Chemotherapy-induced Nausea and Vomiting—Where We Stand Now

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) has been a major supportive care concern since the development of cisplatin, which was probably the major factor that drove antiemetic research. If strategies, particularly using combination antiemetic therapy, had not been developed and studied, cancer chemotherapy research would also likely to have been stymied. The past 30 years or more have seen our understanding of the physiology of vomiting grow from the understanding of the medullary brain structures we call the chemoreceptor trigger zone and the vomiting center, as well as the neurotransmitters located about that site. The current view of chemotherapy-induced vomiting is that two main pathways are involved—a peripheral pathway from the gut to the vomiting center that is mediated by increased release of serotonin by enterochromaffin cells in the gastrointestinal tract mucosa that binds to vagal terminals terminating in the nucleus tractus solitarius, and a central pathway in the brain that involves substance P binding at neurokinin 1 receptors near the vomiting center. Development of antiemetics that target these specific receptors, plus the use of dexamethasone, has resulted in prevention of acute vomiting in 70–80 % of patients receiving highly emetogenic chemotherapy. The scientific evidence resulting from this antiemetic research, along with clinical application knowledge, forms the basis of current chemotherapy antiemetic guidelines. Although these are useful to clinical practice, they do no replace clinical assessment and follow up of individual patients. Furthermore, about half of patients receiving moderately or highly emetogenic chemotherapy experience distressing delayed nausea, which can alter a patient's life activities, cause debilitating physical consequences, and interfere with their ability and willingness to undergo chemotherapy.

Keywords

Nausea, vomiting, CINV, chemoreceptor trigger zone, vomiting center, serotonin, $5HT_3$ receptors, substance, NK_1 receptors, emetogenicity, antiemetic guidelines

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It has been almost 50 years since the first study of an antiemetic (prochlorperazine versus placebo) for chemotherapy-induced nausea and vomiting (CINV) was published.[1] However, we have not reached the point where CINV is never a problem for any patient receiving antineoplastic therapies. On the other hand, momentous discoveries during the intervening years have increased our understanding of the physiology of chemotherapy-related emesis, and have led to the corresponding development of receptor-targeted antiemetics, and resulted in evidence-based antiemetic guidelines from several professional oncology organizations in Europe and the US. Nausea and vomiting (N&V) are relatively common for patients with cancer and may occur from progressive disease, radiation therapy—especially when fields include the upper abdomen—and from MEC/HEC. CINV is this article's focus, but clinicians should remember other possible causes that may worsen CINV or radiation therapy-induced N&V (RINV), or increase the risk for N&V secondary to advanced disease.[2,3]

The Physiology of Vomiting

Emesis is an important, highly conserved reflex in vertebrates that protects against accidental ingestion of harmful substances. Borison's and Wang's sentinel works[4,5] were critical to understanding how it occurs. They identified the so-called vomiting center (VC), which is not an organ but a group of neurons near the nucleus tractus solitarius (NTS) of the vagus nerve in brainstem medulla, which may also influence nausea, taste, salivation, swallowing and gagging, and gut motility. The chemoreceptor trigger zone (CTZ), a circumventricular organ in the area postrema (AP), is near the VC. Together the CTZ, NTS, and VC make up the final common pathway for vomiting.[6]

Given the importance of emesis, it is not surprising that there are multiple peripheral and central sites that can transmit neural signals to the CTZ, NTS, and VC, and with direct or indirect contributions of several neurotransmitters and receptors.[7] In addition, emetic chemical stimuli in the bloodstream or the cerebral spinal fluid can reach the CTZ, which has a relatively permeable blood–brain barrier.[8] Numerous neurotransmitters (e.g. acetylcholine, dopamine, serotonin [5HT], histamine [H1], gamma-aminobutyric acid [GABA], and substance P [SP]) have been identified near and in the NTS and AP and may play some role in N&V.

Afferent neural inputs to the central nervous system (CNS) and the VC include the gastrointestinal (GI) tract—particularly via the vagus nerve and stretch receptors, the vestibular apparatus of the inner ear that plays a role

in motion sickness, and several sites in the brain including the limbic region that assigns emotion to distressing events, the cortex, and other receptor sites such as cannabinoid 1 (CB1) receptors. An emetic stimulus may induce N&V via more than one pathway and the nervous system is characterized by plasticity, so a second (or third) pathway may come into play if the 'message' to vomit is significant or blocked in another pathway.[8] The challenge in many cases is to identify the mechanisms involved to select antiemetic that target particular pathways, neurotransmitters, and receptors.[9]

We know less about the mechanisms of nausea, which is more difficult to study in humans or in animals and is more difficult to control than vomiting. The cortex recognizes the distressing manifestations of nausea, which probably involves some of the same brain structures as vomiting.[8] Toxins and other agents may act directly on the brain to cause nausea, and animal studies suggest a role for cannabinoid 1 (CB1) in the brain.[10] Other neural mechanisms may be involved, depending on the etiology. For example, gastric dysrhythmias are associated with functional dyspepsia and accompanied by nausea, which may differ from nausea with pregnancy or chemotherapy.[11] It is also difficult to explain nausea that persists for 1 to 2 weeks or more after autologous stem cell transplant.[12] Upper GI vagal afferents are likely involved as nausea is typically accompanied by decreased appetite and dietary intake, delayed gastric emptying, and perhaps vomiting with intense stimuli.

Chemotherapy-induced Nausea and Vomiting

The two main pathways for CINV are a peripheral pathway arising in the GI tract and involving 5HT release and binding to 5HT receptors (particularly $5HT_3$ receptors), and a central pathway comprising SP and neurokinin 1 (NK_1) receptors. Enterochromaffin cells (EC) are dispersed throughout the GI epithelium and store >85 % of body's 5HT, which has a major role in normal GI function. Large amounts of 5HT are constitutive in the GI tract, where it functions as a neurotransmitter and a local hormone to influence GI motility and secretion. EC release even more 5HT in response to emetogens, such as some chemotherapy drugs or radiation therapy to the upper abdomen, amplified stretch or tone, or to other stimuli.[13,14] 5HT crosses GI connective tissue to various 5HT receptors. Binding at $5HT_3$ receptors on the vagal afferents transmits information from the GI tract to the brain—particularly the NTS—and also slows GI motility; binding at 5HT4 receptors affects G I smooth muscle tone and increases peristalsis, thereby causing an indirect effect to decrease N&V.[15]

Cisplatin is the most widely studied emetogenic chemotherapy agent because it will cause severe N&V within a few hours of administration in virtually all patients not given prophylactic antiemetics. Human and animal studies have confirmed several emetogenic effects of cisplatin: it induces EC to release higher levels of 5HT shortly after administration, causes damage to the stomach and the gut wall, leads to ileal changes, and alters contractility.[16,17] Conversely, pretreatment with a $5HT_3$ receptor antagonist ($5HT_3$-RA) inhibits 5HT release and decreases intestinal mucosal changes.

SP, a tachykinin peptide, and NK_1 receptors are found in the CNS and in the gut, but emetogenic chemotherapy and other stimuli induce vomiting primarily by central SP binding at NK_1 receptors in the NTS and AP.[18] Receptor binding at vagal terminals in the gut may play a lesser role in N&V. The only commercially available NK_1 antagonist (aprepitant, fosaprepitant) penetrates brain tissues, where it is retained for ≥48 hours.[19] Early animal studies showed aprepitant prevented emesis from a wide variety of agents including cisplatin, cyclophosphamide, radiation, copper sulphate, ipecacuanha, and morphine—demonstrating the importance of the central pathway and the effectiveness of NK_1-RAs.[18]

Blocking one or both of these pathways by administering antagonist agents does not completely control CINV, so other peripheral and central mechanisms, neurotransmitters, and receptors likely have some role. Current thinking is that the most important mechanisms to control in CINV are 5HT and $5HT_3$ binding, SP and NK_1 binding, and dopamine binding at dopamine 2 (D2) receptors.[20] In addition, there is 'crosstalk' between $5HT_3$ and NK_1-receptor signaling pathways, so they may synergistic in controlling CINV.[21,22] And as with N&V from other causes, different neurotransmitters and receptors, such as corticosteroids, H1s, cannabinoids, other 5HT subtypes, acetylcholines, GABAminergics, or opioids acting in the brain or the gut may have lesser roles.

Defining Chemotherapy-induced Nausea and Vomiting

The phases or types of CINV were arbitrarily defined in early antiemetic studies of high-dose metoclopramide for cisplatin-based chemotherapy.[23] Patients were hospitalized so assessment of vomiting was easy. Emesis was most severe in the first 24 hours after administration, which was considered acute CINV, and the following 24 to 120 hours were defined as delayed CINV. Patients were not followed after 120 hours, but on day 5 about 40 % of patients still were experiencing nausea and about 20 % had some vomiting. Different emetogenic agents can cause different patterns of CINV, and it is not unusual for delayed nausea to persist for longer than 5 days. Breakthrough CINV usually occurs despite prophylactic prechemotherapy antiemetic administration when the patient has returned home, and anticipatory nausea (a conditioned response in which the events surrounding chemotherapy administration evoke the response) as well as refractory CINV occur with inadequate prevention of acute and delayed CINV.

Standard of Care Antiemetics for Chemotherapy-induced Nausea and Vomiting

An immense number of antiemetic studies for CINV have been reported in the past 40 years, as standard of care antiemetics moved from recommended doses of anti-dopaminergic drugs (i.e. phenothiazines, butyrophenones, and metoclopramide), to high-dose metoclopramide, to adding dexamethasone [dex]) to enhance antiemetic effect, and including diphenhydramine or lorazepam to decrease the incidence of extrapyramidal symptoms (EPS). Preventing EPS (drug-induced movement disorders) is most important with repeated dosing or high doses of agents that bind to D2 receptors. Manifestations can include acute akithisia, myoclonus, or acute dystonia (e.g. oromandibular, spasmodic torticollis, or laryngeal/respiratory).[24] EPS was more common when high doses of metoclopramide (2–3 mg/kg) were administered: these more effectively controlled CINV than 10 mg to 20 mg doses, but also were associated with sedation, headache, fatigue, and diarrhea.[25] These older antiemetics (except dex) are now reserved for delayed or breakthrough CINV, or are added to individualized regimens for patients with refractory N&V.

The current mantra is that 5HT release and binding at $5HT_3$ receptors in the GI tract is most important during acute CINV, whereas SP binding at NK_1 receptors in the CNS have greater involvement during delayed CINV.[26]

This is probably an overly simplistic notion, and multiple overlapping neurotransmitters including 5HT, SP, dopamine, and prostaglandins acting in the peripheral and central nervous systems are likely involved in acute and delayed CINV.[21]

$5HT_3$ Receptor Antagonists

The four first-generation $5HT_3$-RAs are ondansetron, dolasetron, granisetron, and tropisetron (not available in the US). The one second-generation $5HT_3$-RA, palonosetron, has the longest half-life and greatest binding affinity (pKi).[27,28] A meta-analysis of five studies that had 2,057 patients concluded palonosetron is superior to ondansetron, granisetron and dolasetron, but it does not control acute and delayed CINV in all instances.[29] Another meta-analysis included 44 randomized studies with >12,000 patients concluded that granisetron and ondansetron are equivalent for highly and moderately emetogenic chemotherapy (HEC and MEC), that granisetron 1 and 3 mg are equally effective, that high doses of ondansetron may be better than low doses for cisplatin-based chemotherapy, and that granisetron 3 mg and ondansetron 24–32 mg are equivalent.[30] These findings support the view that $5HT_3$-RAs are equally efficacious in equivalent doses; however, unique patient differences may influence antiemetic response to particular $5HT_3$-RAs (see *Table 1*). In particular, dolasetron, ondansetron, palonosetron, and tropisetron are metabolized by CYP2D6 and inheritance of particular cytochrome P450 polymorphisms may result in differences in metabolism (i.e. poor metabolizer, normal metabolizer, or ultrarapid metabolizer) and efficacy.[31,32] Furthermore, patients may not respond identically to a particular $5HT_3$-RA because they are not structurally and chemically identical or have differences in half-life, receptor affinity, dose-response curves, and gender differences in GI 5HT reuptake transporter (SERT).[33–35]

In addition to oral and intravenous (IV) formulations, granisetron is available for transdermal administration.[36,37] Transdermal drug patches must be applied about 24 hours before the desired effect, and lead to a steady rate of delivery over the time the patch remains intact (as opposed to peaks and valleys with intermittent oral or IV administration), and then gradually falls off after patch removal (because of a skin depot effect). The manufacturer (Prostrakan, Bridgewater, New Jersey) recommends leaving the patch on for a maximum of 7 days, which was performed in studies, but there is 34.3 mg of granisetron in the patch that administers about 3.1 mg/day (10 to 11 days of drug). In the clinical studies, patches were applied to patients' upper arms, but can be applied to other areas of high blood flow and where they will easily adhere. Some patients have skin reactions to the patches, which prevents transdermal granisetron use.

Neurokinin 1 Receptor Antagonist

Oral aprepitant (or IV fosaprepitant) is the only NK_1-RA approved for prevention of acute and delayed CINV from HEC and MEC. Aprepitant is not to be used alone, but given with a $5HT_3$-RA and dex before chemotherapy, which improves control of acute and delayed CINV—particularly in women.[38] The recommended effective doses are 125 mg on the day of chemotherapy and then 80 mg on days 2 and 3.[39] A recent randomized, double-blind study of patients (n=2,247) receiving cisplatin-based chemotherapy compared IV fosaprepitant 150 mg on day 1 only or 3 days of standard doses of aprepitant regimens with ondansetron plus dex.[40] Complete control, measured as no vomiting or retching and no rescue antiemetics, was no different in the one 1 versus 3 days of aprepitant groups (71.9 % versus 72.3 %, respectively), nor was control of nausea over 5 days (53 % and 50.9 %). This study also highlights the fact that despite standard of care antiemetics, about 30 % of patients had acute and delayed vomiting, and almost half experienced nausea. This, and other similar studies, typically do not query patients about their ratings of and satisfaction with antiemetic control.

Other Antiemetics

There are no randomized, prospective antiemetic studies of dex alone for CINV, but the benefit of dex was unmistakably supported in a meta-analysis of 32 randomized trials that included 5,457 patients: the probability of no acute or delayed vomiting was 25 % to 30 % better with added dex (or other steroid) versus a $5HT_3$ antagonist or other antiemetic alone.[41] The most-common dose for acute CINV was 20 mg (range 8 mg to 100 mg) and the mean dose for delayed CINV was 56 mg. Possible side effects of corticosteroids may include insomnia, agitation, and dyspepsia, as well as increased appetite and weight gain.[9]

There is limited research examining older antiemetics or other agents, particularly for delayed or breakthrough CINV. One relatively small study (n=232) examined the benefit of twice daily oral prochlorperazine (15 mg), ondansetron (8 mg), or dex 8 mg for 4 days after prophylactic oral ondansetron and dex on day 1.[42] About 80 % of all patients took their assigned antiemetic, but half had delayed CINV. Nausea was usually mild, and 25 % of patients vomited during the 4-day study period—no matter which antiemetic they took. In an observational study, 96 patients took oral prochlorperazine or a $5HT_3$-RA for breakthrough CINV after receiving standard of care antiemetics on day 1 to prevent acute CINV.[43] Twenty-eight percent needed to take an antiemetic to control breakthrough nausea and/or vomiting. Twenty-four of 27 patients took prochlorperazine and the other three patients similarly took a $5HT_3$-RA, both of which reduced nausea by 75 % without side effects.

Olanzapine and mirtazapine are atypical antipsychotic agents that are often used in supportive to increase appetite (and perhaps lead to weight gain), decrease nausea, and treat depression.[44–46] These agents have high binding affinity for several receptors involved in N&V including D2, 5HT ($5HT_3$ and others), H1, muscarinic cholinergic, and alpha1-adrenergic.[9]

Olanzapine is also being studied for its efficacy for CINV. One randomized study compared 'standard antiemetics' (an IV 5HT2-RA available in China plus dex 10 mg) to standard antiemetics plus oral olanzapine 10 mg on the day of chemotherapy in 229 patients receiving MEC/HEC.[47] The Hoosier Oncology Group has carried out several studies including olanzapine for CINV. The most recent was a phase III study comparing olanzapine to aprepitant, both in combination with palonosetron and dex.[48] Two hundred and forty-one chemotherapy-naïve patients who were to receive HEC—cisplatin ≥70 mg/m^2 or cyclophosphamide ≥500 mg/m^2 plus doxorubicin ≥50 mg/m^2—were evaluable after cycle one. Eligible patients were randomized to either olanzapine (10 mg by mouth [PO]), palonosetron (0.25 mg IV), and dex (20 mg IV) (OPD) prior to chemotherapy, plus olanzapine 10 mg PO days 2 through 4; or aprepitant (125 mg PO), palonosetron (0.25 mg IV), and dex (12 mg IV) (APD) prior to chemotherapy, plus aprepitant (80 mg/day PO on days 2 and 3, and dex (4 mg PO twice/day on days 2 through 4. There was no difference in complete control of acute emesis (no vomiting and no rescue antiemetics) or acute nausea in

the OPD (97 %, 87 %) or APD (87 %, 87 %) groups. Prevention of delayed emesis was similar in both groups: 77 % (OPD) versus 73 % (ADP), while control of delayed nausea was 69 % versus 38 %, respectively (p<0.01). There were no significant side effects with either regimen, and the OPD regimen offers clear economic advantage over the ADP regimen.

Risk Factors for Chemotherapy-Induced Nausea and Vomiting

The antineoplastic agents administered are the most significant risk factors for CINV. Dose, administration schedule, and route of administration may alter risk (see *Table 2*). Patient risk factors that may impact the severity of CINV are female gender, age younger than 50, and history of prior CINV.[9] Other risk factors may include little or no alcohol use, tumor burden, anxiety or expectation for CINV, dehydration, concomitant medications and medical conditions (e.g. hypercalcemia, uremia), or past hyperemesis of pregnancy or motion sickness.

Current Antiemetic Guidelines

The American Society for Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the Multinational Association for Supportive Cancer Care (MASCC)[49–51] have developed similar antiemetic guidelines, which can be downloaded from their corresponding websites. Guidelines are relatively similar regarding underlying management principles (see *Box*) and recommended antiemetics for acute and delayed CINV for HEC/MEC (see *Table 3*).[49–54]

Limitations of Antiemetic Guidelines

Antiemetic guidelines should be used to aid clinicians to select appropriate antiemetics, but prescribing standard of care antiemetics does not guarantee patients will not experience CINV—particularly on the days after chemotherapy. The ASCO guideline most clearly articulates how important it is for clinicians to make sure patients fill prescriptions for rescue antiemetic(s), as well as to assess patients for the presence and severity of both N&V throughout the chemotherapy cycle.[49] Physicians and nurses often underestimate the likelihood of acute and delayed chemotherapy-related vomiting and nausea, which may have dire physical consequences for patients and decrease their quality of life.[55]

Guidelines encourage clinicians to consider patient risk factors for CINV, but these are not incorporated into risk estimates. In addition, guidelines do not address recommendations for appropriate, second-line antiemetics if the first regimen was less than optimal for an individual patient. This is probably related to the lack of evidence because of how difficult it would be to do studies of second-line antiemetics with the uncontrollable effects of numerous intervening variables.

We should also remember that evidence-based guidelines are limited by studies that were not performed, cannot be performed, or might have had a different design. For instance, the fact that $5HT_3$-RAs are not recommended after HEC seems curious, given their recommended use after MEC. This is probably based on randomized studies in which patients who were receiving HEC received a $5HT_3$-RA alone or a $5HT_3$-RA plus dex for delayed CINV. The primary outcome variable in these studies was the incidence of delayed emesis only[56] so the finding of no statistically significant differences led to recommendations to use the least costly antiemetic. However, in some studies, the differences in control of emesis with two antiemetics as opposed to one was in the range of 10 %—a difference that might be clinically significant even if not statistically significant. And, of course, the major problem with this interpretation of the studies was that they did not consider the effect of delayed nausea that is more problematic—particularly if long lasting. Perhaps studies with a third arm in which patients receiving a $5HT_3$-RA and dex, and the control of delayed nausea may have more clearly demonstrated superiority and led to different conclusions and guideline recommendations.

Another matter related to costs is that new antiemetics are at least as effective and have fewer and more tolerable side effects than some older antiemetics. They are virtually never used for 'off label' indications such as palliative control of N&V in patients with advanced cancer because they are so expensive. Costs probably have limited research that would possibly support their use for many patients based on a logical application of the physiology of N&V and a few case studies. This is an important concern for healthcare payers—whether single payer system, health insurance company, or self-pay by patients that should be addressed.[57,58] The high cost of antiemetics may also limit institutional or practice formularies from stocking more than one $5HT_3$-RA or aprepitant—all

Table 1: Characteristics of $5HT_3$ Receptor Antagonists

Agent	Half-life	Cyp450 Metabolism	pKi*	Comments
Dolasetron	7.5 hours	Yes	7.6	
Granisetron	9 hours	No	8.9	
Ondansetron	4 hours	Yes	8.4	
Palonosetron	40 hours	Yes	10.5	
Tropisetron	6–8 hours	Yes	9	Absolute bioavailability is inversely related to CYP2D6 activity

**pKi = log scale for binding efficiency.*

Box: Principles of Chemotherapy-induced Nausea and Vomiting Management

Prevention of acute and delayed CINV is the goal
- The risk for delayed CINV is at least 3 days after HEC and 2 days after MEC
- Patients need antiemetic protection through the entire period of risk

Select antiemetics based on most emetogenic agent in chemotherapy regimen

Oral and intravenous $5HT_3$ antagonists are equally effective when used in appropriate doses

Antiemetic selection should be based on emetogenicity of chemotherapy, prior experiences with antiemetics, and patient factors

Consider the toxicity of specific antiemetic(s)

There are other factors for nausea and vomiting in cancer patients, consider:
- Partial or complete bowel obstruction
- Vestibular problems
- Brain metastases
- Electrolyte imbalance (hypercalcemia, hyponatremia)
- Hyperglycemia
- Uremia
- Concomitant drugs (e.g. opioids, digitalis toxicity)
- Gastroparesis (secondary to tumor, chemotherapy [vincristine], diabetes)
- Psychologic (anticipatory nausea, anxiety)

CINV = chemotherapy-induced nausea and vomiting; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy.

Table 2: Emetogenic Potential of Antineoplastic Agents without Prophylactic Antiemetics

Predicted Emetogenicity	Agents		
	Intravenous		Oral
High >90 %	AC regimen (doxorubicin or epirubicin + cyclophosphamide) Carmustine >250 mg/m^2 Cisplatin Cyclophosphamide >1,500 mg/m^2	Dacarbazine Doxorubicine >60 mg/m^2 Epirubicin >90 mg/m^2 Ifosfamide >2 G/m^2 Mechlorethamine Streptozocin	Hexamethylmelamine Procarbazine
Moderate 30–90 %	Aldesleukin >12–15 million IU/m^2 Alemtuzumab Amifostine >300 mg/m^2 Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide ≤1,500 mg/m^2 Cytarabine > 200 mg/m^2 Dactinomycin	Daunorubicin Doxorubicin ≤60 mg/m^2 Epirubicin ≤90 mg/m^2 Ifosfamide ≤2 G/m^2 Idarubicin Interferon alpha ≥10 million IU/m^2 Irinotecan Melphalan Methotrexate ≥250 mg/m^2 Oxaliplatin	Cyclophosphamide Imatinib Temozolomide Vinorelbine
Low 10 % to <30 %	Aldesleukin ≤12 million IU/m^2 Amifostine ≤300 mg/m^2 Bortezomib Cabazitaxel Catumaxomab Cetuximab Cytarabine 100–200 mg/m^2 Docetaxel Eribulin Etoposide Doxorubicin hydrochloride liposome injection 5-fluorouracil Floxuridine Gemcitabine Interferon alpha >5 <10 million IU/m^2	Ixabepilone Methotrexate>50 <250 mg/m^2 Mitomycin Mitoxantrone Paclitaxel Paclitaxel-albumin Panitumumab Pemetrexed Pentostatin Pralatrexate Romidepsin Temsirolimus Thiotepa Topotecan Trastuzumab	Capecitabine Everolimus Etoposide Fludarabine Lapatinib Lenalidomide Sunitinib Tegafur-uracil Thalidomide
Minimal <10 %	Alemtuzumab Asparaginase Bevacizumab Bleomycin Bortezomib Busulfan Cetuximab Cladribine Cytarabine <100 mg/m^2 Decitabine Denileukin difitox Dexrazoxane Fludarabine Interferon alpha <5 million IU/m^2	Ipilumumab Methotrexate <50 mg/m^2 Nelarabine Ofatumumab Panitumumab Pegasparase Peginterferon Retuximab Temsirolimus Trastuzumab Valrubicin Vinblastine Vincristine Vinorelbine	Chlorambucil Erlotinib Gefitinib Hydroxyurea L-Phenylalanine mustard Methotrexate Sorafenib 6-thioguanine

Source: Basch et al 2011; Grunberg et al. 2011; NCCN 2013; Roila et al. 2010.

topics worth discussing among institutions, oncologists or hematologists, oncology nurses and pharmacists, and patients.[49]

Conclusion

Using an evidence-based antiemetic guideline is highly recommended. Practice sites can review the current guidelines and then interpret them into practice or clinical site documents such as protocols or medical order templates for antiemetic prescription and assessment follow-up, particularly in outpatient settings where patients return home and are 'out of sight, out of mind' when they are at greatest risk for delayed vomiting and delayed nausea. A simple paper and pencil or computer-based tool could be used to assess patients at home for delayed symptoms might be completed once a day and ask about nausea severity, vomiting severity, antiemetics taken, and patient rating of control during the last 24 hours. The oncologist or oncology nurse could teach the patient (and a responsible family caregiver) that certain responses or cut-off scores means they must call their physician or nurse. Other points that are important are:

Table 3: Recommended Doses and Schedules of Standard of Care Antiemetics

Risk	Acute Chemotherapy-induced Nausea and Vomiting	Delayed Chemotherapy-induced Nausea and Vomiting
High >90 %	$5HT_3$ antagonist	Not recommended
	Palonosetron 0.25 mg IV (preferred) or	
	Ondansetron 16–24 mg PO or 8–24 mg (max 32 mg) IV or 0.15 mg/kg IV	
	Granisetron 2 mg PO once or 1 mg PO bid or	
	1 mg IV or 0.1 mg/kg IV or 34.3 mg transdermal patch (apply 24–48 hours before chemotherapy, maximum duration 7 days)	
	Tropisetron 5 mg PO OR	
	Dolasetron 100 mg PO or 100 mg IV	
	NK_1 antagonist	
	Aprepitant 125 mg PO or	Aprepitant 80 mg PO days 2 and 3 or
	Fosaprepitant 115 mg IV (plus days 2 and 3) or	Aprepitant 80 mg PO days 2 and 3 or
	Fosaprepitant 150 mg IV (day 1 only)	No aprepitant
	Corticosteroid	
	Dexamethasone 12 mg PO or IV	Dexamethasone 8 mg days 2, 3, 4
Moderate 30–90 %	$5HT_3$ antagonist (see doses in High Risk section)	
	Palonosetron (preferred) or	
	Ondansetron or	8 mg BID or 16 mg X 1 days 2 and 3
	Granisetron or Maintain transdermal patch for 7 days	2 mg PO x1 or 1 mg PO bid or
	Tropisetron or	
	Dolasetron or	100 mg, days 2 and 3
	Corticosteroid monotherapy	
	Dexamethasone 12 mg PO or IV	Dexamethasone 8 mg days 2, 3
Low 10% to <30 %	Dexamethasone 12 mg PO or IV or	Breakthrough CINV, add drug from another class:
	Metoclopramide 10–40 mg PO or IV; repeat every 4–6 hours PRN or	Benzodiazepine: lorazepam Cannabinoid: dronabinol or nabilone
	Prochlorperazine 10 mg PO or IV; repeat every 4–6 hours PRN	Dopamine antagonist: prochlorperazine, haloperidol, or metoclopramide
	± Lorazepam* 0.5–2 mg PO, IV, SL every 4–6 hours	Histamine blocker: promethazine or scopolamine
	± H_2 blocker or proton pump inhibitor*	
Minimal <10 %	No routine prophylaxis $5HT_3$-RA Steroid: dexamethasone	Other: olanzapine

**Not recommended by Multinational Association for Supportive Cancer Care. $5HT_3$ = ; Bid = twice a day; IV = intravenous; PO= oral; SL = sublingual; PRN = as needed. Source: Roila et al. 2010; NCCN 2013; Basch et al. 2011; Kris et al. 2011; Herrstedt et al. 2011.*

- Any materials developed or adapted must be clinically useful, brief, and easy to use.
- Ask patients about non-drug measures they have successfully used for past instances of N&V. These may add benefit to standard of care antiemetics for some patients.
- Many patients like to use complementary methods, which may increase their sense of control, and discuss methods that have evidence to support their use in some cases, such as acupressure or ginger.[59–61]
- Review the recommended use of alternate antiemetics for breakthrough or inadequately controlled CINV. When it comes to individual patients, the fact that a given antiemetic is effective for 70 % or 80 % of patients may not be clinically relevant. When reviewing a list of alternative drugs think about whether a drug has antiemetic efficacy in some instances and consider the benefits and burdens (e.g. decreased nausea with increased sleepiness).

And finally, remember that guidelines do not replace caring oncology professionals who know what current recommendations are as well as have some understanding of their rationale, and who develop and implement patient-centered antiemetic management plans. ■

1. Moertel CG, Reitemeier RJ, Gage RP, A controlled clinical evaluation of antiemetic drugs, *JAMA*, 1963;186:116–18.
2. 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;56:231–8.
3. Cohen L, de Moor CA, Eisenberg P, et al. Chemotherapy-induced nausea and vomiting—incidence and impact on patient quality of life at community oncology settings, *Support Care Cancer*, 2007;15:497–503.
4. Borison HL Wang SC, Functional localization of central coordinating mechanism for emesis in cat, *J Neurophysiol*, 1949;12:305–13.
5. Borison HL Wang SC, Physiology and pharmacology of vomiting, *Pharmacol Rev*, 1953;5:193-230.
6. Hesketh PJ, Chemotherapy-induced nausea and vomiting, *New Engl J Med*, 2008;358:2482–94.
7. Borison HL, Borison R, McCarthy LE, Phylogenic and neurologic aspects of the vomiting process, *J Clin Pharmacol*, 1981;21:23S–29S.
8. Sanger GJ, Andrews PLR, Treatment of nausea and vomiting: Gaps in our knowledge, *Auton Neurosci-Basic*, 2006;29:3–16.
9. Feyer P, Jordan K, Update and new trends in antiemetic

therapy: the continuing need for novel therapies, *Ann Oncol*, 2011;22:30–38.
10. Limebeer CL, Rock EM, Mechoulam R, et al., The anti-nausea effects of CB1 agonists are mediated by an action at the visceral insular cortex, *Br J Pharmacol*, 2012;167: 1126–36.
11. Levine ME, Sickness and satiety: physiological mechanisms underlying perceptions of nausea and stomach fullness, *Curr Gastroenterol Rep*, 2005;7:280–88.
12. DiBaise JK, Lyden E, Tarantolo SR, et al., A prospective study of gastric emptying and its relationship to the development of nausea, vomiting, and anorexia after autologous stem cell transplantation, *Am J Gastroenterol*, 2005;100:1571–7.
13. Blackshaw LA, Brookes SJH, Grundy D, et al., Sensory transmission in the gastrointestinal tract, *Neurogastroenterol Motil*, 2007;19(Suppl. 1):1–19.
14. Lesurtel M, Soll C, Graf R, et al., Role of serotonin in the hepato-gastroIntestinal tract: an old molecule for new perspectives, *Cell Mol Life Sci*, 2008;65:940–52.
15. Gerson MD, Review article: serotonin receptors and transporters—roles in normal and abnormal gastrointestinal motility. Aliment Pharmacol Ther, 2004;20(Suppl. 7):3–14.
16. Endo T, Hamaue N, Ihira E, et al., Effects of granisetron, a 5-HT3 receptor antagonist, on 5-hydroxytryptamine (5-HT) release from the isolated ileum in a delayed-emesis rat model, *Res Comm Mol Pathol Pharmacol*, 2002;111:55–68.
17. Sung EZH, Arasaradnam RP, Jarvie EM, et al., Effects of neo-adjuvant chemotherapy for oesophago-gastric cancer on neuro-muscular gastric function, *Mol Biol Rep*, 2012;39:9989–94.
18. Diemunsch P, Grelot L, Potential of substance P antagonists as antiemetics, *Drugs*, 2000;60:533–46.
19. Huskey S-RW, Dean BJ, Bakhtiar R, et al., Brain penetration of aprepitant, a substance p antagonist, in ferrets, *Drug Metab Dispos*, 2003;31:785–91.
20. Lohr L, Chemotherapy-induced nausea and vomiting, *Cancer J*, 2008;14:85–93.
21. Darmani NA, Chebolu S, Amos B, et al., Synergistic antiemetic interactions between serotonergic 5-HT3 and tachykininergic NK1-receptor antagonists in the least shrew (*Cryptotis parva*), *Pharmacol Biochem Behav*, 2011;99:573–9.
22. Rojas C, Li Y, Zhang J, et al., The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses *In vitro* and *In vivo*, *J Pharmacol Exp Ther*, 2010;335:362–8.
23. Kris MG, Gralla RJ, Clark RA, et al., Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin, *J Clin Oncol*, 1985;3:1379–84.
24. Chouinard G, New nomenclature for drug-induced movement disorder including tardive dyskinesia, *J Clin Psychiatry*, 2004;65(Suppl. 9):9–15.
25. De Mulder PHM, Seynaeve C, Vertnorken JB, et al., Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting, *Ann Intern Med*, 1990;113:834–40.
26. Hesketh PJ, Van Belle S, Aapro M, et al., Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists, *Eur J Cancer*, 2003;39:1074–80.
27. Wong EH, Clark R, Leung E, et al., The interaction of RS 25259-197, a potent and selective antagonist, with 5-HT3 receptors, *in vitro*, *Br J Pharmacol*, 1995;114:851–9.
28. Rubenstein EB, Palonosetron: A unique 5-HT3 receptor antagonist indicated for the prevention of acute and delayed chemotherapy-induced nausea and vomiting, *Clin Adv Hematol Oncol*, 2004;2: 284–9.
29. Botrel TEA, Clark OAC, Clark L, et al., Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis, *Support Care Cancer*, 2011;19:823–32.
30. 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;15:1023–33.
31. Kees F, Farber L, Bucher M, et al., Pharmacokinetics of therapeutic doses of tropisetron in healthy volunteers, *Br J Clin Pharmacol*, 2001;52:705–707
32. Bernard S, Neville KA, Nguyen AT, et al., Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: Clinical implications, *Oncologist*, 2006;11:126–35.
33. Gregory RE, Ettinger DS, 5-HT3 Receptor Antagonists for the Prevention of Chemotherapy-Induced Nausea and Vomiting. A Comparison of Their Pharmacology and Clinical Efficacy, *Drugs*, 1998;55:173–89.
34. de Wit R, Aapro M, Blower PR, et al., Is there a pharmacological basis for differences in 5-HT3-receptor antagonist efficacy in refractory patients? *Cancer Chemother Pharmacol*, 2005;56:231–8.
35. Tremblay P-B, Kaiser R, Sezer O, et al., Variations in the 5-Hydroxytryptamine type 3B receptor gene as predictors of the efficacy of antiemetic treatment in cancer patients, *J Clin Oncol*, 2003;21:2147–55.
36. Howell J, Smeets J, Drenth H-J, et al., Pharmacokinetics of a granisetron transdermal system for the treatment of chemotherapy induced nausea and vomiting, *J Oncol Pharm Practice*, 2009;15:223–31.
37. Keating GM, Duggan ST, Curran MP, Transdermal granisetron: A guide to its use in preventing nausea and vomiting induced by chemotherapy, *CNS Drugs*, 2012;26:787–90.
38. Hesketh PJ, Aapro M, Street JC, et al., Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy, *Support Care Cancer*, 2010;18:1171–7.
39. Chawla SP, Grunberg SM, Gralla RJ, et al., Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting, *Cancer*, 2003;97:2290–300.
40. Grunberg S, Chua D, Maru A, et al., Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE, *J Clin Oncol*, 2011;29:1495–1501.
41. Ioannidis JPA, Hesketh PJ, Lau J, Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: A meta-analysis of randomized evidence, *J Clin Oncol*, 2000;18:3409–22.
42. Lindley C, Goodin S, McCune J, et al., Prevention of delayed chemotherapy-induced nausea and vomiting after moderately high to highly emetogenic chemotherapy, *Am J Clin Oncol*, 2005;28:270–76.
43. Jones JM, Qin R, Bardia A, et al., Antiemetics for chemotherapy-induced nausea and vomiting occurring despite prophylactic antiemetic therapy, *J Palliat Med*, 2011;14:810–14.
44. Kim S-W, Shin I-S, Kim J-M, et al., Effectiveness of mirtazapine for nausea and insomnia in cancer patients with depression, *Psychiatry Clin Neurosci*, 2008;62:75–83.
45. Licup N, Baumrucker S, Olanzapine for nausea and vomiting, *Am J Hospice Palliat Med*, 2010;27:432–4.
46. Jackson WC, Tavernier L, Olanzapine for Intractable nausea in palliative care patients, *J Palliat Med*, 2003;6:251–5.
47. Tan L, Liu J, Liu X, et al., Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting, *J Exper Clin Cancer Res*, 2009;28:131 (open access).
48. Navari RM, Gray SE, Kerr AC, Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A randomized phase III trial, *J Support Oncol*, 2011;9:188–95.
49. Basch E, Prestrud AA, Hesketh PJ, et al., Antiemetics: American Society of Clinical Oncology clinical practice guideline update, *J Clin Oncol*, 2011;29:4189–98.
50. NCCN Clinical Practice Guidelines in Oncology. Antiemesis, Version 1.2013. National Comprehensive Cancer Network (nccn.org).
51. Roila F, Herrstedt J, Aapro M, et al., Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference, *Ann Oncol*, 2010;21(Suppl. 5):v232–v243.
52. Grunberg SM, Warr D, Gralla RJ, et al., Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—state of the art, *Support Care Cancer*, 2011;19(Suppl. 1):S43–S47.
53. Kris MG, Tonato M, Bria E, et al., Consensus recommendations for the prevention of vomiting and nausea following high-emetic-risk chemotherapy, *Support Care Cancer*, 2011;9(Suppl. 1):S25–S32.
54. Herrstedt J, Rapoport B, Warr D, et al., Acute emesis: moderately emetogenic chemotherapy, *Support Care Cancer*, 2011;19(Suppl. 1):S15–S23.
55. Grunberg SM, Deuson RR, Mavros P, et al., Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Perception versus reality, *Cancer*, 2004;100:2261–8.
56. Geling O Eichler H-G, Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications, *J Clin Oncol*, 2005;23:1289–94.
57. Burke TA, Wisniewski T, Ernst FR, Resource utilization and costs associated with chemotherapy-induced nausea and vomiting (CINV) following highly or moderately emetogenic chemotherapy administered in the US outpatient hospital setting, *Support Care Cancer*, 2011;19:131–40.
58. Haiderali A, Menditto L, Good M, et al., Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population, *Support Care Cancer*, 2011;19:843–51.
59. Konno R, Cochrane review summary for cancer nursing: acupuncture-point stimulation for chemotherapy-induced nausea or vomiting, *Cancer Nurs*, 2010;33:479–80.
60. Molassiotis A, Helin AM, Dabbour R, et al., The effects of P6 acupressure in the prophylaxis of chemotherapy-related nausea and vomiting in breast cancer patients, *Complement Ther Med*, 2007;15:3–12.
61. Zick SM, Ruffin MT, Lee J, et al., Phase II trial of encapsulated ginger as a treatment for chemotherapy-induced nausea and vomiting, *Support Care Cancer*, 2009;17:563–72.