving role of drug delivery systems for antiemetic therapy will be discussed.

Prophylaxis and Treatment of Emesis: All Options Are Not Created Equal

HIGH THERAPEUTIC INDEX ORAL ANTIEMETICS

The vomiting reflex is a complex mechanism that can be activated from multiple stimuli at several anatomic sites, including the peripheral afferents of the gastrointestinal tract

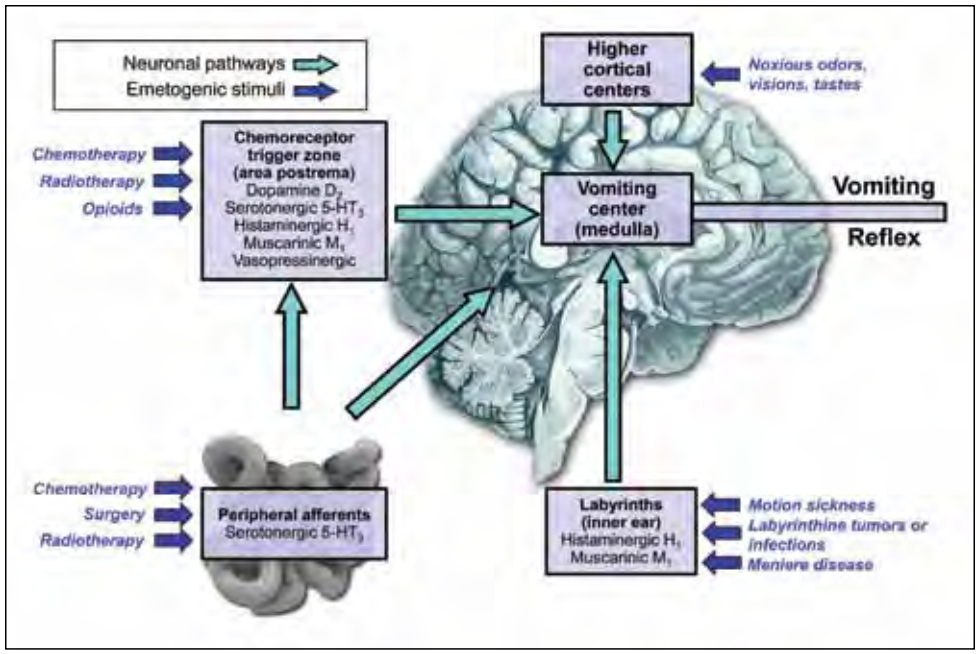

Figure 1 The Vomiting Reflex Is Triggered from Multiple Anatomic Sites
Adapted, in part, from Quigley et al[47]

and the cerebral cortex. In addition, the receptors that are activated at these sites are diverse and continue to be defined (Figure 1).[47] With this complicated pathophysiology, it is not surprising that the treatment options both available and in development for managing nausea and vomiting are varied and complex as well. Currently available agents used to treat nausea and vomiting are listed in Table 1.[47,50–54] Although several options are available, their documented efficacy and tolerability vary significantly. To date, the principal drug classes with the highest therapeutic index for managing CINV, RINV, and PONV are serotonin 5-HT_3 receptor antagonists (5-HT_3RAs), corticosteroids, and NK_1 receptor antagonists (NK_1RAs).[50,55,56]

The development of the first-generation 5-HT_3RAs (dolasetron [Anzemet], ondansetron, granisetron, and tropisetron) significantly improved antiemetic therapy in the early 1990s, and to date, they remain the most effective antiemetic agents in the prophylaxis of acute CINV and RINV.[6,50,57] These agents have demonstrated equivalent efficacy and, therefore, appear to be interchangeable, based on conclusions supported by category 1 evidence from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the Multinational Association of Supportive Care in Cancer (MASCC) guidelines.[1,6,56–60] Few adverse events occur with 5-HT_3RAs at typical doses, and those that do occur are usually limited to headaches, elevated liver enzymes, constipation, and diarrhea.[50,56–58,61] However, these agents are generally less effective for preventing delayed emesis.[50,57,62]

Palonosetron (Aloxi) is a novel 5-HT_3RA approved by the US Food and Drug Administration (FDA) in 2003. It has a 100-fold greater binding affinity for the 5-HT_3 receptor and a significantly longer half-life of 40 hours than the other 5-HT_3RAs; therefore, palonosetron is considered a second-generation drug in this class of agents.[63] Intravenous palonosetron has produced statistically significant improvements in complete response rates compared with ondansetron or dolasetron in head-to-head clinical trials of patients receiving MEC.[64,65] However, no significant difference in complete response rates was observed between palonosetron and ondansetron in patients receiving HEC.[66] An oral formulation of palonosetron is now available and has been approved for control of delayed emesis in patients receiving MEC.[57]

The NK_1RA aprepitant (Emend) is the first in a novel class of drugs to be approved for the management of nausea and vomiting. These agents block the NK_1 receptor in the brainstem's emetogenic center and gastrointestinal tract and may enhance the overall efficacy of 5-HT_3RAs due to their complementary mechanisms of action.[67,68]

Several studies have shown that the addition of aprepitant to a standard antiemetic regimen of 5-HT_3RA and dexamethasone significantly improves control of acute and delayed emesis in patients receiving HEC[67,69,70] and improves overall CINV management in breast cancer patients receiving MEC with cyclophosphamide ± anthracycline.[5] Thus, aprepitant is recommended by the MASCC, ASCO, and NCCN guidelines for patients receiving HEC and, in select cases, MEC.[1,5,57,60]

Despite the promising results aprepitant has demonstrated in advancing the management of CINV, several concerns remain regarding its optimal effective use. For example, the role of aprepitant in MEC remains undefined. In a study by Warr and colleagues, aprepitant without dexamethasone did not significantly improve control of delayed nausea and vomiting on days 2 and 3 following chemotherapy.[5] Aprepitant alone or in combination with dexamethasone does not appear to control emesis as well as a standard antiemetic regimen of 5-HT_3RA and dexamethasone, thus limiting its use as an addition to 5-HT_3RA–based antiemetic regimens that have clinically established efficacy.[71]

Aprepitant also has a complex metabolism; it is simultaneously a substrate, inhibitor, and inducer of the cytochrome P450 3A4 enzyme and an inducer of the P450 2C9 pathway. Therefore, aprepitant can alter the metabolism and change the plasma concentrations of several drugs that are substrates for these pathways.[50,57] For example, dexamethasone, a substrate of the cytochrome P450 3A4 pathway, demonstrates increased plasma concentrations when coadministered with aprepitant.[72] Several antineoplastic agents are also substrates of the 3A4

Table 1

Currently Used Agents to Treat Emesis

DRUG CLASS AND NAME	CLINICAL USES	COMMON SIDE EFFECTS	FORMULATIONS
High therapeutic index			
5-HT_3 receptor antagonists • Ondansetron • Granisetron • Dolasetron • Tropisetron[a] • Palonosetron	CINV, RINV, PONV, severe nausea and vomiting	Asthenia, constipation, dizziness, mild headache	• C/T/G • S/L/C (ondansetron, granisetron) • Parenteral • Subdermal patch (granisetron) • Film strip (ondansetron)
Corticosteroids • Dexamethasone	Adjunct for chemotherapy-related symptoms	Increased energy, insomnia, mood changes	• C/T/G • S/L/C • Parenteral
NK_1 receptor antagonists • Aprepitant	CINV, PONV	Fatigue, nausea, hair loss, hiccups, loss of appetite, constipation, diarrhea, headache	• C/T/G • Parenteral
Low therapeutic index			
Antihistamines • Diphenhydramine • Dimenhydrinate • Meclizine	Migraine, motion sickness, vertigo	Drowsiness	• C/T/G • S/L/C (diphenhydramine, dimenhydrinate) • Parenteral • Film strip (diphenhydramine)
Benzodiazepines • Alprazolam • Diazepam • Lorazepam	Adjunct for chemotherapy-related symptoms	Sedation	• C/T/G • S/L/C • Parenteral (diazepam, lorazepam)
Butyrophenones • Droperidol[b] • Haloperidol	Anticipatory and acute CINV, PONV	Agitation, restlessness, sedation	• C/T/G (haloperidol) • S/L/C (haloperidol) • Parenteral
Cannabinoids • Dronabinol • Nabilone	Refractory CINV	Ataxia, dizziness, euphoria, hypotension, sedation	• C/T/G
Phenothiazines • Chlorpromazine[c] • Prochlorperazine • Promethazine	Migraine, motion sickness, CINV, PONV, severe episodes of nausea and vomiting, vertigo	EPS, orthostatic hypotension, sedation	• C/T/G • S/L/C • Parenteral • Suppository
Substituted benzamides[d] • Trimethobenzamide • Metoclopramide	Diabetic gastroenteropathy, gastroparesis	EPS, fatigue, hyperprolactinemia	• C/T/G • S/L/C (metoclopramide) • Parenteral

5-HT_3 = 5-hydroxytryptamine (serotonin); CINV = chemotherapy-induced nausea and vomiting; RINV = radiation-induced nausea and vomiting; PONV = postoperative nausea and vomiting; C/T/G = capsule/tablet/gel; S/L/C = syrup/liquid/concentration; NK_1 = neurokinin-1; EPS = extrapyramidal symptoms (eg, akathisia, dyskinesia, dystonia, oculogyric crises, opisthotonos)

[a] Not available in the United States

[b] Not widely used in the United States due to "black box" warning

[c] Low incidence of side effects

[d] Use limited by high occurrence of side effects

pathway, which can potentially lead to increased toxicity and altered plasma concentrations when oral chemotherapeutic agents metabolized by this pathway are administered with aprepitant.[57] Moreover, aprepitant is relatively expensive compared with other options.[6] Finally, the MASCC and American Society of Anesthesiologists (ASA) guidelines currently do not recommend NK_1RAs for the management of RINV or PONV, respectively.

Although it has never been officially approved by the FDA as an antiemetic in the United States, the corticosteroid dexamethasone is recommended by the MASCC, ASCO, and NCCN guidelines to manage CINV.[1,57,60] Less is known about the antiemetic mechanism of action of corticosteroids compared with the 5-HT_3RA and NK_1RA drug classes. Nonetheless, dexamethasone has demonstrated notable efficacy in the management of acute and delayed CINV—particularly when administered in combination with another antiemetic agent—and therefore remains a key component of nearly all CINV management regimens.[4,50,61] Dexamethasone is also recommended by the MASCC in combination with a 5-HT_3RA for patients at moderate or high risk for RINV[1] and singly or in combination for the management of PONV.[73] Although short-term use of corticosteroids is effective and recommended for managing emesis, long-term use may not be advisable, as substantial morbidity is often associated with the prolonged use of these agents.[60,61]

LOW THERAPEUTIC INDEX ORAL ANTIEMETICS

Additional antiemetic drug classes with a lower therapeutic index include antihistamines, benzodiazepines, butyrophenones, cannabinoids, phenothiazines, and substituted benzamides. Although these agents typically demonstrate lower

activity and/or tolerability than do higher therapeutic index antiemetics, several of these drugs continue to be prescribed in place of antiemetics with clinically demonstrated superior efficacy.[50,55]

OTHER ANTIEMETICS IN DEVELOPMENT

The antipsychotic olanzapine (Zyprexa) blocks neurotransmitter activity at multiple dopaminergic, serotonergic, muscarinic, and histaminic receptors, suggesting it may have therapeutic value as an antiemetic agent.[74] Olanzapine has shown efficacy in managing chronic nausea due to opioid therapy in patients with advanced cancer.[75] Results of a phase II study demonstrated that olanzapine was effective in managing acute and delayed emesis in 30 patients given cyclophosphamide, doxorubicin, and/or cisplatin.[76] Promising initial results have also been shown for the anticonvulsant gabapentin for reducing delayed nausea in a small group of patients with breast cancer receiving adjuvant doxorubicin and cyclophosphamide.[77] Additional studies are clearly warranted to demonstrate the efficacy of these agents in other antiemetic regimens and patient populations.

ALTERNATIVE ANTIEMETIC THERAPIES

Although antiemetic medications remain the recommended first-line treatment across all guidelines for nausea and vomiting management, several nonpharmacologic and behavioral therapies may also help patients manage emesis in select situations. Acupuncture at the P6 pressure point,[78,79] transcutaneous electrical nerve stimulation,[80] relaxation training,[81] music therapy,[82] massage therapy,[83] hypnosis,[84] ginger root,[85] and peppermint aromatherapy[86] have demonstrated varying levels of efficacy in managing CINV and PONV in select trials. Although these therapies require further research to support their therapeutic value, they may be useful as complementary adjuncts to standard pharmacologic antiemetics.

CLASSIFICATION OF CINV, RINV, AND PONV RISK FACTORS

Among the highly diverse assortment of chemotherapy drugs, the emetogenic potential varies widely. One schema (originally designed by Hesketh and colleagues) classifies chemotherapy drugs by their emetogenic level and includes four categories: minimal risk, low risk, moderate risk, and severe risk.[1,50] Emetogenic risk levels for radiation therapy are also divided into a similar schema of minimal-, low-, moderate-, and high-risk categories, which are based primarily on the site of the irradiated area (Table 2).[1,50]

Although these classification systems guide physicians to provide suitable antiemetic regimens for patients receiving chemotherapy, radiation therapy, or surgery, several additional

Table 2

Emetic Risk Levels for Intravenous and Oral Chemotherapy Drugs and Radiotherapy

CHEMOTHERAPY	MINIMAL (< 10%)	LOW (10%–30%)	MODERATE (30%–90%)	HIGH (> 90%)
Intravenous	Bevacizumab Bleomycin Busulfan Cladribine Fludarabine Vinblastine Vincristine Vinorelbine	Bortezomib Cetuximab Cytarabine (≤ 100 mg/m^2 of body surface area) Docetaxel Etoposide Fluorouracil Gemcitabine Ixabepilone Lapatinib Methotrexate Mitomycin Mitoxantrone Paclitaxel Pemetrexed Temsirolimus Topotecan Trastuzumab	Carboplatin Cyclophosphamide (≤ 1.5 g/m^2) Cytarabine (> 1 g/m^2) Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin	Carmustine Cisplatin Cyclophosphamide (> 1.5 g/m^2) Dacarbazine Mechlorethamine Streptozocin
Oral	Chlorambucil Erlotinib Gefitinib Hydroxyurea Methotrexate Phenylalanine mustard Thioguanine	Capecitabine Fludarabine	Cyclophosphamide Etoposide Imatinib Temozolomide Vinorelbine	Hexamethylmelamine Procarbazine
RADIOTHERAPY	MINIMAL (< 30%)	LOW (30%–59%)	MODERATE (60%–90%)	HIGH (> 90%)
Irradiated area	Head and neck, extremities, cranium, and breast	Cranium (radiosurgery) and craniospinal area; lower thoracic region and pelvis	Upper abdomen	Total-body irradiation

Reprinted, with permission, from Roila et al[1] and Hesketh.[51]

Table 3

Patient- and Treatment-Related Risk Factors Associated with CINV, RINV, and PONV

PATIENT-RELATED FACTORS	TREATMENT-RELATED FACTORS
Chemotherapy-induced nausea and vomiting (CINV)	
• Female gender • Younger age • Low alcohol intake history • History of CINV • Performance status • Pretreatment expectations of severe nausea • History of motion sickness • History of emesis during pregnancy	• Emetogenicity of antineoplastic agents • Chemotherapy dose • Route of administration (oral vs IV) • Schedule and rate of administration
Radiation-induced nausea and vomiting (RINV)	
• Female gender • Younger age • Low alcohol intake history • History of RINV • Tumor stage • Recent concurrent chemotherapy	• Irradiated area • Radiation frequency • Radiation dose • Field size
Postoperative nausea and vomiting (PONV)	
• Female gender • Nonsmoking status • History of PONV • History of motion sickness • History of migraines • Childhood (after infancy and younger adult) • Preoperative anxiety • Better ASA physical stature	• Volatile anesthetics • Balanced vs total IV anesthesia • Nitrous oxide • Large-dose (≥ 2.5 mg) neostigmine • Intra-, peri-, or postoperative opioids • Prolonged duration of anesthesia • Type of surgery in adults[a] and children[b] • Prolonged duration of surgery

ASA = American Society of Anesthesiology

[a] Including intra-abdominal surgery, neurosurgery, laparoscopy, orthopedic surgery, major gynecologic surgery, thyroid surgery, breast surgery, and plastic surgery

[b] Including strabismus, hernia repair, orchiopexy, penile surgery, and ear-nose-throat procedures (including adenotonsillectomy)

factors must also be addressed. For example, it is important to differentiate between the management of acute or delayed nausea and vomiting, a feature that is often overlooked by antiemetic schemas and guidelines. In the case of CINV, this distinction is further complicated by the increased use of oral cytotoxics and targeted agents, which are administered on varying schedules over several days or weeks.[1] Additionally, several emetogenic risk factors, both patient-related (eg, gender, age, history of emesis) and treatment-related (eg, route of administration, dose, infusion rate, irradiation site, analgesic use), have been shown to impact the rate of CINV, RINV, and PONV in multiple studies (Table 3).[1,10,11,17,30,50,55,57,87–89] Thus, potential emetogenic risk factors should be assessed in all patients, as they might influence the choice of antiemetic regimen for each individual.

ANTIEMETIC GUIDELINES FOR CINV, RINV, AND PONV

Antiemetic prophylaxis guidelines for CINV, RINV, and PONV continue to evolve as useful tools that are periodically updated with the latest clinical research and drug development. Currently, guidelines for managing CINV remain the most comprehensive, with evidence-based recommendations developed by the MASCC,[1] ASCO,[60] and NCCN.[57] The Oncology Nursing Society (ONS) has also developed evidence-based guidelines, which include CINV, to help nurses improve symptom management and patient outcomes.[90]

In general, there is consensus among all three guidelines on the classification of CINV into three categories: acute onset (occurs within 24 hours of initial chemotherapy), delayed onset (occurs >24 hours following initial chemotherapy and may last up to 5 days), and anticipatory onset (emetic episodes triggered by a conditioned response due to prior severe nausea and vomiting with chemotherapy).[1,57,60]

For acute CINV prophylaxis in HEC or MEC, the guidelines unanimously recommend a combination of a 5-HT_3RA, dexamethasone, and the NK_1RA aprepitant within the first 24 hours of chemotherapy (aprepitant is optional for MEC). For low emetogenic chemotherapy (LEC), both the MASCC and ASCO guidelines recommend corticosteroids alone within the first 24 hours, whereas the NCCN guidelines suggest dexamethasone, prochlorperazine, or metoclopramide.[1,5,57,60]

For delayed CINV with HEC, dexamethasone plus aprepitant is recommended. For MEC, dexamethasone is the preferred agent, but aprepitant with or without dexamethasone may be considered as a replacement (MASCC, ASCO). A 5-HT_3RA can be used (NCCN) if aprepitant was used previously to treat acute CINV. For LEC, delayed CINV prophylaxis is not recommended by any of the guidelines.[1,57,60]

The MASCC prophylaxis guidelines for RINV are also categorized by the risk level for emesis (Table 2).[1,17] For patients receiving high- or moderate-risk radiotherapy, prophylaxis with a 5-HT_3RA plus dexamethasone is recommended. Patients receiving low-risk radiotherapy are recommended to receive prophylaxis or rescue treatment with 5-HT_3RA monotherapy, whereas patients treated with minimal-risk radiotherapy should receive rescue treatment with a dopamine or 5-HT_3RA. Although the level of consensus is uniformly high (consensus by more than two-thirds of MASCC panelists) for all risk levels, the level of scientific confidence is considered lower for cranium (radiosurgery) and craniospinal patients and for minimal-risk patients.[1,17]

The ASA practice guidelines for postanesthetic care are comparatively broader for the prevention and management of PONV.[73] When indicated, 5-HT_3RAs, droperidol, dexamethasone, and metoclopramide alone or in combination are suggested for prophylaxis or treatment. Although other antiemetic or nonpharmacologic agents may be used for treatment when indicated, evidence supporting their use to manage PONV is less robust.[73]

The Role of Novel Drug Delivery Systems in Improving Control of Emesis

ANTIEMETIC DRUG DELIVERY SYSTEMS IMPACT PATIENT COMPLIANCE AND CONVENIENCE

Despite their inherently greater convenience in comparison with intravenous drugs, oral antiemetics are often burdened

with several potential problems. Conventional oral delivery systems, including tablets, capsules, solutions, and suspensions, are often difficult to administer to patients with dysphagia.[48,49]

Swallowing difficulties also occur often in specific populations, including elderly, very young, and developmentally disabled patients, which may impede their use of prescribed oral medications. Nauseated patients also frequently experience difficulties with oral medications, as they are often unable to keep these agents down due to active symptoms.[47] Finally, patients who frequently receive oral antiemetic medications, which are often associated with a bitter taste, may develop learned taste aversions that further limit the use of these drugs.[91,92]

In addition to swallowing difficulties, convenience is also a notable concern associated with oral antiemetics. Patients taking tablet formulations often require drinking water to ease swallowing, which is not always available.[44] Also, crushing tablets or removing contents from capsules may significantly alter the absorption profile of a drug, consequently changing its efficacy and tolerability.[45,46,48]

Intravenous antiemetic drugs are associated with a different set of drawbacks. Although infusions by a nurse or physician usually improve compliance, they are inconvenient for patients, as they typically require frequent and prolonged dosing schedules that preclude outpatient use.[43] Thus, in addition to improved antiemetic agents, novel drug delivery systems that rapidly, effectively, and conveniently distribute medications to patients with minimal side effects are clearly necessary and are under development to improve the overall administration of antiemetic therapy.

NOVEL ANTIEMETIC DRUG DELIVERY SYSTEMS IN DEVELOPMENT

In addition to its oral and intravenous formulations, granisetron is now available as a transdermal patch. When compared with oral granisetron (2 mg daily), transdermal granisetron demonstrated noninferior efficacy in complete control of acute CINV. However, the efficacy of the granisetron patch in the delayed setting has not yet been defined.[93]

Intranasal formulations are another direct mode of drug delivery that may offer rapid absorption while circumventing the problems of first-pass metabolism that occur with some oral agents.[94] Initial results of an ongoing double-blind phase II clinical study comparing the preventive efficacy of intranasal granisetron in cancer patients receiving HEC have demonstrated improved control of acute CINV, with no reported adverse events related to the study drug.[95] Intranasal formulations of metoclopramide and ondansetron are also in early development but have not yet proceeded to clinical studies.[96,97]

IMPROVEMENTS IN ORAL DOSING FORMULATIONS

In addition to the creation of nontraditional drug delivery systems, oral delivery formulations have continued to evolve to promote rapid dissolution and absorption while maintaining the convenience and portability intrinsic with oral agents.[44,92,98,99] Nanoparticle technology—the creation of engineered molecules < 100 nm in diameter—is leading to the creation of new drugs with improved bioavailability to target tissues. Aprepitant has demonstrated enhanced drug exposure and decreased food effects when developed as an oral nanoparticle formulation.[94,100] Although this delivery technology appears promising, with several applications both within and outside antiemetic therapy, there remain several safety concerns about the introduction of nanoparticles into patients that warrant further evaluation.[101]

Orally dissolving tablets (ODTs) have been designed to allow a solid dose to be rapidly dissolved by saliva in the oral cavity without the need for drinking water.[44,92,98,99] Although these drugs are effective in delivering their antiemetic medications—particularly among patients who experience difficulty swallowing conventional oral medications, such as pediatric, geriatric, bedridden, or developmentally disabled patients,[44,49,102,103]—there are notable challenges to their use. Patients must be specifically educated not to chew, swallow, or drink water with the tablet.[104] Also, because administering bitter-tasting antiemetics as an ODT formulation would offset their use, taste masking is required.[92,99] Currently, the only antiemetics available in ODT formulations are ondansetron, metoclopramide, and olanzapine.

In recent years, a novel oral delivery system known as oral-soluble film (OSF) strips has appeared in the over-the-counter (OTC) market space. These are thin polymer-coated strips designed to adhere upon contact with the tongue and then dissolve into the saliva.[104–107] Unlike other novel delivery systems, which often experience a relatively slow acceptance due to the need to educate patients on their proper administration, OSF technology was initially introduced to the public as breath-freshening strips. Consumer awareness of their overall concept, novelty, and use was therefore achieved through commercial marketing campaigns, ultimately minimizing the need for instruction when several OTC medications were eventually introduced in this form.[104,105,107]

There are several unique advantages to the OSF drug delivery systems that may improve their overall convenience and make them a natural evolution for the administration of all oral agents, including antiemetics.[104] The polymeric film coating is 50–150 microns, which facilitates rapid dissolution due to the large surface area exposed to wetting. Quick wetting of the OSF causes immediate adhesion to the tongue, preventing swallowing before dissolution. The films are flexible and can be bent or folded, improving their overall portability while avoiding product breakage—a disadvantage commonly associated with tablets and ODTs. This lack of friability, which can occur during the transportation or handling of the drug, allows the entire intended OSF dose to be taken by the patient. Individual printed packaging of OSF medications improves chemical and product stability, provides child resistance to opening the product, and may also limit dosing errors at healthcare institutions. Finally, OSF drugs can be consumed with or without water.[104,107,108]

The only notable issues currently associated with OSF are related to the processing of the medication. The product must

be uniformly distributed across the film-strip polymers, and taste masking is required (either by blocking taste receptors or by adding a flavor coating to the strip) due to the close contact of the medication dose with the tongue.[104,106,107]

Continued efforts have been made to improve antiemetic therapy with ondansetron through the use of an OSF delivery system. Recently, the FDA approved the ondansetron OSF film strip (Zuplenz) for the prevention of highly and moderately emetogenic CINV, RINV, and PONV. This approval was granted based on clinical study data comparing the bioequivalence of the OSF and ODT formulations for ondansetron. The pharmacokinetic results of these studies demonstrated that a single dose of the OSF film, taken with or without water and under fed and fasting conditions, was comparable to the ODT formulation.[109] Additional studies are under development for the ondansetron OSF strip to determine the safety and bioequivalence of the formulation in pediatric patients.[110]

Conclusion

Supportive care of nausea and vomiting following chemotherapy, radiation therapy, and surgery has markedly improved over the past 20 years. Despite this continued progress, however, several issues remain unaddressed. The results of the ANCHOR study demonstrate the underestimated scope of nausea and vomiting in these treatment settings and highlight the need to improve the overall diagnosis and management of CINV, RINV, and PONV. Delayed nausea and vomiting are both poorly defined phenomena and a difficult treatment challenge. Currently, corticosteroids remain the most effective option in this setting regardless of never having achieved FDA approval for antiemetic use in the United States. Continued research into the pathophysiology of delayed emesis, identification of additional risk factors for emesis, and the separation of nausea and vomiting into distinct categories may improve outcomes in these patients.

The evolving understanding of the causes and management of CINV, RINV, and PONV has resulted in the development of novel, more effective oral antiemetic agents, such as 5-HT_3RAs and NK_1RAs. In addition, the emergence of other novel agents and continued research into complementary nonpharmacologic options indicate that the list of effective antiemetic treatment options will most likely continue to expand. Finally, the development of novel oral drug delivery options, such as ODTs and the promising OSF formulation, should help improve the overall convenience of oral antiemetic use and enhance quality of life for patients who are prescribed these agents.

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The working group meeting was co-chaired by Richard Gralla, MD, and Brenda Nevidjon, RN, MSN, FAAN. Attendees included Rekha Chaudhary, MD; Rebecca Clark-Snow, RN; Diane Cope, PhD, ARNP; Sue Dibble, DNSc, RN; Bridget Fowler, PharmD; Cindy Hughes McNally, RN; Marcelle Kaplan, RN; Jiyeon Lee, PhD, RN; Philip Philip, MD, PhD; Jan Tipton, RN; Rita Wickham, PhD, RN; and Gail Wilkes, RN.

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References

PubMed ID in brackets

1. 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;17:20–28. [16314401]

2. Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. Anesthesiology 1992;77:162–184. [1609990]

3. Jantunen IT, Kataja VV, Muhonen TT. An overview of randomised studies comparing 5-HT_3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. Eur J Cancer 1997;33:66–74. [9071902]

4. 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;18:3409–3422. [11013282]

5. 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;23:2822–2830. [15837996]

6. Jordan K. Chemotherapy-induced nausea and vomiting: great achievements but room for improvement. Oncology 2007;21:1018–1019.

7. Clavel M, Soukop M, Greenstreet YL. Improved control of emesis and quality of life with ondansetron in breast cancer. Oncology 1993;50:180–185. [8459989]

8. Soukop M. Management of cyclophosphamide-induced emesis over repeat courses. Oncology 1996;53(suppl 1):39–45. [8692549]

9. Jenns K. Importance of nausea. Cancer Nurs 1994;17:488–493. [7820827]

10. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. Anesthesiology 1999;91:693–700. [10485781]

11. Radiation-induced emesis: a prospective observational multicenter Italian trial. The Italian Group for Antiemetic Research in Radiotherapy. Int J Radiat Oncol Biol Phys 1999;44:619–625. [10348292]

12. Roscoe JA, Morrow GR, Hickok JT, Stern RM. Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. J Pain Symptom Manage 2000;20:113–121. [10989249]

13. Geling O, Eichler HG. 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;23:1289–1294. [15718327]

14. Cancer Care Ontario Practice Guidelines Initiative: Use of 5-HT_3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. Practice Guideline Report #12-3 2000, 1/2003 update. www.cancercare.on.ca.

15. Grunberg SM, Deuson RR, Mavros P, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer 2004;100:2261–2268. [15139073]

16. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 2006;24:4472–4478. [16983116]

17. Feyer PCh, Maranzano E, Molassiotis A, et al. Radiotherapy-induced nausea and vomiting (RINV): antiemetic guidelines. Support Care

Cancer 2005;13:122–128. [15592688]

18. Carroll NV, Miederhoff P, Cox FM, Hirsch JD. Postoperative nausea and vomiting after discharge from outpatient surgery centers. Anesth Analg 1995;80:903–909. [7726432]

19. Apfel CC, Shi S, Kovac A, et al. Postdischarge nausea and vomiting: an under-recognized problem after ambulatory anesthesia. Anesth Analg 2009;108:S-1–S-332. Abstract S-8.

20. Aass N, Håtun DE, Thoresen M, Fossa SD. Prophylactic use of tropisetron or metoclopramide during adjuvant abdominal radiotherapy of seminoma stage I: a randomised, open trial in 23 patients. Radiother Oncol 1997;45:125–128. [9424001]

21. Ondansetron + dexamethasone vs metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. Italian Group for Antiemetic Research. Lancet 1992;340:96–99. [1352024]

22. Griffin AM, Butow PN, Coates AS, et al. On the receiving end V: patient perceptions on the side effects of cancer chemotherapy in 1993. Ann Oncol 1996;7:189–195. [8777177]

23. Love RR, Leventhal H, Easterling DV, Nerenz DR. Side effects and emotional distress during cancer chemotherapy. Cancer 1989;63:604–612. [2912536]

24. de Boer-Dennert M, de Wit R, Schmitz PI, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 1997;76:1055–1061. [9376266]

25. Cooper S, Georgiou V. The impact of cytotoxic chemotherapy—perspectives from patients, specialists and nurses. Eur J Cancer 1992;28A(suppl 1):S36–S38. [1627406]

26. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? the perspective of patients. Anesth Analg 1999;89:652–658. [10475299]

27. Osoba D, Zee B, Warr D, Latreille J, Kaizer L, Pater J. Effect of postchemotherapy nausea and vomiting on health-related quality of life. The Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. Support Care Cancer 1997;5:307–313. [9257427]

28. Rusthoven JJ, Osoba D, Butts CA, Yelle L, Findlay H, Grenville A. The impact of postchemotherapy nausea and vomiting on the quality of life after moderately emetogenic chemotherapy. Support Care Cancer 1998;6:389–395. [9695208]

29. Scuderi PE, Conlay LA. Postoperative nausea and vomiting and outcome. Int Anesthesiol Clin 2003;41:165–174. [14574220]

30. Gan TJ. Risk factors for postoperative nausea and vomiting. Anesth Analg 2006;102:1884–1898. [16717343]

31. Gold BS, Kitz DS, Lecky JH, Neuhaus JM. Unanticipated admission to the hospital following ambulatory surgery. JAMA 1989;262:3008–3010. [2810644]

32. Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth 2002;88:659–668. [12067003]

33. Carroll NV, Miederhoff PA, Cox FM, Hirsch JD. Costs incurred by outpatient surgical centers in managing postoperative nausea and vomiting. J Clin Anesth 1994;6:364–369. [7986507]

34. Rose JB, Watcha MF. Postoperative nausea and vomiting in paediatric patients. Br J Anaesth 1999;83:104–117. [10616338]

35. Hirsch J. Impact of postoperative nausea and vomiting in the surgical setting. Anaesthesia 1994;49(suppl):30–33. [8129160]

36. Franzén L, Nyman J, Hagberg H, et al. A randomised placebo controlled study with ondansetron in patients undergoing fractionated radiotherapy. Ann Oncol 1996;7:587–592. [8879372]

37. Levine AM, Richardson JL, Marks G, et al. Compliance with oral drug therapy in patients with hematologic malignancy. J Clin Oncol 1987;5:1469–1476. [3625261]

38. Coates A, Abraham S, Kaye SB, et al. On the receiving end—patient perception of the side-effects of cancer chemotherapy. Eur J Cancer Clin Oncol 1983;19:203–208. [6681766]

39. Richardson JL, Marks G, Levine A. The influence of symptoms of disease and side effects of treatment on compliance with cancer therapy. J Clin Oncol 1988;6:1746–1752. [3183704]

40. Maranzano E, Feyer PCh, Molassiotis A, et al; on behalf of Participants in the Perugia Consensus Conference 2004. Evidence-based recommendations for the use of antiemetics in radiotherapy. Radiother Oncol 2005;76:227–233. [16150504]

41. O'Brien BJ, Rusthoven J, Rocchi A, et al. Impact of chemotherapy-associated nausea and vomiting on patients' functional status and costs: survey of five Canadian centres. CMAJ 1993;149:296–302. [8339175]

42. Rusthoven JJ, Rocchi A, O'Brien B, et al. A survey of costs of chemotherapy-induced nausea and vomiting at five Canadian cancer centers. 1992 ASCO Annual Meeting;11:A1381.

43. Kris MG, Baltzer L, Pisters KM, Tyson LB. Enhancing the effectiveness of the specific serotonin antagonists: combination antiemetic therapy with dexamethasone. Cancer 1993;72(suppl 11):3436–3442. [8242576]

44. Chang RK, Guo X, Burnside BA, Couch RA. Fast-dissolving tablets. Pharmaceutical Technology 2000;24:52–58.

45. Charatan F. Time-release analgesic drug causes fatal overdoses in United States. West J Med 2001;175:82. [11483541]

46. Mitchell JF, Pawlicki KS. Oral solid dosage forms that should not be crushed: 1994 revision. Hosp Pharm 1994;27:666–668, 670–675. [10135147].

47. Quigley EM, Hasler WL, Parkman HP. AGA technical review on nausea and vomiting. Gastroenterology 2001;120:263–286. [11208736]

48. Wright D. Medication administration in nursing homes. Nurs Stand 2002;16:33–38. [12216309]

49. Carnaby-Mann G, Crary M. Pill swallowing by adults with dysphagia. Arch Otolaryngol Head Neck Surg 2005;131:970–975. [16301368]

50. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med 2008;358:2482–2494. [18525044]

51. Scorza K, Williams A, Phillips JD, Shaw J. Evaluation of nausea and vomiting. Am Fam Physician 2007;76:76–84. [17668843]

52. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed May 18, 2009.

53. Hasler WL, Chey WD. Nausea and vomiting. Gastroenterology 2003;125:1860–1867. [14724837]

54. Koivuranta M, Läärä E, Snåre L, Alahuhta S. A survey of postoperative nausea and vomiting. Anaesthesia 1997;52:443–449. [9165963]

55. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines: American Society of Clinical Oncology. J Clin Oncol 1999;17:2971–2994. [10561376]

56. Schwartzberg LS. Chemotherapy-induced nausea and vomiting: which antiemetic for which therapy? Oncology (Williston Park) 2007;21:946–953. [17715696]

57. National Comprehensive Cancer Network. NCCN Practice Guidelines in Oncology: Antiemesis. V.2.2010. http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf Accessed June 14, 2010.

58. Schwartzberg LS. Chemotherapy-induced nausea and vomiting: clinician and patient perspectives. J Support Oncol 2007;5(suppl 1):5–12. [17366928]

59. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. Support Care Cancer 2007;15:1023–1033. [17205281]

60. American Society of Clinical Oncology, Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006;24:2932–2947. [16717289]

61. National Cancer Institute. Nausea and Vomiting. http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/healthprofessional/allpages. Accessed May 21, 2010.

62. Navari RM. Pathogenesis-based treatment of chemotherapy-induced nausea and vomiting—two new agents. J Support Oncol 2003;1:89–103. [15352652]

63. Grunberg SM, Koeller JM. Palonosetron: a unique 5-HT_3 receptor antagonist for the prevention of chemotherapy-induced emesis. Expert Opin Pharmacother 2003;4:2297–2303. [14640928]

64. 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;14:1570–1577. [14504060]

65. 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;98:2473–2482. [14635083]

66. 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;17:1441–1449. [16766588]

67. 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;21:4112–4119. [14559886]

68. Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother 2005;39:77–85. [15562136]

69. 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: results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003;97:3090–3098. [12784346]

70. 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;17:1000–1006. [16524979]

71. Navari RM, Province PS. Emerging drugs for chemotherapy-induced emesis. Expert Opin Emerg Drugs 2006;11:137–151. [16503832]

72. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin$_1$ receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003;74:17–24. [12844131]

73. American Society of Anesthesiologists Task Force on Postanesthetic Care. Practice guidelines for postanesthetic care: a report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. Anesthesiology 2002;96:742–752. [11873052]

74. 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;430:341–349. [11711053]

75. Passik SD, Lundberg J, Kirsh KL, et al. A pilot exploration of the antiemetic therapy of olanzapine for the relief of nausea in patients with advanced cancer and pain. J Pain Symptom Manage 2002;23:526–532. [12067777]

76. Navari RM, Einhorn LH, Passik SD, et al. A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. Support Care Cancer 2005;13:529–534. [15700131]

77. Guttuso T Jr, Roscoe J, Griggs J. Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. Lancet 2003;361:1703–1705. [12767738]

78. Apfel CC, Kinjo S. Acustimulation of P6: an antiemetic alternative with no risk of drug-induced side-effects. Br J Anaesth 2009;102:585–587. [19359394]

79. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev 2009;Apr 15:CD003281. [19370583].

80. Pearl ML, Fischer M, McCauley DL, Valea FA, Chalas E. Transcutaneous electrical nerve stimulation as an adjunct for controlling chemotherapy-induced nausea and vomiting in gynecologic oncology patients. Cancer Nurs 1999;22:307–311. [10452208]

81. Van Fleet S. Relaxation and imagery for symptom management: improving patient assessment and individualizing treatment. Oncol Nurs Forum 2000;27:501–510. [10785903]

82. Ezzone S, Baker C, Rosselet R, Terepka E. Music as an adjunct to antiemetic therapy. Oncol Nurs Forum 1998;25:1551–1556. [9802051]

83. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. J Pain Symptom Manage 2004;28:244–249. [15336336]

84. Marchioro G, Azzarello G, Viviani F, et al. Hypnosis in the treatment of anticipatory nausea and vomiting in patients receiving cancer chemotherapy. Oncology 2000;59:100–104. [10971166]

85. Ernst E, Pittler MH. Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials. Br J Anaesth 2000;84:367–371. [10793599]

86. Tate S. Peppermint oil: a treatment for postoperative nausea. J Adv Nurs 1997;26:543–549. [9378876]

87. Pollera CF, Giannarelli D. Prognostic factors influencing cisplatin-induced emesis: definition and validation of a predictive logistic model. Cancer 1989;64:1117–1122. [2667749]

88. du Bois A, Meerpohl HG, Vach W, Kommoss FG, Fenzl E, Pfleiderer A. Course, patterns, and risk-factors for chemotherapy-induced emesis in cisplatin-pretreated patients: a study with ondansetron. Eur J Cancer 1992;28:450–457. [1534250]

89. Roscoe JA, Bushunow P, Morrow GR, et al. Patient expectation is a strong predictor of severe nausea after chemotherapy: a University of Rochester Community Clinical Oncology Program study of patients with breast carcinoma. Cancer 2004;101:2701–2708. [15517574]

90. Eaton L, Tipton J. Putting Evidence into Practice; Improving Oncology Patient Outcomes. Pittsburgh, PA: Oncology Nursing Society; 2009.

91. Bernstein IL. Taste aversion learning: a contemporary perspective. Nutrition 1999;15:229–234. [10198919]

92. Khan S, Kataria P, Nakhat P, Yeole P. Taste masking of ondansetron hydrochloride by polymer carrier system formulation of rapid-disintegrating tablets. AAPS PharmSciTech 2007;8:E1–E7. [17622121]

93. Sancuso (granisetron transdermal system) [package insert]. Bedminster, NJ: ProStrakan Inc; August 2008.

94. Berkowitz AC, Goddard DM. Novel drug delivery systems: future directions. J Neurosci Nurs 2009;41:115–120. [19361127]

95. First report on results of US phase 2 clinical study of intranasal granisetron [press release]. Shin Nippon Biochemical Laboratories, Ltd; August 3, 2009. http://www.trltd.co.jp/pdf/release090803_Eng.pdf. Accessed June 11, 2010.

96. Mahajan HS, Gattani SG. Nasal administration of ondansetron using a novel microspheres delivery system: Part II: ex vivo and in vivo studies. Pharm Dev Technol 2009 Dec 18 [Epub ahead of print].

97. Mahajan HS, Gattani SG. Nasal administration of ondansetron using a novel microspheres delivery system. Pharm Dev Technol 2009;14:226–232. [19519195]

98. Habib W, Khankari R, Hontz J. Fast-dissolve drug delivery systems. Crit Rev Ther Drug Carrier Syst 2000;17:61–72. [10755211]

99. Doijad RC, Manvi FV, Khalandar KS. A comparative study on mouth dissolving tablets of granisetron with different super disintegrants: formulation and evaluation. Internet J Pharmacol 2008;5.

100. Olver I, Shelukar S, Thompson KC. Nanomedicines in the treatment of emesis during chemotherapy: focus on aprepitant. Int J Nanomedicine 2007;2:13–18. [17722507]

101. Patel P, Acharya MA, Patel J. Nanoparticles in cancer research: a novel drug delivery and pharmacological approach. Drug Delivery Technol 2009;9:48–52.

102. Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: a review. Indian Drugs (Bombay) 2004;41:187–193.

103. Shu T, Suzuki H, Hironaka K, Ito K. Studies of rapidly disintegrating tablets in oral cavity using co-ground mixtures of mannitol with crospovidone. Chem Pharm Bull (Tokyo) 2002;50:193–198. [11848208]

104. Hariharan M, Bogue A. Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms. Drug Delivery Technol 2009;9:24–29.

105. Borsadia SD, O'Halloran D, Osborne JL. Quick-dissolving films—a novel approach to drug delivery. Drug Delivery Technol 2003;3:63–66.

106. Barnhardt SD, Sloboda MS. The future of dissolvable films. Drug Delivery Technol 2007;7:34–37.

107. Vondrak B, Barnhart S. Dissolvable films for flexible product format in drug delivery. Pharm Tech April 2008. http://pharmtech.findpharma.com/pharmtech/Drug+delivery+Article/Dissolvable-Films-Dissolvable-Films-for-Flexible-P/ArticleStandard/Article/detail/505380?ref=25. Accessed June 11, 2010.

108. Van Arnum P. Advancing ODT technology. Pharm Technol 2007;31:66.

109. FDA Approves Strativa Pharmaceuticals' Zuplenz® (ondansetron) Oral Soluble Film [press release]. Woodcliff Lake, NJ: Par Pharmaceutical Companies, Inc; July 2, 2010. http://investors.parpharm.com/phoenix.zhtml?c=81806&p=irol-newsArticle&ID=1444076&highlight=. Accessed July 8, 2010.

110. Data on file. Par Pharmaceutical.