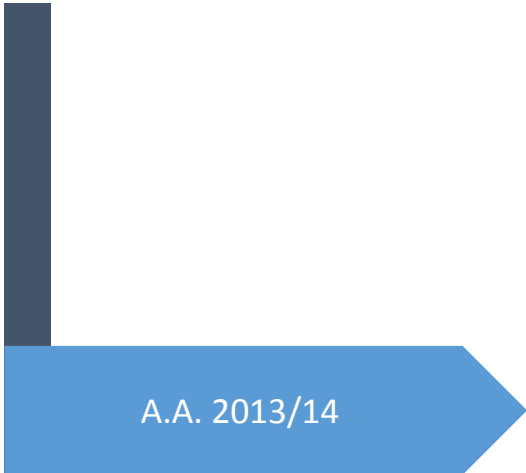
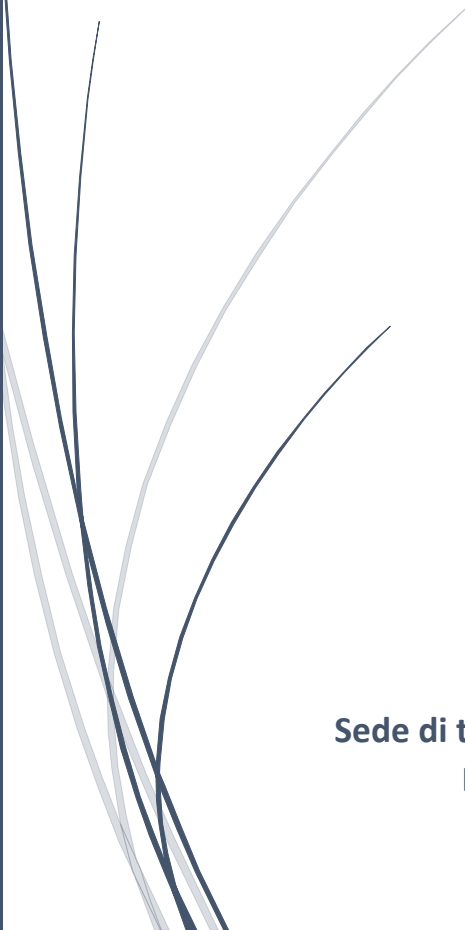


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A.A. 2013/14

# NAUSEA E VOMITO DA CHEMIOTERAPIA

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Indelicato Valentina

Corso di Laurea in Infermieristica

**Sede di tirocinio: A.O. CITTA' DELLA SALUTE E DELLA SCIENZA  
Presidio Molinette - Reparto di Ematologia 1**

## Introduzione

Durante il tirocinio in Ematologia mi è capitato quasi ogni giorno di dover fronteggiare episodi di nausea ed emesi in pazienti in trattamento chemioterapico. Ho deciso di approfondire l'argomento e cercare un articolo che fosse il più possibile completo sia sulle cause, sia sul trattamento (farmacologico e non). L'articolo che ho scelto tratta ampiamente il discorso della terapia farmacologica: nonostante non sia compito dell'Infermiere prescrivere i farmaci, è importante che sappia quali sono le dosi massime somministrabili, le interazioni con altre sostanze e gli effetti collaterali/indesiderati.

L'insorgenza di nausea e vomito indotti da farmaci antitumorali può essere influenzata da molte caratteristiche soggettive del paziente e dal trattamento scelto per la cura della neoplasia. Ciò che accomuna i pazienti con nausea e vomito è l'impatto che questi ultimi hanno sulla qualità della vita. Un trattamento antiemetico inadeguato può influenzare sensibilmente i pazienti e il loro modo di affrontare le sedute successive, aumentando il rischio di mancata compliance e portando i pazienti a interrompere la terapia. Inoltre, possono causare anoressia e disidratazione con un conseguente calo delle riserve nutritive e dei sali minerali.

Nonostante i significativi progressi che si sono avuti in ambito oncologico, il vomito e in particolare la nausea rimangono i due effetti avversi più frequenti. E' utile conoscere anche i comportamenti volti a prevenire o ridurre queste reazioni, per educare il paziente coadiuvando il trattamento farmacologico, per esempio:

- evitare cibi grassi, dolci o speziati
- preferire cibi secchi
- praticare con regolarità esercizi di respirazione
- fare pasti piccoli e frequenti a base di cibi facilmente digeribili

Sul sito dell'NCBI (National Center for Biotechnology Information), digitando le parole "nausea and vomiting" nella sezione "Bookshelf", ho trovato questo documento che offre una panoramica su tutto ciò che concerne la nausea e il vomito indotti dalla chemioterapia (e un cenno alla radioterapia). Nella stessa sezione è inoltre disponibile la versione dedicata ai pazienti, che potrebbe essere tradotta e usata per creare un libretto da consegnare a chi si sottopone a questa terapia per la prima volta.

# Nausea and Vomiting (PDQ®)

## Health Professional Version

Last Update: October 21, 2013.

## Overview

Prevention and control of nausea and vomiting (emesis) (N&V) are paramount in the treatment of cancer patients. N&V can result in the following:

- Serious metabolic derangements.
- Nutritional depletion and anorexia.
- Deterioration of patients' physical and mental status.
- Esophageal tears.
- Fractures.
- Wound dehiscence.
- Withdrawal from potentially useful and curative antineoplastic treatment.
- Degeneration of self-care and functional ability.

(See [Table 1](#) for criteria on grading severity.)

Despite advances in pharmacologic and nonpharmacologic management, N&V remain two of the more distressing and feared side effects to cancer patients and their families, and incidence may be underestimated by physicians and nurses.[\[1-5\]](#)

In this summary, unless otherwise stated, evidence and practice issues as they relate to adults are discussed. The evidence and application to practice related to children may differ significantly from information related to adults. When specific information about the care of children is available, it is summarized under its own heading.

## Introduction

Nausea is a subjective phenomenon of an unpleasant, wavelike sensation experienced in the back of the throat and/or the epigastrium that may culminate in vomiting (emesis). Vomiting is the forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral cavity. Retching is gastric and esophageal movements of vomiting without expulsion of vomitus and is also referred to as dry heaves.

## Classifications

Various classifications of N&V have been used,[\[1,6\]](#) including acute, delayed, late or persistent, chronic, anticipatory, breakthrough, or refractory, as well as distinctions related to type of treatment (e.g., chemotherapy induced or radiation induced) and clinical course of disease (e.g., advanced or terminal disease).[\[7,8\]](#) Despite this variety, the most commonly described types of N&V are acute, delayed, and anticipatory chemotherapy-induced N&V and chronic N&V in advanced cancer patients. Although there are no standard definitions, the following are commonly used to classify the different types.

- **Acute N&V:** N&V experienced during the first 24-hour period after chemotherapy administration is considered acute N&V.[\[1\]](#)
- **Delayed (or late) N&V:** N&V that occurs more than 24 hours after chemotherapy administration is considered delayed, or late, N&V. Delayed N&V is associated with cisplatin, cyclophosphamide, and other drugs (e.g., doxorubicin and ifosfamide) given at high doses or on 2 or more consecutive days.

- **Anticipatory nausea and vomiting (ANV):** ANV is nausea and/or vomiting that occurs prior to the beginning of a new cycle of chemotherapy in response to conditioned stimuli such as the smells, sights, and sounds of the treatment room. ANV is a classically conditioned response that typically occurs after three or four prior chemotherapy treatments, following which the person experienced acute or delayed N&V.
- **Chronic N&V in advanced cancer patients:** Chronic N&V in the advanced cancer patient is N&V associated with a variety of potential etiologies. A definitive understanding of cause is neither well known nor well researched, but potential causal factors include gastrointestinal, cranial, metabolic, drug-induced (e.g., morphine), cytotoxic chemotherapy, and radiation-induced mechanisms.[9]

**Table 1. National Cancer Institute's Common Terminology Criteria for Adverse Events: N&V<sup>a</sup>**

| Adverse Event         | Grade | Description                                                                               |
|-----------------------|-------|-------------------------------------------------------------------------------------------|
| Nausea <sup>b</sup>   | 1     | Loss of appetite without alteration in eating habits                                      |
|                       | 2     | Oral intake decreased without significant weight loss, dehydration, or malnutrition       |
|                       | 3     | Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated  |
|                       | 4     | Grade not available                                                                       |
|                       | 5     | Grade not available                                                                       |
| Vomiting <sup>c</sup> | 1     | 1–2 episodes (separated by 5 min) in 24 h                                                 |
|                       | 2     | 3–5 episodes (separated by 5 min) in 24 h                                                 |
|                       | 3     | ≥6 episodes (separated by 5 min) in 24 h; tube feeding, TPN, or hospitalization indicated |
|                       | 4     | Life-threatening consequences; urgent intervention indicated                              |
|                       | 5     | Death                                                                                     |

N&V = nausea and vomiting (emesis); TPN = total parenteral nutrition.

<sup>a</sup>Adapted from National Cancer Institute.[10]

<sup>b</sup>Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.

<sup>c</sup>Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.

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## Neurophysiology

Progress has been made in understanding the neurophysiologic mechanisms that control nausea and vomiting (emesis) (N&V). Both are controlled or mediated by the central nervous system but by different mechanisms. Nausea is mediated through the autonomic nervous system. Vomiting results from the stimulation of a complex reflex that is coordinated by a putative true vomiting center, which may be located in the dorsolateral reticular formation near the medullary respiratory centers. The vomiting center presumably receives convergent afferent stimulation from several central neurologic pathways, including the following:[1,2]

- A chemoreceptor trigger zone (CTZ).
- The cerebral cortex and the limbic system in response to sensory stimulation (particularly smell and taste), psychologic distress, and pain.
- The vestibular-labyrinthine apparatus of the inner ear in response to body motion.
- Peripheral stimuli from visceral organs and vasculature (via vagal and spinal sympathetic nerves) as a result of exogenous chemicals and endogenous substances that accumulate during inflammation, ischemia, and irritation.

The CTZ is located in the area postrema, one of the circumventricular regions of the brain on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle. Unlike vasculature within the blood-brain diffusion barrier, the area postrema is highly vascularized with fenestrated blood vessels, which lack tight junctions (*zonae occludentes*) between capillary endothelial cells. The CTZ is anatomically specialized to readily sample elements present in the circulating blood and cerebrospinal fluid (CSF).[3,4]

Currently, evidence indicates that acute emesis following chemotherapy is initiated by the release of neurotransmitters from cells that are susceptible to the presence of toxic substances in the blood or CSF. Area postrema cells in the CTZ and enterochromaffin cells within the intestinal mucosa are implicated in initiating and propagating afferent stimuli that ultimately converge on central structures corresponding to a vomiting center. The relative contribution from these multiple pathways culminating in N&V symptoms is complex and is postulated to account for the variable emetogenicity (intrinsic emetogenicity and mitigating factors [i.e., dosage, administration route, and exposure duration]) and emetogenic profile (i.e., time to onset, symptom severity, and duration) of agents.

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## General Risk Factors and Etiologies

Not all cancer patients will experience nausea, vomiting (emesis), or both. The most common causes are emetogenic chemotherapy drugs and radiation therapy to the gastrointestinal (GI) tract, liver, or brain. Several patient characteristics have also been identified. These include the following:

- Incidence and severity of nausea and vomiting (N&V) during past courses of chemotherapy. Patients with poor control of N&V during prior chemotherapy cycles are likely to experience N&V in subsequent cycles.
- History of chronic alcohol use. N&V is less likely in patients with a history of chronic high intake of alcohol.[1]
- Age. N&V is more likely in patients younger than 50 years old.[2]
- Gender. N&V and more likely in women.[2,3]

Other possible causes include the following:

- Fluid and electrolyte imbalances such as hypercalcemia, volume depletion, or water intoxication.
- Tumor invasion or growth in the GI tract, liver, or central nervous system, especially the posterior fossa.
- Constipation.
- Certain drugs such as opioids.
- Infection or septicemia.
- Uremia.

The psychological variables of state anxiety (level of anxiety during chemotherapy infusions) and pretreatment expectations for N&V (self-fulfilling prophecy) have also been investigated as predictors of posttreatment nausea.[4-9] Studies have found mixed results that vary because of different research methods. However, better designed studies have found state anxiety and patient expectations for nausea to be predictors of posttreatment nausea, even after controlling for known physiological predictors (susceptibility to nausea during pregnancy and motion sickness) and emetogenic potential of the chemotherapy drugs.[6-8,10,11] It is important to note that patients' fears and expectations about chemotherapy can be variable and change over time.[12] In a longitudinal study,[12] patients' anticipatory fears of vomiting decreased significantly from pretreatment to a period 3 to 6 months later, particularly when their chemotherapy included antiemetic medications.

Clinicians treating N&V must be alert to all potential causes and factors, especially in cancer patients who may be receiving combinations of several treatments and medications. (Refer to the PDQ summary on [Pain](#) for more information on opioid-induced N&V.)

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## Anticipatory Nausea and Vomiting (Emesis)

### Prevalence

The prevalence of anticipatory nausea and vomiting (emesis) (ANV) has varied, owing to changing definitions and assessment methods.[1] However, anticipatory nausea appears to occur in approximately 29% of patients receiving chemotherapy (about one of three patients), while anticipatory vomiting appears to occur in 11% of patients (about one of ten patients).[2] With the introduction of new pharmacologic agents (5-hydroxytryptamine-3 or 5-HT<sub>3</sub> receptor antagonists), it was anticipated that the prevalence of ANV might decline; however, studies have shown mixed results. One study found a lower incidence of ANV,[3] and three studies found comparable incidence rates.[2,4,5] It appears that the 5-HT<sub>3</sub> agents reduce postchemotherapy vomiting but not postchemotherapy nausea,[2,5] and the resulting impact on ANV is unclear.

### Classical Conditioning

Although other theoretical mechanisms have been proposed,[6] ANV appears to be best explained by classical conditioning (also known as Pavlovian or respondent conditioning).[7] In classical conditioning, a previously neutral stimulus (e.g., smells of the chemotherapy environment) elicits a conditioned response (e.g., ANV) after a number of prior pairings or learning trials. In cancer chemotherapy, the first few chemotherapy infusions are the learning trials. The chemotherapy drugs are the unconditioned stimuli that elicit postchemotherapy nausea and vomiting (N&V) (in some patients). The drugs are paired with a variety of other neutral, environmental stimuli (e.g., smells of the setting, oncology nurse, chemotherapy room). These previously neutral stimuli then become conditioned stimuli and elicit ANV in future chemotherapy cycles. ANV is not an indication of psychopathology but is rather a learned response that, in other life situations (e.g., food poisoning), results in adaptive avoidance.

A variety of correlational studies provide empirical support for classical conditioning. For example, the prevalence of ANV prior to any chemotherapy is very rare, and few patients ever experience ANV without prior postchemotherapy nausea.[8] Also, most studies have found (1) a higher probability of ANV with increasing numbers of chemotherapy infusions, and (2) the intensity of ANV increasing as patients get closer to the actual time of their infusion.[9] In one experimental study, it was shown that a novel beverage could become a conditioned stimulus to nausea when paired with several chemotherapy treatments.[10]

### Variables Correlated with ANV

Many variables have been investigated as potential factors that correlate with the incidence of ANV in hopes of developing a list of risk factors. There is currently no agreement on which factors predict ANV. A patient with fewer than three of the first eight characteristics listed below, however, is unlikely to develop ANV, and screening following the first chemotherapy infusion could identify those patients at increased risk.[11]

### Variables Found to Correlate With ANV

1. Age younger than 50 years.
2. N&V after last chemotherapy session.
3. Posttreatment nausea described as moderate, severe, or intolerable.
4. Posttreatment vomiting described as moderate, severe, or intolerable.
5. Feeling warm or hot all over after last chemotherapy session.
6. Susceptibility to motion sickness.
7. Sweating after last chemotherapy session.
8. Generalized weakness after last chemotherapy session.
9. Female gender.
10. High-state anxiety (anxiety reactive to specific situations).[\[12,13\]](#)
11. Greater reactivity of the autonomic nervous system and slower reaction time.[\[14\]](#)
12. Patient expectations of chemotherapy-related nausea before beginning treatment.[\[15,16\]](#)
13. Percentage of infusions of chemotherapy followed by nausea.[\[17\]](#)
14. Postchemotherapy dizziness.
15. Lightheadedness.
16. Longer latency of onset of posttreatment N&V.[\[18\]](#)
17. Emetogenic potential of various chemotherapeutic agents. Patients receiving drugs with a moderate to severe potential for posttreatment N&V are more likely to develop ANV.[\[12\]](#)
18. Morning sickness during pregnancy.

### Treatment of ANV

Antiemetic drugs do not seem to control ANV once it has developed;[\[2\]](#) however, a variety of behavioral interventions have been investigated.[\[19\]](#) These include the following:

- Progressive muscle relaxation with guided imagery.[\[20\]](#)
- Hypnosis.[\[21\]](#)
- Systematic desensitization.[\[22\]](#)
- Electromyography and thermal biofeedback.[\[23\]](#)
- Distraction via the use of video games.[\[24,25\]](#)

Progressive muscle relaxation with guided imagery, hypnosis, and systematic desensitization has been studied the most and is the recommended treatment. Referral to a psychologist or other mental health professional with specific training and experience in working with cancer patients is recommended when ANV is identified. The earlier ANV is identified, the more likely treatment will be effective; thus, early screening and referral are essential. However, physicians and nurses underestimate the incidence of chemotherapy-induced nausea and vomiting.[\[26\]](#)[Level of evidence: II]

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## Acute/Delayed Nausea and Vomiting (Emesis) Etiology

### Acute Nausea and Vomiting (N&V)

- Incidence:

-

The incidence of acute and delayed N&V was investigated in highly and moderately emetogenic chemotherapy treatment regimens. Patients were recruited from 14 oncology practices in six countries. Overall, more than 35% of patients experienced acute nausea, and 13% experienced acute emesis. In patients receiving highly emetogenic chemotherapy, 60% experienced delayed nausea, and 50% experienced delayed emesis. In patients receiving moderately emetogenic chemotherapy, 52% experienced delayed nausea, and 28% experienced delayed emesis.[1] Chemotherapy-induced nausea and vomiting (CINV) was a substantial problem for patients receiving moderately emetogenic chemotherapy in ten community oncology clinics.[2] Thirty-six percent of patients developed acute CINV, and 59% developed delayed CINV.

- Etiologies:

-

Chemotherapy is the most common treatment-related cause of N&V. The incidence and severity of acute emesis in persons receiving chemotherapy varies according to many factors, including the particular drug, dose, schedule of administration, route, and individual patient variables. In most cancer patients, these symptoms can be prevented or controlled.

- Risk factors for acute emesis include:[3]

-

Poor control with prior chemotherapy.

-

Female gender.

-

Younger age.

- Emetic classifications: The American Society of Clinical Oncology has developed a rating system for chemotherapeutic agents and their respective risk of acute and delayed emesis.[3]

-

High risk: Emesis that has been documented to occur in more than 90% of patients:

- Cisplatin (Platinol).
- Mechlorethamine (Mustargen).
- Streptozotocin (Zanosar).
- Cyclophosphamide (Cytosan), 1,500 mg/m<sup>2</sup> or more.
- Carbustine (BiCNU).
- Dacarbazine (DTIC-Dome).
- Dactinomycin.

-

Moderate risk: Emesis that has been documented to occur in 30% to 90% of patients:

- Carboplatin (Paraplatin).
- Cyclophosphamide (Cytosan), less than 1,500 mg/m<sup>2</sup>.
- Daunorubicin (DaunoXome).
- Doxorubicin (Adriamycin).
- Epirubicin (Pharmorubicin).
- Idarubicin (Idamycin).
- Oxaliplatin (Eloxatin).
- Cytarabine (Cytosar), more than 1 g/m<sup>2</sup>.
- Ifosfamide (Ifex).
- Irinotecan (Camptosar).

-

Low risk: Emesis that has been documented to occur in 10% to 30% of patients:

- Mitoxantrone (Novantrone).
- Paclitaxel (Taxol).
- Docetaxel (Taxotere).
- Mitomycin (Mutamycin).
- Topotecan (Hycamtin).
- Gemcitabine (Gemzar).
- Etoposide (Vepesid).
- Pemetrexed (Alimta).
- Methotrexate (Rheumatrex).
- Cytarabine (Cytosar), less than 1,000 mg/m<sup>2</sup>.
- Fluorouracil (Efudex).
- Bortezomib (Velcade).
- Cetuximab (Erbix).
- Trastuzumab (Herceptin).

-

Minimal risk: Emesis that has been documented to occur in fewer than 10% of patients:

- Vinorelbine (Navelbine).
- Bevacizumab (Avastin).
- Rituximab (Rituxan).
- Bleomycin (Blenoxane).
- Vinblastine (Velban).
- Vincristine (Oncovin).
- Busulphan (Myleran).

- Fludarabine (Fludara).
- 2-Chlorodeoxyadenosine (Leustatin).

In addition to emetogenic potential, the dose and schedule used are also extremely important factors. For example, a drug with a low emetogenic potential given in high doses may cause a dramatic increase in the potential to induce N&V. Standard doses of cytarabine rarely produce N&V, but these are often seen with high doses of this drug. Another factor to consider is the use of drug combinations. Because most patients receive combination chemotherapy, the emetogenic potential of all of the drugs combined and individual drug doses needs to be considered.

## Delayed N&V

Delayed (or late) N&V occurs more than 24 hours after chemotherapy administration. Delayed N&V is associated with cisplatin, cyclophosphamide, and other drugs (e.g., doxorubicin and ifosfamide) given at high doses or given on 2 or more consecutive days.

- Etiologies:
  - Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis.
- Risk factors:
  - All predictive characteristics for acute emesis are considered risk factors for delayed emesis.
- Emetic classifications:
  - Refer to the Acute Nausea and Vomiting (Emesis) (N&V) section of this summary for more information.

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## Prevention of Acute/Delayed Nausea and Vomiting (Emesis)

Antiemetic agents are the most common intervention in the management of treatment-related nausea and vomiting (N&V). The basis for antiemetic therapy is the neurochemical control of vomiting. Although the exact mechanism is not well understood, peripheral neuroreceptors and the chemoreceptor trigger zone (CTZ) are known to contain receptors for serotonin, histamine (H1 and H2), dopamine, acetylcholine, opioids, and numerous other endogenous neurotransmitters.[1,2] Many antiemetics act by competitively blocking receptors for these substances, thereby inhibiting stimulation of peripheral nerves at the CTZ and possibly at the vomiting center. Most drugs with proven antiemetic activity can be categorized into one of the following groups:

- Competitive antagonists at dopaminergic (D2 subtype) receptors:
  - Phenothiazines.

-  
Substituted benzamides.

-  
Butyrophenones.

- Competitive antagonists at serotonergic (5-hydroxytryptamine-3 or 5-HT<sub>3</sub> subtype) receptors.
- Substance P antagonists (NK-1 receptor antagonists).
- Corticosteroids.
- Cannabinoids.
- Benzodiazepines.
- Olanzapine.

Although all routes of administration are listed for each of the following drugs, the intramuscular (IM) route is used only when no other access is available. IM delivery is painful, is associated with erratic absorption of drug, and may lead to sterile abscess formation or fibrosis of the tissues. This is particularly important when more than one or two doses of a drug are to be given.

## Phenothiazines

Phenothiazines act on dopaminergic receptors at the CTZ, possibly at other central nervous system (CNS) centers, and peripherally. With the exception of thioridazine, many phenothiazines possess antiemetic activity, including chlorpromazine given in the 10- to 50-mg dose range orally, IM, intravenously (IV), and rectally (pediatric dose for patients >12 years: 10 mg every 6–8 hours; for patients <12 years: 5 mg every 6–8 hours); thiethylperazine given in the 5- to 10-mg dose range orally, IM, and IV; and perphenazine. The primary consideration in selecting phenothiazines are differences in their adverse effect profiles, which substantially correlate with their structural classes. Generally, aliphatic phenothiazines (e.g., chlorpromazine, methotrimeprazine) produce sedation and anticholinergic effects, while piperazines (e.g., prochlorperazine, thiethylperazine, perphenazine, fluphenazine) are associated with less sedation but greater incidence of extrapyramidal reactions (EPRs).

## Prochlorperazine

Prochlorperazine is perhaps the most frequently (and empirically) used antiemetic and, in low doses, is generally effective in preventing nausea associated with radiation therapy and in treating N&V attributed to very low to moderately emetogenic chemotherapeutic drugs. Prochlorperazine is a phenothiazine and can be given orally, IM, IV, and rectally. It is usually given in the 10- to 50-mg dose range (pediatric dose for children who weigh >10 kg or who are >2 years: orally or rectally, 0.4 mg/kg/dose tid–qid; or IM, 0.1–0.15 mg/kg/dose tid–qid, maximum 40 mg/d). Higher prochlorperazine doses (e.g., 0.2–0.6 mg/kg/dose) are also given IV for patients receiving chemotherapy with high emetogenic potential.[3];[4][Level of evidence: I] Phenothiazines may be of particular value in treating patients who experience delayed N&V (postacute phase symptoms) on cisplatin regimens.[5][Level of evidence: I]

As with other dopaminergic antagonists, the most common side effects of prochlorperazine are EPRs (acute dystonias, akathisias, neuroleptic malignant syndrome [uncommon], and rarely, akinesias and dyskinesias) and sedation. Marked hypotension may also result if IV prochlorperazine is administered rapidly at high doses. Administration over at least 30 minutes appears adequate to prevent hypotensive episodes.[6–8]

## Butyrophenones

### Droperidol and haloperidol

Droperidol and haloperidol represent another class of dopaminergic (D2 subtype) receptor antagonists that are structurally and pharmacologically similar to the phenothiazines. While droperidol is used primarily as an

adjunct to anesthesia induction, haloperidol is indicated as a neuroleptic antipsychotic drug; however, both agents have some antiemetic activity. Droperidol is administered IM or IV, typically from 1 to 2.5 mg every 2 to 6 hours, but higher doses (up to 10 mg) have been safely given.[9,10] Haloperidol is administered IM, IV, or orally, typically from 1 to 4 mg every 2 to 6 hours.[11] Results of a small, uncontrolled, open-label study showed some efficacy for haloperidol in palliative care patients.[12] Both agents may produce EPRs, akathisia, hypotension, and sedation.

## Dopamine 2 Antagonists

### Metoclopramide

Metoclopramide is a substituted benzamide, which, prior to the introduction of serotonin (5-HT<sub>3</sub>) receptor antagonists, was considered the most effective single antiemetic agent against highly emetogenic chemotherapy such as cisplatin. Although metoclopramide is a competitive antagonist at dopaminergic (D<sub>2</sub>) receptors, it is most effective against acute vomiting when given IV at high doses (e.g., 0.5–3 mg/kg/dose), probably because it is a weak competitive antagonist (relative to other serotonin antagonists) at 5-HT<sub>3</sub> receptors. It may act on the CTZ and the periphery. Metoclopramide also increases lower esophageal sphincter pressure and enhances the rate of gastric emptying, which may factor into its overall antiemetic effect. It can be administered IV at the U.S. Food and Drug Administration (FDA)–approved dose of 1 to 2 mg/kg every 2 hours (or less frequently) for three to five doses. Metoclopramide has also been safely given by IV bolus injection at higher single doses (up to 6 mg/kg) and by continuous IV infusion, with or without a loading bolus dose, with efficacy comparable to multiple intermittent dosing schedules.[13–15]

Metoclopramide is associated with akathisia and dystonic extrapyramidal effects; akathisia is seen more frequently in patients older than 30 years, and dystonic extrapyramidal effects are seen more commonly in patients younger than 30 years. Diphenhydramine, benztropine mesylate, and trihexyphenidyl are commonly used prophylactically or therapeutically to pharmacologically antagonize EPRs.[7,16] While cogwheeling rigidity, acute dystonia, and tremor are responsive to anticholinergic medications, akathisia—the subjective sense of restlessness or inability to sit still—is best treated by the following:

- Switching to a lower potency neuroleptic for vomiting, if possible.
- Lowering the dose.
- Adding a benzodiazepine (e.g., lorazepam) or beta blocker (e.g., propranolol).

## 5-HT<sub>3</sub> Receptor Antagonists

Four serotonin receptor antagonists—ondansetron, granisetron, dolasetron, and palonosetron—are available in the United States. Tropisetron, while not approved by the FDA, is available internationally. Agents in this class are thought to prevent N&V by preventing serotonin, which is released from enterochromaffin cells in the gastrointestinal (GI) mucosa, from initiating afferent transmission to the CNS via vagal and spinal sympathetic nerves.[17] The 5-HT<sub>3</sub> receptor antagonists may also block serotonin stimulation at the CTZ and other CNS structures.

### Ondansetron

Several studies have demonstrated that ondansetron produces an antiemetic response that equals or is superior to high doses of metoclopramide, but ondansetron has a superior toxicity profile compared with dopaminergic antagonist agents.[18–22][Level of evidence: I][23,24] Ondansetron (0.15 mg/kg) is given IV 15 to 30 minutes prior to chemotherapy and is repeated every 4 hours for two additional doses. Alternatively, for patients older than 18 years, a large multicenter study determined that a single 32-mg dose of ondansetron is more effective in treating cisplatin-induced N&V than a single 8-mg dose and is as effective as the standard regimen of three doses at 0.15 mg/kg given every 4 hours starting 30 minutes before chemotherapy.[25][Level of evidence: I] A single-center retrospective chart review has reported ondansetron-loading doses of 16 mg/m<sup>2</sup> (maximum, 24 mg) IV to be safe in infants, children, and adolescents.[26]



Currently, the oral and injectable ondansetron formulations are approved for use without dosage modification in patients older than 4 years, including elderly patients and patients with renal insufficiency. Oral ondansetron is given 3 times daily starting 30 minutes before chemotherapy and continuing for up to 2 days after chemotherapy is completed. Patients older than 12 years are given 4 mg per dose. Ondansetron is not approved for use in children younger than 4 years. Ondansetron clearance is diminished in patients with severe hepatic insufficiency; therefore, such patients receive a single injectable or oral dose no higher than 8 mg. There is currently no information available evaluating the safety of repeated daily ondansetron doses in patients with hepatic insufficiency. Other effective dosing schedules such as a continuous IV infusion (e.g., 1 mg/h for 24 h) or oral administration have also been evaluated.[25]

The major adverse effects include the following: [27]

- Headache (which can be treated with mild analgesics).
- Constipation or diarrhea.
- Fatigue.
- Dry mouth.
- Transient asymptomatic elevations in liver function tests (alanine and aspartate transaminases), which may be related to concurrent cisplatin administration.

Ondansetron has been etiologically implicated in a few case studies involving thrombocytopenia, renal insufficiency, and thrombotic events.[28] In addition, a few case reports have implicated ondansetron in causing EPRs. However, it is not clear in some cases whether the events described were in fact EPRs; in other reports, the evidence is confounded by concurrent use of other agents that are known to produce EPRs. Nevertheless, the greatest advantage of serotonin receptor antagonists over dopaminergic receptor antagonists is that they have fewer adverse effects. Despite prophylaxis with ondansetron, many patients receiving doxorubicin, cisplatin, or carboplatin will experience acute and delayed-phase N&V.[29][Level of evidence: II] A randomized, double-blind, placebo-controlled trial suggests that the addition of aprepitant, a neurokinin-1 (NK-1) receptor antagonist, may mitigate N&V.[30][Level of evidence: I] The optimal dose of aprepitant may be 125 mg on day 1 followed by 80 mg on days 2 to 5.[31][Level of evidence: I]

### Granisetron

Granisetron has demonstrated efficacy in preventing and controlling N&V at a broad range of doses (e.g., 10–80 µg/kg and empirically, 3 mg/dose). In the United States, granisetron injection, transdermal patch, and oral tablets are approved for initial and repeat prophylaxis for patients receiving emetogenic chemotherapy, including high-dose cisplatin. Granisetron is pharmacologically and pharmacokinetically distinct from ondansetron; however, clinically it appears equally efficacious and equally safe.[32–35][Level of evidence: I] Both granisetron formulations are given before chemotherapy, as either a single IV dose of 10 µg/kg (0.01 mg/kg) or 1 mg orally every 12 hours.

Both granisetron formulations and ondansetron injection share the same indication against highly emetogenic chemotherapy. In contrast, the oral ondansetron formulation has been approved only for use against N&V associated with moderately emetogenic chemotherapy.

Currently, granisetron injection is approved for use without dosage modification in patients older than 2 years, including elderly patients and patients with hepatic and renal insufficiency. Oral granisetron has not yet been approved for use in pediatric patients.

### Dolasetron

Both oral and injection formulations of dolasetron are indicated for the prevention of N&V associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses. Oral dolasetron may be dosed as 100 mg within 1 hour before chemotherapy. Dolasetron is given IV or orally at 1.8 mg/kg as a single dose approximately 30 minutes before chemotherapy.

The effectiveness of oral dolasetron in the prevention of chemotherapy-induced nausea and vomiting (CINV) has been proven in a large randomized, double-blind, comparative trial of 399 patients.[36][Level of evidence: I] Oral dolasetron was administered in the range of 25 to 200 mg 1 hour prior to chemotherapy. The other study arm consisted of oral ondansetron (8 mg) administered 1.5 hours before chemotherapy and every 8 hours after chemotherapy for a total of three doses. Complete response (CR) rates improved with increasing doses of dolasetron. Both dolasetron 200 mg and ondansetron had significantly higher CR rates as compared with dolasetron 25 or 50 mg. (CR was defined as no emetic episodes and no use of escape antiemetic medications.) Dolasetron injection has also been proven effective in the prevention of CINV.[37][Level of evidence: I]

### Palonosetron

Palonosetron is a 5-HT<sub>3</sub> receptor antagonist (second generation) that has antiemetic activity at both central and GI sites. In comparison to the older 5-HT<sub>3</sub> receptor antagonists, it has a higher binding affinity to the 5-HT<sub>3</sub> receptors, a higher potency, a significantly longer half-life (approximately 40 hours, four to five times longer than that of dolasetron, granisetron, or ondansetron), and an excellent safety profile.[38][Level of evidence: I] A dose-finding study demonstrated that the effective dose was 0.25 mg or higher.[38] In two large studies of patients receiving moderately emetogenic chemotherapy, CR (no emesis, no rescue) was significantly improved in the acute and the delayed period for patients who received 0.25 mg of palonosetron alone compared with either ondansetron or dolasetron alone.[39];[40][Level of evidence: I] Dexamethasone was not given with the 5-HT<sub>3</sub> receptor antagonists in these studies, and it is not yet known whether the differences in CR would persist if dexamethasone was used. In another study,[41][Level of evidence: I] 650 patients receiving highly emetogenic chemotherapy (cisplatin ≥60 mg/m<sup>2</sup>) also received either dexamethasone and one of two doses of palonosetron (0.25 mg or 0.75 mg) or dexamethasone and ondansetron (32 mg). Single-dose palonosetron was as effective as ondansetron in preventing acute CINV with dexamethasone pretreatment; it was significantly more effective than ondansetron throughout the 5-day postchemotherapy period. In an analysis of the patients in the above studies who received repeated cycles of chemotherapy, one author [42] reported that the CR rates for both acute and delayed CINV were maintained with single IV doses of palonosetron without concomitant corticosteroids. These data will require further review.

On the basis of the studies described above, palonosetron was approved by the FDA in July 2003 for the prevention of acute N&V associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and for the prevention of delayed N&V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. One randomized, double-blind, phase III trial compared palonosetron plus dexamethasone with granisetron plus dexamethasone for the prevention of CINV in patients receiving highly emetogenic chemotherapy. Palonosetron was equivalent to granisetron in the acute phase (first 24 hours) and better than granisetron in the delayed phase (24–120 hours), with a comparable safety profile for the two treatments.[43][Level of evidence: I] An open-label study was completed in a cohort of patients who had participated in this phase III randomized controlled trial comparing palonosetron to granisetron, with those who initially responded to palonosetron continuing the treatment over repeated cycles of chemotherapy. The investigators reported a good safety profile over time but provided limited data about adverse events. Another limitation of the study was that no more than 25% of patients were receiving palonosetron by cycle 4; the reasons for these withdrawals—whether lack of effect, adverse events, or other issues—were not reported.[44]

### Comparison of agents

Studies suggest that there are no major differences in efficacy or toxicity of the three first-generation 5-HT<sub>3</sub> receptor antagonists (dolasetron, granisetron, and ondansetron) in the treatment of acute CINV. These three agents are equivalent in efficacy and toxicity when used in appropriate doses.[45];[46-48][Level of evidence: I] Although these agents have been shown to be effective in the first 24 hours postchemotherapy (acute phase), they have not been demonstrated to be effective in days 2 to 5 postchemotherapy (delayed phase).[29,49,50]



Palonosetron, the second-generation 5-HT<sub>3</sub> receptor antagonist, has been approved for the control of delayed emesis for patients receiving moderately emetogenic chemotherapy.[39];[40][Level of evidence: I]

Despite the use of both first-generation and second-generation 5-HT<sub>3</sub> receptor antagonists, the control of acute CINV, and especially delayed N&V, is suboptimal, and there is considerable opportunity for improvement with either the addition or substitution of new agents in current regimens.[29][Level of evidence: II];[51][Level of evidence: I][49,50]

### Substance P Antagonists (NK-1 Receptor Antagonists)

The initial clinical studies using the NK-1 receptor antagonists [52-54][Level of evidence: I][55] demonstrated that the addition of an NK-1 receptor antagonist (CP-122,721, CJ-11,794, MK-0869 [aprepitant]) to a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone prior to cisplatin chemotherapy improved the control of acute emesis compared with a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone and improved the control of delayed emesis compared with placebo. In addition, as a single agent, aprepitant (MK-0869) had an effect similar to that of ondansetron on cisplatin-induced acute emesis but was superior in the control of delayed emesis.

Subsequent studies [56,57][Level of evidence: I] showed that the combination of aprepitant and dexamethasone was similar to a 5-HT<sub>3</sub> receptor antagonist plus dexamethasone in controlling acute emesis but was inferior in controlling acute emesis compared with triple therapy (aprepitant, 5-HT<sub>3</sub> receptor antagonist, and dexamethasone). These studies also confirmed the improvement of delayed emesis with the use of aprepitant compared with placebo. Two studies [31,58][Level of evidence: I] have also shown an improvement in cisplatin-induced delayed emesis with the combination of aprepitant and dexamethasone compared with dexamethasone alone, with the improvement maintained over repeat cycles of cisplatin chemotherapy.

In two randomized, double-blind, parallel, multicenter, controlled studies (520 patients in each study), patients received cisplatin ( $\geq 70$  mg/m<sup>2</sup>) and were randomly assigned to receive either standard therapy with a 5-HT<sub>3</sub> receptor antagonist (ondansetron) and dexamethasone prechemotherapy and dexamethasone postchemotherapy (days 2–4) or standard therapy plus aprepitant prechemotherapy and on days 2 and 3 postchemotherapy.[30,59][Level of evidence: I] The CR (no emesis, no rescue) of the aprepitant group in both studies was significantly higher in both the acute period (83%–89%) and the delayed period (68%–75%), compared with the CR of the standard therapy group in the acute period (68%–78%) and delayed period (47%–56%). Nausea was improved in the aprepitant group for some, but not all of the various specific measures of nausea.[30] The studies discussed above formed the basis for the approval of aprepitant by the FDA in March 2003. In combination with other antiemetics, aprepitant is indicated for the prevention of acute and delayed N&V associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. An additional study confirmed the efficacy of aprepitant in the delayed period, when it was compared with ondansetron.[60][Level of evidence: I]

All of the initial studies using aprepitant were conducted in patients receiving highly emetogenic chemotherapy such as cisplatin-based chemotherapy regimens. Subsequently, one group [61][Level of evidence: I] presented a study on the use of aprepitant in 862 breast cancer patients receiving moderately emetogenic chemotherapy (e.g., cyclophosphamide, doxorubicin). Two regimens were compared. Because the chemotherapy was moderately emetogenic, steroids were omitted from both arms, as illustrated in Table 2.

**Table 2. Comparison of Aprepitant and Standard Regimens**

| Regimen           | Day 1                                                                                                | Days 2 and 3                  |
|-------------------|------------------------------------------------------------------------------------------------------|-------------------------------|
| <u>Aprepitant</u> | Prechemotherapy: <u>aprepitant</u> (125 mg), <u>ondansetron</u> (8 mg), <u>dexamethasone</u> (12 mg) | <u>Aprepitant</u> (80 mg/d)   |
|                   | After 8 h: <u>ondansetron</u> (8 mg)                                                                 |                               |
| Standard          | Prechemotherapy: <u>ondansetron</u> (8 mg), <u>dexamethasone</u> (20 mg)                             | <u>Ondansetron</u> (8 mg bid) |
|                   | After 8 h: <u>ondansetron</u> (8 mg)                                                                 |                               |

bid = twice a day.

There was a significant improvement in CR (no emesis, no rescue) in the 24 hours after chemotherapy in the patients receiving aprepitant; however, there was no significant improvement in CR on days 2 to 5 in the postchemotherapy period when aprepitant alone was compared with ondansetron alone. The overall (days 1–5) CR was significantly improved for the aprepitant-containing regimen, most likely because of the improvement in the first 24 hours. The control of nausea in moderately emetogenic chemotherapy was not improved with the use of aprepitant without steroids on days 2 and 3 postchemotherapy. These results were consistent for multiple cycles of chemotherapy.[62] The role of aprepitant in moderately emetogenic chemotherapy remains undetermined.

One open-label study demonstrated that in the 5 days postchemotherapy, aprepitant in combination with palonosetron and dexamethasone is safe and highly effective in preventing CINV in patients receiving moderately emetogenic chemotherapy.[63][Level of evidence: II] Another study reported that aprepitant combined with ondansetron and dexamethasone provided superior efficacy in the prevention of acute and delayed CINV in a broad range of patients receiving moderately emetogenic chemotherapy (both anthracycline-cyclophosphamide regimens and nonanthracycline-cyclophosphamide regimens).[64] It is not known whether aprepitant is necessary in all moderately emetogenic regimens.

A randomized phase III trial evaluated the use of aprepitant in combination with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in patients with germ cell tumors who were receiving 5-day cisplatin combination chemotherapy.[65] There was a significant reduction in the amount of emesis and use of rescue medications with the use of aprepitant. This study suggests that aprepitant may be useful in the prevention of CINV in multiday chemotherapy regimens.

Fosaprepitant dimeglumine, a water-soluble, phosphorylated analog of aprepitant, is rapidly converted to aprepitant after IV administration.[66] Fosaprepitant (115 mg) was approved by the FDA as an alternative to the 125-mg oral aprepitant dose on day 1 of a 3-day regimen. As demonstrated in a randomized, double-blind study of patients receiving cisplatin chemotherapy, single-dose IV fosaprepitant (150 mg) given with ondansetron and dexamethasone was noninferior to the standard 3-day dosing of oral aprepitant in preventing CINV.[67]

## Corticosteroids

Steroids are sometimes used as single agents against mildly to moderately emetogenic chemotherapy but are more often used in antiemetic drug combinations.[68][Level of evidence: II];[69,70][Level of evidence: I] Their antiemetic mechanism of action is not fully understood, but they may affect prostaglandin activity in the brain. Clinically, steroids quantitatively decrease or eliminate episodes of N&V and may improve patients' mood, thus producing a subjective sense of well-being or euphoria (although they also can cause depression and anxiety). In combination with high-dose metoclopramide, steroids may mitigate adverse effects such as the frequency of diarrheal episodes.

Steroids are often given IV before chemotherapy and may or may not be repeated. Dosages and administration schedules are selected empirically. Dexamethasone is often the treatment of choice in treating N&V in patients receiving radiation to the brain, as it also reduces cerebral edema. It is administered orally, IM, or IV in the dose range of 8 mg to 40 mg (pediatric dose: 0.25–0.5 mg/kg).[71–75] Methylprednisolone is also administered orally, IM, or IV at doses and schedules that vary from 40 mg to 500 mg every 6 to 12 hours for up to 20 doses.[70,76]

Dexamethasone is also used orally for delayed N&V. Long-term corticosteroid use, however, is inappropriate and may cause substantial morbidity, including the following:

- Immunosuppression.
- Proximal muscle weakness (especially involving the thighs and upper arms).
- Aseptic necrosis of the long bones.
- Cataract formation.

- Hyperglycemia and exacerbation of preexisting diabetes or escalation of subclinical diabetes to clinical pathology.
- Adrenal suppression with hypocortisolism.
- Lethargy.
- Weight gain.
- GI irritation.
- Insomnia.
- Anxiety.
- Mood changes.
- Psychosis.

A study that examined chemotherapy in a group of patients with ovarian cancer found that short-term use of glucocorticoids as antiemetics had no negative effects on outcomes (e.g., overall survival or efficacy of chemotherapy).[77] As previously shown with metoclopramide, numerous studies have demonstrated that dexamethasone potentiates the antiemetic properties of 5-HT<sub>3</sub>-blocking agents.[78-82] If administered by IV, dexamethasone may be given over 10 to 15 minutes, since rapid administration may cause sensations of generalized warmth, pharyngeal tingling or burning, or acute transient perineal and/or rectal pain.[74,83-85]

Prednisone and adrenocorticotrophic hormone (ACTH) given concomitantly with other active antiemetic agents have also demonstrated efficacy against N&V caused by cisplatin-containing chemotherapy during the acute phase (within 24 hours after receiving chemotherapy).[86-88] In a double-blind, randomized study of metoclopramide and dexamethasone with or without 1 mg of ACTH, patients receiving ACTH prophylaxis for cisplatin-containing chemotherapy experienced a significantly decreased incidence and severity of delayed emesis for up to 72 hours after treatment.[88]

## ***Cannabis***

The plant *Cannabis* contains more than 60 different types of cannabinoids, or components that have physiologic activity. The most popular, and perhaps the most psychoactive, is delta-9-tetrahydrocannabinol (delta-9-THC).[89] There are two FDA-approved products for CINV:

- Dronabinol (a synthetic delta-9-THC), as prophylaxis for CINV, 5 mg/m<sup>2</sup> orally 1 to 3 hours before chemotherapy and every 2 to 4 hours after chemotherapy, for a total of no more than 6 doses per day.
- Nabilone, 1 to 2 mg orally twice a day, for CINV that has failed to respond to other antiemetics.

With respect to CINV, *Cannabis* products probably target cannabinoid-1 (CB-1) and CB-2 receptors, which are in the CNS.[90] Another product, Sativex, a cannabidiol that is a buccal spray, is under investigation.[91,92]

Much of the research on this class of agent was conducted in the late 1970s and 1980s and compared *Cannabis* to older antiemetic agents that targeted the dopamine receptor, such as prochlorperazine (Compazine) and metoclopramide (Reglan).[89,93-100] This group of studies demonstrated that *Cannabis* was as effective for moderately emetogenic chemotherapy as dopaminergic antiemetics or was more effective than placebo.[89] Side effects of *Cannabis* products included euphoria, dizziness, dysphoria, hallucinations, and hypotension.[89] Despite earlier reports of efficacy, in at least one study, patients did not significantly prefer *Cannabis* agents because of the side effects.[93]

Since the 1990s, research in nausea and vomiting has elucidated newer and more physiologic targets, namely 5-HT<sub>3</sub> and NK-1 receptors. Subsequently, 5-HT<sub>3</sub> and NK-1 receptor antagonists have become standard prophylactic therapy for CINV. Studies investigating the role of *Cannabis* with these newer agents

are few; therefore, limited conclusions can be drawn. In published trials, however, *Cannabis* has not demonstrated more efficacy than 5-HT<sub>3</sub> receptor antagonists, and synergistic or additive effects have not been fully investigated.[90,101,102]

In summary, the place of *Cannabis* in today's arsenal of antiemetics for the prevention and treatment of CINV is not known. Discussions with patients about its use may include responses to available agents, known side effects of *Cannabis*, and an assessment of the risks versus benefits of this therapy.[103]

For a broader discussion of the issues surrounding *Cannabis* use, refer to the PDQ summary on Cannabis and Cannabinoids.

## Benzodiazepines

Benzodiazepines such as lorazepam, midazolam, and alprazolam have become recognized as valuable adjuncts in the prevention and treatment of anxiety and the symptoms of anticipatory nausea and vomiting (ANV) associated with chemotherapy, especially with the highly emetogenic regimens given to children.[104-106] Benzodiazepines have not demonstrated intrinsic antiemetic activity as single agents. Therefore, their place in antiemetic prophylaxis and treatment is adjunctive to other antiemetic agents.[107] Benzodiazepines presumably act on higher CNS structures, the brainstem, and spinal cord, and they produce anxiolytic, sedative, and anterograde amnesic effects. In addition, they markedly decrease the severity of EPRs, especially akathisia, associated with dopaminergic receptor antagonist antiemetics.

### Lorazepam

Lorazepam may be administered orally, IM, IV, and sublingually. Dosages range from 0.5 to 3 mg (alternatively, 0.025–0.05 mg/kg, or 1.5 mg/m<sup>2</sup>, but ≤4 mg per dose) in adults and 0.03 to 0.05 mg/kg in children every 6 to 12 hours.[108][Level of evidence: I][104,109,110] Midazolam produces mild-to-marked sedation for 1 to 4.5 hours at doses equal to 0.04 mg/kg given IV over 3 to 5 minutes.[111,112] Alprazolam has been shown to be effective when given in combination with metoclopramide and methylprednisolone. [113]

The adverse effects of lorazepam include the following:[114]

- Sedation.
- Perceptual disturbances.
- Disorders of micturition and/or defecation.
- Visual disturbances.
- Hypotension.
- Anterograde amnesia.
- Psychological dependence.
- Confusion.
- Ataxia.
- Depressed mental acuity with intoxication.

### Olanzapine

Olanzapine is an antipsychotic in the thienobenzodiazepine drug class that blocks multiple neurotransmitters: dopamine at D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, and D<sub>4</sub> brain receptors; serotonin at 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>6</sub> receptors; catecholamines at alpha-1 adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at H<sub>1</sub> receptors.[115] Common side effects include the following:[116-118]

- Sedation.

- Dry mouth.
- Increased appetite.
- Weight gain.
- Postural hypotension.
- Dizziness.

Olanzapine has also been associated with increased risk of hyperlipidemia, hyperglycemia, new-onset diabetes and, in rare cases, diabetic ketoacidosis.[116,118,119] Olanzapine is used with caution in elderly patients; it has been associated with increased risk of death and increased incidence of cerebrovascular adverse events in patients with dementia-related psychosis and carries a boxed warning to that effect.[116] Olanzapine's activity at multiple receptors, particularly at the D<sub>2</sub> and 5-HT<sub>3</sub> receptors that appear to be involved in N&V, suggests that it may have significant antiemetic properties.

There have been case reports on the use of olanzapine as an antiemetic.[120][Level of evidence: II];[121-124] These case reports prompted a phase I study in which olanzapine was used for the prevention of delayed emesis in cancer patients receiving their first cycle of chemotherapy consisting of cyclophosphamide, doxorubicin, cisplatin, and/or irinotecan. [125] The protocol was completed by 15 patients, and no grade 4 toxicities were seen. The maximum tolerated dose was 5 mg/day for 2 days prior to chemotherapy and 10 mg/day for 7 days postchemotherapy. On the basis of these data, olanzapine appeared to be a safe and effective agent for the prevention of delayed emesis in chemotherapy-naïve cancer patients receiving cyclophosphamide, doxorubicin, cisplatin, and/or irinotecan.

Using the maximum tolerated dose of olanzapine in the phase I trial, a phase II trial was performed for the prevention of CINV in patients receiving their first course of either highly emetogenic or moderately emetogenic chemotherapy. Olanzapine was added to granisetron and dexamethasone prechemotherapy and to dexamethasone postchemotherapy. CR (no emesis, no rescue) was 100% for the acute period (24 hours postchemotherapy), 80% for the delayed period (days 2–5 postchemotherapy), and 80% for the overall period (0–120 hours postchemotherapy) in ten patients receiving highly emetogenic chemotherapy (cisplatin, ≥70 mg/m<sup>2</sup>). CR was also 100% for the acute period, 85% for the delayed period, and 85% for the overall period in 20 patients receiving moderately emetogenic chemotherapy (doxorubicin, ≥50 mg/m<sup>2</sup>). Nausea was very well controlled in the patients receiving highly emetogenic chemotherapy, with no patient having nausea (0 on a scale of 0–10, M. D. Anderson Symptom Inventory) in the acute or delayed periods. Nausea was also well controlled in patients receiving moderately emetogenic chemotherapy, with no nausea in 85% of patients in the acute period and in 65% of patients in the delayed and overall periods. There were no grade 3 or 4 toxicities. On the basis of these data, olanzapine appeared to be safe (sedation was the only dose-limiting toxicity) and effective in controlling acute and delayed CINV in patients receiving highly emetogenic and moderately emetogenic chemotherapy.[126][Level of evidence: II]

Subsequent studies have shown the effectiveness of olanzapine as an antiemetic. Olanzapine combined with a single dose of dexamethasone and a single dose of palonosetron was very effective in controlling acute and delayed CINV in patients receiving either moderately emetogenic chemotherapy or highly emetogenic chemotherapy.[127] A large end study [128][Level of evidence: I] demonstrated that in patients receiving either highly emetogenic chemotherapy or moderately emetogenic chemotherapy, the addition of olanzapine to azasetron and dexamethasone improved the CR of delayed CINV.

## Other Pharmacologic Agents

### Ginger

The antiemetic effect of ginger powder (*Zingiber officinale*) was explored in a double-blind, placebo-controlled, randomized trial among 32 children and young adults, aged 8 to 21 years, with newly diagnosed bone sarcomas.[129] Cycles of chemotherapy were randomly assigned to ginger powder (1,000 to 2,000 mg per day) or placebo on days 1 to 3 of treatment. Patients were allowed to receive the standard antiemetic medications ondansetron and dexamethasone. The primary endpoint was the incidence and severity of

acute N&V (occurring  $\leq 24$  hours from the start of chemotherapy) and delayed N&V (occurring  $> 24$  hours after completion of chemotherapy).

The authors reported a reduction in the incidence of moderate to severe acute nausea in the experimental arm (55.6% of cycles), compared with the placebo arm (93.3% of cycles) ( $P = .003$ ). Decreased incidence of moderate to severe vomiting was found in the experimental arm (33.3%), compared with the placebo arm (76.7%) ( $P = .002$ ). The authors also reported decreased incidence of moderate to severe delayed nausea ( $P < .001$ ) and vomiting ( $P = .022$ ) in the experimental arm, compared with placebo. No adverse events were reported.[129]

Although these results are encouraging, the study was limited by a small sample size, lack of stratification by antiemetic regimen, and no intra- or interindividual reporting.

A phase III, randomized, dose-finding trial of 576 patients with cancer evaluated 0.5 g, 1 g, and 1.5 g of ginger versus placebo in twice-a-day dosing for the prevention of acute nausea (defined as day 1 postchemotherapy) in patients experiencing some level of nausea (as measured on an 11-point scale) caused by their current chemotherapy regimen, despite standard prophylaxis with a 5-HT<sub>3</sub> receptor antagonist. Patients began taking ginger or placebo capsules 3 days before each chemotherapy treatment and continued them for 6 days. For average nausea, 0.5 g of ginger was significantly better than placebo; both 0.5 g and 1 g were significantly better than placebo for “worst nausea.” Effects for delayed nausea and vomiting were not significant. Emetogenicity of chemotherapy regimens was not controlled for. Adverse events were infrequent and were not severe.[130]

## Management of CINV

Current guidelines [131,132] recommend that prechemotherapy management of CINV be based on the emetogenic potential of the chemotherapy agent(s) selected. For patients receiving regimens with high emetogenic potential, the combination of a 5-HT<sub>3</sub> receptor antagonist, aprepitant, and dexamethasone is recommended prechemotherapy; lorazepam may also be used. Aprepitant and dexamethasone are recommended postchemotherapy for the prevention of delayed emesis.

For patients receiving moderately emetogenic chemotherapy, the combination of a 5-HT<sub>3</sub> receptor antagonist and dexamethasone is used prechemotherapy, with or without lorazepam. Patients receiving the combination of an anthracycline and cyclophosphamide and select patients receiving certain other agents of moderate emetic risk, such as cisplatin ( $< 50$  mg/m<sup>2</sup>) or doxorubicin, may also receive aprepitant. Postchemotherapy, a 5-HT<sub>3</sub> receptor antagonist, dexamethasone, or both are recommended for the prevention of delayed emesis.

For regimens with low emetogenic potential, dexamethasone is recommended with or without lorazepam. For regimens with minimal emetogenic risk, no prophylaxis is recommended.[131,132]

Antiemetic guidelines [131,132] have included the available oral 5-HT<sub>3</sub> receptor antagonists as optional therapy for the prevention of delayed emesis, but the level of evidence supporting this practice is low.[49]

Studies have strongly suggested that patients experience more acute and delayed CINV than is perceived by practitioners.[49,133,134] One study suggested that patients who are highly expectant of experiencing nausea appear to experience more postchemotherapy nausea.[135] In addition, the current and new agents have been used as prophylaxis for acute and delayed CINV and have not been studied for use in established CINV.[49,50] One study reported the effective use of IV palonosetron and dexamethasone for the prevention of CINV in patients receiving multiple-day chemotherapy.[136]

Pre- and postchemotherapy recommendations by emetogenic potential are summarized in Table 3.

**Table 3. Antiemetic Recommendations by Emetic Risk Categories<sup>a</sup>**



| Emetic Risk Category    | ASCO Guidelines                                                                                                                                                                                                                                                                                                                           | NCCN Guidelines                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| High (>90%) risk        | Three-drug combination of a 5-HT <sub>3</sub> receptor antagonist, <u>dexamethasone</u> , and <u>aprepitant</u> recommended prechemotherapy.                                                                                                                                                                                              | Prechemotherapy, a 5-HT <sub>3</sub> receptor antagonist ( <u>ondansetron</u> , <u>granisetron</u> , <u>dolasetron</u> , or <u>palonosetron</u> <sup>b</sup> ), <u>dexamethasone</u> (12 mg), and <u>aprepitant</u> (125 mg) recommended, with or without <u>lorazepam</u> .                                                                                                                                                                                                                                                                                                                                                                      |
|                         | For patients receiving <u>cisplatin</u> and all other agents of high emetic risk, the two-drug combination of <u>dexamethasone</u> and <u>aprepitant</u> recommended for prevention of delayed emesis.                                                                                                                                    | For prevention of delayed emesis, <u>dexamethasone</u> (8 mg) on days 2–4 plus <u>aprepitant</u> (80 mg) on days 2 and 3 recommended, with or without <u>lorazepam</u> on days 2–4.                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Moderate (30%–90%) risk | For patients receiving an anthracycline and <u>cyclophosphamide</u> , the three-drug combination of a 5-HT <sub>3</sub> receptor antagonist, <u>dexamethasone</u> , and <u>aprepitant</u> recommended prechemotherapy; single-agent <u>aprepitant</u> recommended on days 2 and 3 for prevention of delayed emesis.                       | For patients receiving an anthracycline and <u>cyclophosphamide</u> and selected patients receiving other chemotherapies of moderate emetic risk (e.g., <u>carboplatin</u> , <u>cisplatin</u> , <u>doxorubicin</u> , <u>epirubicin</u> , <u>ifosfamide</u> , <u>irinotecan</u> , or <u>methotrexate</u> ), a 5-HT <sub>3</sub> receptor antagonist ( <u>ondansetron</u> , <u>granisetron</u> , <u>dolasetron</u> , or <u>palonosetron</u> <sup>b</sup> ), <u>dexamethasone</u> (12 mg), and <u>aprepitant</u> (125 mg) recommended, with or without <u>lorazepam</u> , prechemotherapy; for other patients, <u>aprepitant</u> is not recommended. |
|                         | For patients receiving other chemotherapies of moderate emetic risk, the two-drug combination of a 5-HT <sub>3</sub> receptor antagonist and <u>dexamethasone</u> recommended prechemotherapy; single-agent <u>dexamethasone</u> or a 5-HT <sub>3</sub> receptor antagonist recommended on days 2 and 3 for prevention of delayed emesis. | For prevention of delayed emesis, <u>dexamethasone</u> (8 mg) or a 5-HT <sub>3</sub> receptor antagonist on days 2–4 or, if used on day 1, <u>aprepitant</u> (80 mg) on days 2 and 3, with or without <u>dexamethasone</u> (8 mg) on days 2–4, recommended, with or without <u>lorazepam</u> on days 2–4.                                                                                                                                                                                                                                                                                                                                         |
| Low (10%–30%) risk      | <u>Dexamethasone</u> (8 mg) recommended; no routine preventive use of antiemetics for delayed emesis recommended.                                                                                                                                                                                                                         | <u>Metoclopramide</u> , with or without <u>diphenhydramine</u> ; <u>dexamethasone</u> (12 mg); or <u>prochlorperazine</u> recommended, with or without <u>lorazepam</u> .                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Minimal (<10%) risk     | No antiemetic administered routinely pre- or postchemotherapy.                                                                                                                                                                                                                                                                            | No routine prophylaxis; consider using antiemetics listed under primary prophylaxis as treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

ASCO = American Society of Clinical Oncology; NCCN = National Comprehensive Cancer Network.



<sup>a</sup>Adapted from Navari.[137]

<sup>b</sup>Order of listed antiemetics does not reflect preference.

## Current Clinical Trials

Check NCI's list of cancer clinical trials for U.S. supportive and palliative care trials about [nausea and vomiting therapy](#) that are now accepting participants. The list of trials can be further narrowed by location, drug, intervention, and other criteria.

General information about clinical trials is also available from the [NCI Web site](#).

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## Nausea, Vomiting (Emesis), Constipation, and Bowel Obstruction in Advanced Cancer

### Frequency

Nausea and vomiting (N&V) are common symptoms in patients with advanced cancer, occurring in approximately 21% to 68% of these patients.[1,2] The underlying pathophysiology and treatment differs somewhat from nausea related to radiation treatment or chemotherapy. Chronic nausea can significantly impair a patient's quality of life.

### Pathophysiology and Causes

Chronic nausea in the advanced cancer setting is often multifactorial in origin.[1-3] Medications, including some that are frequently prescribed in this setting—such as opioids, nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitor antidepressants—may be responsible.

In the case of opioids, nausea frequently resolves spontaneously a few days after initiation of treatment. In some cases, however, it may persist. Nausea resulting from the accumulation of active opioid metabolites (morphine-6-glucuronide) has been described,[4] and patients with impaired renal function may be at increased risk. Opioids invariably produce constipation if prophylactic measures are not taken (namely, the use of a regular laxative regimen), and constipation is one of the most common causes of nausea in patients with advanced cancer.[5-8]

Opioid-induced gastrointestinal (GI) motility problems may compound the problem of diminished GI motility that many patients experience as part of the anorexia-cachexia syndrome of advanced cancer. The autonomic dysfunction that often accompanies this syndrome results in decreased GI motility, early satiety, and chronic nausea.[9-11] Other causes of chronic nausea in these patients include the following:[12]

- Raised intracranial pressure (from metastatic brain disease or primary brain tumors).
- Metabolic abnormalities such as hypercalcemia, hyponatremia, and uremia.
- Dehydration.
- Malignant bowel obstruction.
- Gastroduodenal ulcers.
- Infections of the mouth, pharynx, or esophagus.

Nausea, like many other symptoms, may have psychological undercurrents that either exacerbate or induce chronic nausea.

### Assessment

A comprehensive history that includes determining the frequency and effectiveness of bowel movements and laxative therapy is essential. Concurrent medications are reviewed, and the frequency and nature of N&V is documented. Examination will assess for bowel obstruction, fecal impaction, dehydration, and raised intracranial pressure. History and physical examination are poor at determining the extent of constipation.[5] A plain flat-plate x-ray of the abdomen can be very useful to this end.[13] Surgical x-ray views of the abdomen may be helpful if a bowel obstruction is suspected. Investigations to determine blood levels of electrolytes, calcium, and renal parameters may also be helpful.

### Management

Management centers on identifying the underlying causes, addressing these when possible, and controlling the symptoms.[1,2] A basic working knowledge of the emetic pathways and identification of possible underlying causes guide antiemetic selection.

Multiple antiemetic regimens have been proposed for the management of chronic nausea in the advanced cancer setting. Prospective studies comparing one regimen with another are lacking. Metoclopramide or domperidone are generally recommended as first-line agents because they improve GI motility and act on the chemoreceptor trigger zone (as a result of their antidopaminergic properties).[14] Metoclopramide can be administered orally or parenterally (subcutaneously or intravenously [IV]) at doses of 10 mg, 4 times a day, or on an every-4-hour basis, depending on the severity of the nausea. Rescue doses are ordered on an as-needed basis to manage the episodic worsening of nausea that may occur.

Extrapyramidal-related adverse effects are a potential complication of these medications but appear to occur infrequently. Domperidone, which is currently unavailable in the United States, is associated with fewer of these adverse effects. Unfortunately, this drug is not available in a parenteral formulation. Dimenhydrinate (Dramamine) or antihistamine agents may be used if a complete bowel obstruction is suspected (in which case prokinetic agents are contraindicated) or if patients are intolerant to other antiemetic agents. Haloperidol, a potent antidopamine agent, may be considered if bowel obstruction is the underlying problem.[15]

The phenothiazine drugs are sometimes used,[16][Level of evidence: II] but the high incidence of adverse effects such as somnolence and anticholinergic-related effects (orthostatic hypotension and confusion) limit their role. Chlorpromazine has modest antiemetic activity but a high incidence of sedation, postural hypotension, and anticholinergic adverse effects, while piperazine derivatives such as prochlorperazine are stronger antiemetics but cause more extrapyramidal side effects. Hyoscine butylbromide, on the other hand, can be useful for patients experiencing colic from complete bowel obstruction.

A continuous parenteral infusion of metoclopramide, at doses of 60 to 120 mg/day, may be helpful for patients with intractable chronic nausea.[17] The judicious use of corticosteroids such as dexamethasone in selected patients may be useful in conjunction with a more traditional antiemetic, although one study has suggested that dexamethasone was not better than placebo in patients who were not controlled with metoclopramide.[18][Level of evidence: I] The exact mechanism of action and the optimal dose of corticosteroids for this indication are not known.

In contrast to radiation therapy–induced nausea or chemotherapy-induced nausea, the role of 5-HT<sub>3</sub> receptor antagonists (such as ondansetron) is not clear in the setting of chronic nausea in advanced cancer, but it appears to be limited to a small number of highly selected cases, specifically those that have failed all other treatments.[19]

A case series study has suggested an antiemetic effect for olanzapine (an atypical antipsychotic) in advanced cancer patients being treated with opioids who are complaining of apparent opiate-induced nausea. However, further study and comparison with standard management are required.[20]

The management of constipation can be divided into general interventions and therapeutic measures.[21] The general interventions include the prevention of constipation by initiating regular laxative regimens, particularly in patients on opioid treatment, and where possible, the elimination of medical factors that may be contributing to constipation (e.g., discontinuation of nonessential constipating drugs). Prophylactic laxative regimens may consist of stool softeners such as docusate and bowel stimulants such as sennosides. Occasionally lactulose may be added. If necessary, a hyperosmolar laxative such as lactulose or polyethylene glycol may be added.[22] These regimens are reviewed on a regular basis and their doses adjusted, depending on the regularity of bowel movements. High-fiber diets, while generally recommended, may be difficult for patients with very advanced cancer. Bulk agents such as psyllium or cellulose are unsuitable for patients with advanced cancer because the high fluid intake required with these agents is often intolerable to patients. (Refer to the PDQ summaries on Gastrointestinal Complications and Pain for more information on the management of constipation caused by opioids.)

Therapeutic interventions for the routine management of constipation may be administered orally or rectally, as follows:

- Oral laxatives, including bulk agents, osmotic agents, contact cathartics, and agents for colonic lavage.

- Saline laxatives, including sodium salts (sodium phosphate) and magnesium salts (magnesium citrate), may be useful to treat established constipation.
- Sodium phosphates are generally administered rectally as an enema, but oral solutions are also available.
- Magnesium citrate is generally administered orally and can be especially useful if the constipation is primarily in the proximal bowel.
- The contact cathartic bisacodyl, available as a suppository, may also be useful for treating established constipation.

Once the constipation is cleared, the background laxative regimen (e.g., sennoside and docusate) is reviewed with a view to optimizing it. The action of the saline and magnesium salts is not physiological, and regular ongoing administration is avoided. Saline laxatives are used with caution in patients with renal impairment or cardiac failure. Mineral oil enemas are used occasionally and act as both lubricants and stool softeners; however, they may interfere with the absorption of fat-soluble vitamins, and there is a risk of lipoid pneumonia in debilitated patients. The use of enemas and rectal suppositories is usually limited to the acute short-term management of more severe episodes of constipation. However, patients with neurogenic bowel problems (e.g., patients with irreversible spinal cord compression) often require regular ongoing treatment with suppositories as part of their bowel care. The rectal route is contraindicated in patients with mucosal integrity/bowel-wall compromise. (Refer to the PDQ summary on Gastrointestinal Complications for more information.)

There have been no adequate comparative studies between the various laxatives to make evidence-based recommendations on which laxative regimen is optimal. Patients with advanced cancer are at risk of becoming constipated and generally require a regular bowel regimen, even if they are not eating. This need is amplified when they are on opioid treatment. On occasion, patients may present with a refractory narcotic bowel syndrome despite aggressive bowel care. Methylnaltrexone, a quaternary derivative of naltrexone, is an opioid antagonist that does not cross the blood-brain barrier. Preliminary studies suggest that it may be effective when given subcutaneously in the management of opioid-associated constipation without causing opioid withdrawal.[23][Level of evidence: I];[24,25] Methylnaltrexone is avoided in cases of bowel obstruction and suspected bowel obstruction. This has not been studied in children.

### **Malignant Bowel Obstruction**

The initial approach to assessing and managing malignant bowel obstruction in the advanced cancer patient involves determining whether the obstruction is reversible and whether the obstruction is partial or complete.[26–28] Suitability for surgery such as resection or intestinal bypassing is assessed. Several medical options are available to improve the comfort of patients with inoperable bowel obstructions.[29,30] Less aggressive surgical procedures such as the insertion of a venting gastrostomy tube can provide considerable relief. When the obstruction is complete and irreversible, the creation of ostomies may also provide relief. Nasogastric tubes may be used temporarily until the obstruction resolves; however, when the obstruction is irreversible, other options such as the insertion of a gastrostomy tube are considered.

Antiemetic agents with prokinetic properties are relatively contraindicated in the presence of a complete obstruction, and alternative agents such as an antihistamine or haloperidol may be required. Clinical experience suggests that corticosteroids (e.g., dexamethasone at a starting dose of 6–10 mg subcutaneously, 3–4 times a day) may be useful for malignant bowel obstruction.[26,27] The optimal dose and duration of treatment has not been clarified.

Hydration and drugs such as opioids and antiemetics are administered via routes other than the oral route. The subcutaneous route can be very convenient and effective for both hydration and opioid administration. This route is as effective as IV administration, is less invasive, and requires less maintenance than the IV route. Octreotide, a somatostatin analog, can be useful at doses of 100 µg to 200 µg subcutaneously, 3 times a day, for refractory obstruction.[26,27,31] In the United States, octreotide is often administered as a continuous infusion. If the obstruction causes severe colic, hyoscine butylbromide may be considered. The use of colonic endoluminal stenting devices in selected patients is gaining increasing attention.[32,33]

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## Nonpharmacologic Management of Nausea and Vomiting (Emesis)

Nonpharmacologic strategies are also used to manage nausea and vomiting. These include the following:

- Dietary alterations. (Refer to the Nausea subsection of the Nutritional Suggestions for Symptom Management section in the PDQ summary on Nutrition in Cancer Care for more information.)
- Hypnosis.
- Acupuncture. (Refer to the PDQ summary on Acupuncture for more information.)
- Acupressure.
- Relaxation techniques.
- Behavioral therapy.
- Guided imagery.

Guided imagery, hypnosis, and systematic desensitization as means to progressive muscle relaxation have been the most frequently studied treatments for anticipatory nausea and vomiting (ANV) and are the recommended treatments for this classically conditioned response. (Refer to the Treatment of ANV section of this summary for more information.)

## Radiation Therapy

### Correlates

Patients receiving radiation to the gastrointestinal (GI) tract or brain have the greatest potential for nausea and vomiting (N&V) as side effects. Because cells of the GI tract are dividing quickly, they are quite sensitive to radiation therapy. Radiation to the brain is believed to stimulate the brain's vomiting center or chemoreceptor trigger zone. Similar to chemotherapy, radiation dose factors also play a role in determining the possible occurrence of N&V. In general, the higher the daily fractional dose and the greater the amount of tissue that is irradiated, the higher the potential for N&V. In addition, the larger the amount of GI tract irradiated (particularly for fields that include the small intestine and stomach), the higher the potential for N&V. Total-body irradiation before bone marrow transplant, for example, has a high probability of inducing N&V as acute side effects.

### Prevalence

N&V from radiation may be acute and self-limiting, usually occurring 30 minutes to several hours after treatment. Patients report that symptoms improve on days that they are not being treated. There are also cumulative effects that may occur in patients receiving radiation therapy to the GI tract.[1]

## Treatment

Complete control rates with 5-HT<sub>3</sub> receptor antagonists for total-body irradiation vary from 50% to 90%.<sup>[2-4]</sup> The role of corticosteroids in combination with 5-HT<sub>3</sub> receptor antagonists has not been studied.

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## Changes to This Summary (10/21/2013)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial and formatting changes were made to this summary.

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## About This PDQ Summary

### Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the pathophysiology and treatment of nausea and vomiting (emesis) (N&V). It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

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Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Nausea and Vomiting are:

- Lillian M. Nail, PhD, RN, FAAN, CNS (Oregon Health & Science University Cancer Institute)
- Rudolph Modesto Navari, MD, PhD (University of Notre Dame)

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