NIH NATIONAL CANCER INSTITUTE

# Nausea and Vomiting Related to Cancer Treatment (PDQ®)–Health Professional Version

## Overview

Prevention and control of nausea and vomiting (N&V) are paramount in the treatment of patients with cancer. Chemotherapy-induced N&V is one of the most common and distressing acute side effects of cancer treatment. It occurs in up to 80% of patients and can have a significant impact on a patient's quality of life. N&V can also result in the following:

- Serious metabolic derangements.

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

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.

# Pathophysiology of N&V

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

Progress has been made in understanding the neurophysiological mechanisms that control nausea and vomiting (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 stimulation of a complex reflex that includes a convergence of afferent stimulation from the following:[1,2]

- A chemoreceptor trigger zone (CTZ, area postrema).
- The cerebral cortex and the limbic system in response to sensory stimulation (particularly smell and taste), psychological 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.

Neurotransmitters (including serotonin, substance P, and dopamine) found in the CTZ, the vomiting center (thought to be located in the nucleus tractus solitarius), and enterochromaffin cells in the gastrointestinal tract release efferent impulses. These impulses are transmitted to the abdominal musculature, salivation center, and

respiratory center. The relative contribution from these multiple pathways, culminating in N&V symptoms, is complex. It is postulated to account for agents' variable emetogenicity (intrinsic emetogenicity and mitigating factors such as dosage, administration route, and exposure duration) and emetogenic profile (i.e., time to onset, symptom severity, and duration).[3,4]

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## General Risk Factors and Etiologies

Although most patients receiving chemotherapy are at risk of nausea and vomiting (N&V), the onset, severity, triggers, and duration vary. Factors related to the tumor, treatment, and patient all contribute to N&V, including tumor location, chemotherapy agents used, and radiation exposure.[1-3]

Patient-related factors may include the following:

- Incidence and severity of N&V during past courses of chemotherapy. Patients with poor control of N&V during past chemotherapy cycles are likely to experience N&V in subsequent cycles.
- History of chronic alcohol use. Patients with a history of chronic high intake of alcohol are less likely to experience cisplatin-induced N&V. [4]
- Age. N&V is more likely to occur in patients younger than 50 years.[5]
- Gender. N&V is more likely to occur in women. [5,6]
- History of morning sickness or emesis during pregnancy.

Additional causal factors may include the following:

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

Clinicians must be aware of all potential causes and factors of N&V, especially in patients with cancer who may receive several treatments and medications. For more information about opioid-induced N&V, see the Adverse effects section in Cancer Pain.

## Classifications

N&V have been classified as acute, delayed, anticipatory, breakthrough, refractory, and chronic, as outlined below:[7-9]

- **Acute N&V:** N&V experienced during the first 24 hours after chemotherapy administration. [10]
- **Delayed (or late) N&V:** N&V that 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 on 2 or more consecutive days.
- **Anticipatory N&V (ANV):** N&V that occurs before 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 chemotherapy treatments that led to acute or delayed N&V.

- **Breakthrough N&V:** Vomiting that occurs within 5 days of prophylactic use of antiemetics and requires rescue.
- **Refractory N&V:** N&V that does not respond to treatment.
- **Chronic N&V in patients with advanced cancer:** N&V associated with a variety of potential etiologies. These etiologies are neither well known nor well researched, but potential causal factors include gastrointestinal, cranial, metabolic, drug-induced (e.g., morphine), cytotoxic chemotherapy–induced, and radiation-induced mechanisms.[11]

The National Cancer Institute has published a descriptive terminology for adverse event reporting (see Table 1). A grading (severity) scale is provided for each term.

# Table 1. National Cancer Institute's Common Terminology Criteria for Adverse Events: N&V[a]

| Adverse Event | Grade | Description |
|---|---|---|
| Nausea[b] | 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 |

| Adverse Event | Grade | Description |
|---|---|---|
| | | fluid intake; tube feeding, TPN, or hospitalization indicated |
| | 4 | Grade not assigned |
| | 5 | Grade not assigned |
| Vomiting[c] | 1 | Intervention not indicated |
| | 2 | Outpatient IV hydration; medical intervention indicated |

| Adverse Event | Grade | Description |
| --- | --- | --- |
| | 3 | Tube feeding, TPN, or hospitalization indicated |
| | 4 | Life-threatening consequences; urgent intervention indicated |
| | 5 | Death |

| Adverse Event | Grade | Description |
|---|---|---|

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

[a]Adapted from National Cancer Institute.[12]

[b]Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.

[c]Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.

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# Anticipatory Nausea and Vomiting

## Prevalence

The prevalence of anticipatory nausea and vomiting (ANV) has varied because of changing

definitions and assessment methods.[1] Anticipatory nausea appears to occur in approximately 29% of patients receiving chemotherapy, while anticipatory vomiting appears to occur in 11% of patients.[2] With the introduction of pharmacological agents such as 5-hydroxytryptamine-3 (5-$HT_3$) receptor antagonists, the prevalence of ANV was expected to decline, but 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-$HT_3$ 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 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, presence of the 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. It is 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 before treatment with any chemotherapy is rare, and few patients ever experience ANV without previous

postchemotherapy nausea.[8] Also, most studies have found (1) a higher probability of ANV with an increasing number of chemotherapy infusions and (2) the intensity of ANV increasing as patients get closer to the 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 risk factors that correlate with the incidence of ANV. There is no agreement on which factors predict ANV. However, a patient with fewer than three of the first eight characteristics listed below is unlikely to develop ANV. Screening after the first chemotherapy infusion could identify patients at increased risk.[11]

### *Variables Found to Correlate With ANV*

1. Age younger than 50 years.
2. N&V after the 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 the last chemotherapy session.
6. Susceptibility to motion sickness.
7. Female gender.
8. High-state anxiety (anxiety reactive to specific situations).[12,13]
9. Greater reactivity of the autonomic nervous system and slower reaction time.[14]
10. Patient expectations of chemotherapy-related nausea before beginning treatment. [15,16]
11. Percentage of chemotherapy infusions followed by nausea.[17]

12. Postchemotherapy dizziness.
13. Longer latency of onset of posttreatment N&V.[18]
14. 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]
15. History of 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 has been investigated.[19] These interventions 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 should be considered as treatment. Referral to a psychologist or other mental health professional with specific training and experience in working with cancer patients should be considered when ANV is identified. The earlier ANV is identified, the more likely treatment will be effective, so early screening and referral are essential. However, physicians and nurses often underestimate the incidence of chemotherapy-induced N&V.[26][Level of evidence: II]

Clearly, the most important aspect of ANV is prevention of acute and delayed N&V associated with chemotherapy. Most antiemetics have not

shown benefit for the treatment of ANV, but their use during chemotherapy may markedly decrease the incidence of ANV. The only class of medication that has shown benefit in some studies is benzodiazepines, most commonly lorazepam.[27] [Level of evidence: IV]

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# Etiology of Acute or Delayed Chemotherapy-Induced Nausea and Vomiting

## Acute Nausea and Vomiting (N&V)

The incidence of acute N&V with moderate- or high-risk chemotherapy ranges from 30% to 90%. [1-3] It can result in significant morbidity and can negatively affect quality of life. However, in recent years many new antiemetic medications and combinations have become available, dramatically decreasing the incidence and severity of this dreaded complication. Risk factors include the following:

- The emetogenic potential of the specific drug.
- The dose used.
- The treatment schedule.
- How chemotherapy agents are combined.

A drug with a low emetogenic potential given in high doses may cause a dramatic increase in the potential to induce N&V.[4] For example, standard doses of cytarabine rarely produce N&V, but high doses often do. Another influence 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.[5-9]

Other risk factors include the following:[10]

- Poor control with previous chemotherapy.
- Female gender.
- Age younger than 50 years.
- Experience with previous chemotherapy.
- History of motion sickness.
- History of morning sickness during pregnancy.
- Dehydration.
- Malnutrition.

- Recent surgery.
- Radiation therapy.

The American Society of Clinical Oncology (ASCO) provides a summary of intravenous chemotherapeutic agents and their respective risk of acute and delayed emesis.[10] For more information, see Table 2.

## Table 2. Intravenous Chemotherapeutic Agents and Their Risk of Acute and Delayed Emesis[a]

| High Risk | Moderate Ris |
| --- | --- |
| Emesis has been documented in >90% of patients. | Emesis has beer documented in 30%–90% of patients. |
| Anthracycline/cyclophosphamide combination | Alemtuzumab |
| Carmustine | Azacitidine |
| Cisplatin | Bendamustine |
| Cyclophosphamide (≥1,500 mg/m$^2$) | Carboplatin |
| Dacarbazine | Clofarabine |

[a]From Hesketh et al.[10]

| High Risk | Moderate Ris |
| --- | --- |
| Dactinomycin | Cyclophospham ($<1{,}500$ mg/m$^2$) |
| Mechlorethamine | Cytarabine (>1,( mg/m$^2$) |
| Streptozotocin | Daunorubicin |
| | Doxorubicin |
| | Epirubicin |
| | Idarubicin |

[a]From Hesketh et al.[10]

| High Risk | Moderate Ris |
| --- | --- |
| | Ifosfamide |
| | Irinotecan |
| | Irinotecan liposomal inject |
| | Oxaliplatin |
| | Romidepsin |
| | Temozolomide |
| | Thiotepa |

[a]From Hesketh et al.[10]

| High Risk | Moderate Ris |
| --- | --- |
| | Trabectedin |
| | |
| | |
| | |
| | |
| | |
| | |

[a]From Hesketh et al.[10]

| High Risk | Moderate Ris |
| --- | --- |
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| | |
| | |

[a]From Hesketh et al.[10]

ASCO also provides a summary of oral chemotherapeutic agents and their respective risk of acute and delayed emesis.[10] For more information, see Table 3.

## Table 3. Oral Chemotherapeutic Agents and Their Risk of Acute and Delayed Emesis[a]

| High Risk | Moderate Risk | Low Ris |
|---|---|---|
| Emesis has been documented in >90% of patients. | Emesis has been documented in 30%–90% of patients. | Emesis ha been document in 10%–30 of patients |
| Altretamine | Bosutinib | Afatinib |

[a]From Hesketh et al.[10]

| High Risk | Moderate Risk | Low Ris |
|---|---|---|
| Procarbazine | Cabozantinib | Alectinib |
| | Ceritinib | Axitinib |
| | Crizotinib | Capecitabi |
| | Cyclophosphamide | Cobimetin |
| | Imatinib | Dabrafenil |
| | Lenvatinib | Dasatinib |
| | Temozolomide | Etoposide |

[a]From Hesketh et al.[10]

| High Risk | Moderate Risk | Low Ris |
|---|---|---|
| | Trifluridine-tipiracil | Everolimu |
| | Vinorelbine | Fludarabir |
| | | Ibrutinib |
| | | Idelalisib |
| | | Ixazomib |
| | | Lapatinib |
| | | Lenalidom |

[a]From Hesketh et al.[10]

| High Risk | Moderate Risk | Low Ris |
|---|---|---|
| | | Olaparib |
| | | Osimertini |
| | | Nilotinib |
| | | Palbociclib |
| | | Panobinos |
| | | Pazopanib |
| | | Ponatinib |

[a]From Hesketh et al.[10]

| High Risk | Moderate Risk | Low Ris |
|---|---|---|
| | | Regorafen |
| | | Sonidegib |
| | | Sunitinib |
| | | Thalidomi |
| | | Trametinib |
| | | Vandetani |
| | | Venetocla |

[a]From Hesketh et al.[10]

| High Risk | Moderate Risk | Low Ris |
| --- | --- | --- |
| | | Vorinostat |

[a]From Hesketh et al.[10]

## 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.[1,11,12]

- 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: For more information, see the Acute Nausea and Vomiting (N&V) section.

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# Prevention and Management of Acute or Delayed Nausea and Vomiting

Several organizations—including the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the Pediatric Oncology Group of Ontario—have published antiemetic guidelines for their members. PDQ does not endorse specific guidelines, but examples can be found in the literature.[1-4]

Antiemetic agents are the most common intervention for 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.[5,6] Many antiemetics act by competitively blocking receptors for these substances, which inhibit stimulation of peripheral nerves at the CTZ and possibly at the vomiting center.

Current guidelines [2,7] recommend that prechemotherapy management of chemotherapy-induced N&V (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-hydroxytryptamine-3 (5-$HT_3$) receptor antagonist, neurokinin-1 (NK-1) receptor antagonist, and dexamethasone with or without olanzapine is recommended prechemotherapy. Aprepitant (if chosen as the NK-1 receptor antagonist prechemotherapy), olanzapine, and dexamethasone are recommended for the prevention of delayed emesis. Guidelines differ with respect to using a three- or four-drug regimen for prophylaxis for highly emetogenic chemotherapy. One guideline includes the option of omitting an NK-1 antagonist completely if dexamethasone, palonosetron, and olanzapine are used.[7]

For patients receiving moderately emetogenic chemotherapy, the combination of a 5-$HT_3$ receptor antagonist and dexamethasone is used prechemotherapy. Patients receiving carboplatin (area under the curve ≥4 mg/mL) may also receive an NK-1 receptor antagonist. Postchemotherapy, a 5-$HT_3$ receptor antagonist, dexamethasone, or both are recommended for the prevention of delayed emesis.

For regimens with low emetogenic potential, dexamethasone or a 5-$HT_3$ receptor antagonist is recommended. For regimens with minimal emetogenic risk, no prophylaxis is recommended. [2,7]

Antiemetic guidelines [2,7] have included oral 5-$HT_3$ receptor antagonists as optional therapy for the prevention of delayed emesis, but the level of evidence supporting this practice is low.[8]

Studies have strongly suggested that patients experience more acute and delayed CINV than is

perceived by practitioners.[8-10] One study suggested that patients who are highly expectant of nausea appear to experience more postchemotherapy nausea.[11] In addition, the current and new agents that have been used as prophylaxis for acute and delayed CINV have not been studied for use in established CINV. One study reported the effective use of intravenous (IV) palonosetron and dexamethasone to prevent CINV in patients receiving multiple-day chemotherapy.[12]

Table 4 summarizes prechemotherapy and postchemotherapy recommendations by emetogenic potential.

## Table 4. Antiemetic Recommendations by Emetic Risk Categories[a,b]

| Emetic Risk Category | ASCO Guidelines | MASCC Guid |
| --- | --- | --- |
| High risk (>90%) | 4-drug combination of NK-1 antagonist, 5-$HT_3$ receptor antagonist, dexamethasone, and olanzapine recommended prechemotherapy | 3-drug combination 1 antagonist, receptor antagonist, a dexamethaso recommende prechemothe |
| | Olanzapine and dexamethasone to be continued on days 2–4 | |

| Emetic Risk Category | ASCO Guidelines | MASCC Guid |
| --- | --- | --- |
| | | |
| | For anthracycline and cyclophosphamide combinations only, olanzapine to be continued on days 2–4 | |
| | Note: Depending on NK-1 antagonist, dosing may be ≥1 day | |

| Emetic Risk Category | ASCO Guidelines | MASCC Guid |
|---|---|---|
| Moderate risk (30%–90%) | Carboplatin AUC ≥4 mg/mL per min; 3-drug combination of NK-1 antagonist, 5-$HT_3$ receptor antagonist, and dexamethasone recommended prechemotherapy | For carboplat containing regimens, 3-d combination 1 antagonist, receptor antagonist, ar dexamethaso recommende prechemothe |

| Emetic Risk Category | ASCO Guidelines | MASCC Guid |
| --- | --- | --- |
| | For patients receiving chemotherapies of moderate emetic risk excluding carboplatin AUC ≥4 mg/mL per min, 2-drug combination of 5-$HT_3$ receptor antagonist and dexamethasone recommended prechemotherapy | For patients receiving chemotherap moderate em risk excluding carboplatin, 2 combination $HT_3$ receptor antagonist an dexamethaso recommende prechemothe |
| | For patients receiving cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents known to cause delayed nausea, | For patients receiving cyclophospha doxorubicin, oxaliplatin, dexamethaso may be offere days 2–3 for prevention of delayed emes |

| Emetic Risk Category | ASCO Guidelines | MASCC Guid |
| --- | --- | --- |
| | dexamethasone may be offered on days 2–3 for prevention of delayed emesis | |
| Low risk (10%–30%) | Single dose of 5-$HT_3$ receptor antagonist or dexamethasone (8 mg) recommended | Single dose o $HT_3$ receptor antagonist or dexamethaso dopamine antagonist recommende |

| Emetic Risk Category | ASCO Guidelines | MASCC Guid |
|---|---|---|
| Minimal risk (<10%) | No antiemetic administered routinely pre- or postchemotherapy | No routine prophylaxis recommende |

5-$HT_3$ = 5-hydroxytryptamine-3; ASCO = American S
AUC = area under the curve; MASCC = Multinational A
Care in Cancer; NCCN = National Comprehensive Ca
neurokinin-1.

[a]Adapted from National Comprehensive Cancer Netv
Hesketh et al.[2]

[b]Order of listed antiemetics does not reflect preferen

Most drugs with proven antiemetic activity can be categorized into one of the following groups:

- Competitive antagonists at dopaminergic ($D_2$ subtype) receptors:
    - Phenothiazines.
    - Butyrophenones (droperidol, haloperidol).
    - Substituted benzamides (metoclopramide).
- Competitive antagonists at serotonergic (5-hydroxytryptamine-3 or 5-$HT_3$ subtype) receptors.
- Substance P antagonists (NK-1 receptor antagonists).
- Corticosteroids.
- Benzodiazepines (lorazepam).
- Cannabinoids.

Although Table 5 lists all routes of administration, 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.

## Table 5. Prevention of Acute or Delayed CINV

| Drug Category | Medication | |
|---|---|---|
| Dopamine antagonists: phenothiazines | Chlorpromazine | 10–25 6h |
| | | 25–50 4h |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C extrapyramidal symptoms; IM = intramuscular; IV = i = sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | Prochlorperazine | 25 mg |
| | | 5–10 q6–8h |
| | Promethazine | 12.5– |
| Dopamine antagonists: butyrophenones | Haloperidol | 0.5–5 divide |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | | |
| | Droperidol | 1–2.5<br>6h |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| Dopamine antagonists: substituted benzamides | Metoclopramide | Preve<br>CINV:<br>x1 do<br>prech<br>then<br>then |
| | | Treat<br>CINV:<br>PO q4<br>0.5 m |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | Trimethobenzamide | 300 m |
| | | 200 m |
| Serotonin (5-$HT_3$) receptor antagonists | Dolasetron[a] | 100 m prech |
| | Granisetron | 1–2 m µg/kg IV wit chem |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C extrapyramidal symptoms; IM = intramuscular; IV = i = sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | | 3.1 m<br>trans |
| | | 10 m<br>prech |
| | Ondansetron | 0.15 m<br>min<br>prech<br>then<br>repea<br>later;<br>16 m |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | | 24 mg<br>befor<br>emet<br>day c |
| | | 8 mg<br>befor<br>emet<br>chem<br>follow<br>8 mg<br>PO q |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | Palonosetron | 0.25 r<br>mg P(<br>prech<br>day 1 |
| Substance P antagonists (NK-1 receptor antagonists) | Aprepitant | 125 m<br>prech<br>day 1<br>daily |
| | Aprepitant, emulsion | 130 m<br>prech<br>day 1 |

$5\text{-HT}_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | | |
| | Fosaprepitant | 150 m<br>prech<br>day 1 |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | Netupitant (combined with palonosetron) | Netup<br>mg/p<br>0.5 m<br>prech<br>day 1 |
| | Fosnetupitant (combined with palonosetron) | Fosne<br>mg/p<br>0.25 r<br>prech<br>day 1 |
| | Rolapitant | 180 n<br>prech<br>day 1 |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | | |
| Corticosteroids | Dexamethasone | 12–20<br>high-<br>chem<br>follow<br>1–2 ti |
| | | 8 mg<br>mode<br>risk<br>chem |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | | follov<br>mg/d |
| | Methylprednisolone | 0.5–1<br>min p<br>and 8<br>postc |
| Benzodiazepines | Alprazolam | 0.25– |
| | Lorazepam | 0.5–2 |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| Atypical antipsychotics | Olanzapine | Preve<br>acute<br>CINV<br>comb<br>5-HT$_3$<br>antag<br>dexar<br>and N<br>antag<br>PO q |
| | | Treat<br>break<br>CINV:<br>daily |

5-HT$_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| Other pharmacological agents | Dronabinol | 5 mg/<br>prech<br>follow<br>h by s<br>up to |
| | | Dose<br>increa<br>increr<br>mg/m<br>maxir<br>mg/m |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = ir
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

| Drug Category | Medication | |
|---|---|---|
| | Nabilone | 1–2 m<br>maxir<br>in 3 d |
| | *Cannabis* | No cu<br>on dc |
| | Ginger | 0.5–2<br>prech |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; C
extrapyramidal symptoms; IM = intramuscular; IV = i
= sublingual; SQ = subcutaneous.

[a]Dolasetron may be difficult to obtain from the manu

# Competitive Dopamine ($D_2$) Antagonists

## Phenothiazines

Phenothiazines act on dopaminergic receptors at the CTZ, possibly at other central nervous system (CNS) centers, and peripherally.

In selecting phenothiazines, the primary consideration is assessing differences in adverse effect profiles, which correlate with the structural classes of the drugs. Generally, aliphatic phenothiazines (e.g., chlorpromazine) produce sedation and anticholinergic effects, while piperazines (e.g., prochlorperazine) are associated with less sedation but higher incidence of extrapyramidal symptoms (EPS) such as acute dystonias, akathisia, neuroleptic malignant syndrome (uncommon), and, rarely, akinesias and dyskinesias. Marked hypotension may also result if

IV doses are administered rapidly at high doses. The concomitant use of H1 blockers, such as diphenhydramine, can often decrease the risk and severity of EPS. Phenothiazines may be of particular value in treating patients who experience delayed N&V with cisplatin regimens. [25-29][Level of evidence: I] Given their anticholinergic properties, phenothiazines are listed in the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.[30]

## Butyrophenones

Droperidol and haloperidol represent butyrophenones, another class of dopaminergic ($D_2$ 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. Results of small, uncontrolled, open-label

studies show some efficacy for haloperidol in patients receiving palliative care.[31,32] Both agents may produce EPS, akathisia, hypotension, and sedation.

## Substituted benzamides

Metoclopramide is a substituted benzamide, which, before serotonin (5-$HT_3$) receptor antagonists were introduced, was considered the most effective antiemetic agent against highly emetogenic chemotherapy. Although metoclopramide is a competitive antagonist at dopaminergic ($D_2$) receptors, it is most effective against acute vomiting when given IV at high doses, probably because it is a weak competitive antagonist (relative to other serotonin antagonists) at 5-$HT_3$ 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. 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 that of multiple intermittent dosing schedules.[33-35]

Metoclopramide is associated with akathisia and dystonic EPS. Akathisia is seen more frequently in patients older than 30 years, and dystonic EPS are seen more commonly in patients younger than 30 years. Diphenhydramine, benztropine mesylate, and trihexyphenidyl are commonly used prophylactically or therapeutically to pharmacologically antagonize EPS.[36] While cogwheeling rigidity, acute dystonia, and tremor are responsive to anticholinergic medications, akathisia is best treated by lowering the metoclopramide dose, changing to a different agent, or adding a benzodiazepine.

Trimethobenzamide is believed to act centrally on the CTZ by blocking emetic impulses. It has been studied in a limited number of oncology patients experiencing nausea from various chemotherapy

regimens. Compared with placebo, trimethobenzamide, 200 mg IM every 6 hours for 2 days, significantly reduced episodes of N&V.[17]

## 5-$HT_3$ Receptor Antagonists

Four serotonin receptor antagonists—ondansetron, granisetron, dolasetron, and palonosetron—are available in the United States. 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.[37-39] The 5-$HT_3$ receptor antagonists may also block serotonin stimulation at the CTZ and other CNS structures. Major side effects of this class of medications include mild headache and constipation. Multiple studies have shown that the 5-$HT_3$ receptor antagonists are most effective when given in conjunction with steroids.

### Comparison of agents

Studies suggest that there are no major differences in efficacy or toxicity of the three first-generation 5-$HT_3$ 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.[40,41]; [42][Level of evidence: I] These agents have been shown to be effective in the first 24 hours postchemotherapy (acute phase), but not on days 2 to 5 postchemotherapy (delayed phase).

Palonosetron, the second-generation 5-$HT_3$ receptor antagonist, has been approved for acute emesis with highly and moderately emetogenic chemotherapy and for delayed emesis in patients receiving moderately emetogenic chemotherapy. [43]; [44][Level of evidence: I]

Despite the use of both first- and second-generation 5-$HT_3$ receptor antagonists, the control of acute CINV, especially delayed N&V, is suboptimal. There is considerable opportunity for improvement with either the addition or

substitution of new agents in current regimens. [8,45-47]

## Ondansetron

Several studies have demonstrated that ondansetron produces an antiemetic response that is equal or superior to that of high doses of metoclopramide, but with an improved toxicity profile, compared with that of dopaminergic antagonist agents.[48-51][Level of evidence: I]; [52,53] A randomized trial of ondansetron, 8 mg and 32 mg, given prophylactically to patients receiving cisplatin found no difference between the doses.[54] A single-center, retrospective chart review has reported ondansetron-loading doses of 16 mg/$m^2$ IV (maximum, 24 mg) to be safe in infants, children, and adolescents.[55] However, data reported to the U.S. Food and Drug Administration (FDA) raise concerns about QT prolongation and potentially fatal arrhythmias with a single 32-mg IV dose. Current drug labeling calls for a maximum single 16-mg IV dose.[56]

Currently, 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. Ondansetron clearance is diminished in patients with severe hepatic insufficiency; these patients receive a single injectable or oral dose no higher than 8 mg. There is currently no information 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.[57]

The major adverse effects of ondansetron include the following:[58]

- Headache (which can be treated with mild analgesics).

- Constipation.
- 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.[59] Rare electrocardiogram changes in the form of QTc prolongation may occur. In addition, a few case reports have implicated ondansetron in causing EPS. However, it is not clear whether the events described were in fact EPS. In other reports, the evidence is confounded by concurrent use of other agents that are known to produce EPS. 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 N&V.[60] Randomized, double-blind, placebo-controlled trials support the addition of aprepitant, an NK-1 receptor antagonist, for additional mitigation of N&V.[61,62][Level of evidence: I]

## Granisetron

Granisetron has shown efficacy in preventing and controlling N&V at a broad range of doses. In the United States, granisetron injection, extended-release 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 is equally efficacious and equally safe.[60-63][Level of evidence: I]

The subcutaneous extended-release formulation of granisetron was compared with palonosetron to prevent CINV for patients receiving moderately or highly emetogenic chemotherapy in a randomized, double-blind noninferiority phase III trial.[64] Patients were randomly assigned to receive IV palonosetron, 0.25 mg; or subcutaneous granisetron, 5 mg or 10 mg. Patients who received palonosetron in cycle 1 were then randomly assigned to receive granisetron in cycles 2 through 4. Both subcutaneous doses of granisetron were noninferior to palonosetron in cycle 1 of moderately emetogenic chemotherapy (74.8% and 76.9% for granisetron 5 mg and 10 mg, respectively, vs. 75.0% for palonosetron) and highly emetogenic chemotherapy (77.7% and 81.3% for granisetron 5 mg and 10 mg, respectively, vs. 80.7% for palonosetron). Subcutaneous granisetron was not superior to palonosetron in the prevention of delayed CINV after highly emetogenic chemotherapy.

Currently, granisetron is approved for use without dosage modification in patients older than 2 years, including elderly patients and patients with hepatic and renal insufficiency.

## Dolasetron

Oral formulations of dolasetron are indicated for the prevention of N&V associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses. However, the drug may be difficult to obtain from the manufacturer. Oral dolasetron may be dosed as 100 mg within 1 hour before chemotherapy. Dolasetron was given IV or orally at 1.8 mg/kg as a single dose approximately 30 minutes before chemotherapy. However, injection formulations are no longer approved for CINV because of the risk of QTc interval prolongation.[65]

The effectiveness of oral dolasetron in the prevention of CINV has been proven in a large randomized, double-blind, comparative trial of 399

patients.[66][Level of evidence: I] Oral dolasetron was administered in the range of 25 to 200 mg 1 hour before 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. Rates of complete response (CR), defined as no emetic episodes and no use of escape antiemetic medications, improved with increasing doses of dolasetron. Both dolasetron 200 mg and ondansetron had significantly higher CR rates than did dolasetron 25 or 50 mg.

## Palonosetron

Palonosetron is a 5-$HT_3$ receptor antagonist (second generation) that has antiemetic activity at both central and GI sites. Palonosetron is FDA approved 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. Compared with the older 5-$HT_3$ receptor antagonists, palonosetron has a higher binding affinity to the 5-$HT_3$ 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.[67][Level of evidence: I] A dose-finding study demonstrated that the effective dose was 0.25 mg or higher.[68-72]

In two large studies of patients receiving moderately emetogenic chemotherapy, CR (no emesis, no rescue) was significantly improved in the acute and delayed periods for patients who received 0.25 mg of palonosetron alone, compared with either ondansetron or dolasetron alone.[43]; [44][Level of evidence: I] Dexamethasone was not given with the 5-$HT_3$ receptor antagonists in these studies, and it is not yet known whether the differences in CR would persist if it were used.

In another study,[73][Level of evidence: I] 650 patients receiving highly emetogenic chemotherapy (cisplatin ≥60 mg/m$^2$) 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 study [74] reported that the CR rates for both acute and delayed CINV were maintained with single IV doses of palonosetron without concomitant corticosteroids.

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

Substance P, found in the vagal afferent neurons in the nucleus tractus solitarius, the abdominal

vagus, and the area postrema, induces vomiting. NK-1 receptor antagonists, including aprepitant, fosaprepitant, netupitant, fosnetupitant, and rolapitant, block substance P from binding to the NK-1 receptor. In combination with a 5-$HT_3$ receptor antagonist and a corticosteroid, NK-1 receptor antagonists are indicated for the prevention of acute and delayed N&V associated with initial and repeat courses of highly and moderately emetogenic chemotherapy. There have been no randomized trials comparing the individual NK-1 receptor antagonists. All are considered effective at their FDA-approved doses.

## Aprepitant and fosaprepitant

Clinical trials [75-78] demonstrated that the addition of aprepitant to a 5-$HT_3$ receptor antagonist plus dexamethasone before cisplatin chemotherapy improved the control of acute emesis, compared with a 5-$HT_3$ receptor antagonist plus dexamethasone. This regimen also improved the control of delayed emesis, compared

with placebo. In two randomized, double-blind, parallel, controlled studies, patients received cisplatin (≥70 mg/m$^2$) and were randomly assigned to receive either (1) standard therapy with ondansetron and dexamethasone prechemotherapy and dexamethasone on days 2 to 4 postchemotherapy or (2) standard therapy plus aprepitant prechemotherapy on days 2 and 3. [79,80][Level of evidence: I] The CR (no emesis, no rescue) of the aprepitant group in both studies was significantly higher in both the acute and the delayed periods. An additional study confirmed the efficacy of aprepitant in the delayed period, when it was compared with ondansetron.[81] [Level of evidence: I] Finally, aprepitant has been shown to be efficacious in preventing N&V in breast cancer patients receiving highly emetogenic chemotherapy with cyclophosphamide and doxorubicin.[82]

The benefit of aprepitant has also been demonstrated outside of highly emetogenic

chemotherapy. The addition of aprepitant to ondansetron and dexamethasone before moderately emetogenic chemotherapy versus ondansetron and dexamethasone alone resulted in improved CINV outcomes.[83-85] An alternative dosing strategy was evaluated in a randomized, double-blind, placebo-controlled, phase III crossover study in patients receiving 5-day cisplatin combination chemotherapy for germ cell tumors.[86] In addition to standard antiemetic therapy, patients received aprepitant 125 mg on day 3, followed by aprepitant 80 mg on days 4 through 7. There was a significant improvement in CINV CR with the three-drug regimen.

Fosaprepitant dimeglumine, a water-soluble, phosphorylated analog of aprepitant, is rapidly converted to aprepitant after IV administration.[87] Fosaprepitant is approved as a single dose of 150 mg before chemotherapy on day 1, as an alternative to the 3-day oral aprepitant 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.[87] Fosaprepitant is formulated with polysorbate 80, a solubilizing agent, which can cause rare but serious hypersensitivity reactions.[88,89] Aprepitant is also available in a parenteral emulsion form, which has a reduced risk of thrombophlebitis and hypersensitivity reactions.[90]

## Netupitant and fosnetupitant

Netupitant is a competitive antagonist to the NK-1 receptor that is marketed as either an oral fixed-combination product containing 300 mg of netupitant and 0.5 mg of palonosetron (NEPA) or an IV fixed-combination product containing 235 mg of fosnetupitant and 0.25 mg of palonosetron. Of note, the IV formulation of NEPA does not contain the surfactant polysorbate 80 or any other allergenic excipients and could be considered for

patients who have had hypersensitivity reactions to fosaprepitant.[91][Level of evidence: I] It is given with dexamethasone before chemotherapy to prevent both acute and delayed CINV. This drug combination has been used successfully for prevention of CINV in a single cycle of both highly and moderately emetogenic chemotherapy regimens.[92,93]

The antiemetic benefit of NEPA was demonstrated throughout multiple cycles of chemotherapy in a randomized, double-blind, controlled trial.[94] [Level of evidence: I] Patients starting combination anthracycline/cyclophosphamide regimens were randomly assigned to receive oral fixed-dose NEPA with 12 mg of dexamethasone or 0.5 mg of oral palonosetron with 20 mg of dexamethasone. The percentage of patients with a CR was significantly greater for NEPA than for oral palonosetron for cycles 1 to 4. The most common treatment-related side effects, headache and constipation, were similar between the two arms.

A Japanese study compared single-agent fosnetupitant to fosaprepitant combined with palonosetron and dexamethasone in patients receiving highly emetic chemotherapy.[95][Level of evidence: I] Fosnetupitant was found to be noninferior to the fosaprepitant regimen. Additionally, fosnetupitant had an improved safety profile with fewer injection site reactions (11% vs. 20.6%, $P < .001$). Single-agent fosnetupitant is not currently FDA approved in the United States.

Similarly, NEPA has been compared with granisetron and aprepitant in patients receiving highly emetogenic chemotherapy. In a phase III, randomized, double-blind study, a single dose of NEPA was shown to be noninferior to a 3-day regimen of granisetron and aprepitant. Additionally, significantly more patients did not need rescue medications when they received NEPA (96.6%), compared with those who received granisetron plus aprepitant (93.5%). Toxicities

were similar between treatment arms.[96][Level of evidence: I]

### Rolapitant

Rolapitant is an oral competitive NK-1 receptor inhibitor. It is approved for the prevention of delayed N&V associated with highly and moderately emetogenic chemotherapy. In addition to granisetron and dexamethasone, rolapitant significantly increases CINV CR versus standard therapy plus placebo for patients receiving both highly and moderately emetogenic chemotherapy. Unlike other drugs in its class, rolapitant has no effect on cytochrome P450 3A4 enzymes; therefore, no dose adjustment for dexamethasone is required.[97-99] The IV formulation has been associated with hypersensitivity reactions, including anaphylaxis, which have limited its use.[100]

## Corticosteroids

Steroids are commonly used in combination with other antiemetics. 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, producing a subjective sense of well-being or euphoria (although they also can cause depression and anxiety). Steroids are sometimes used as single agents against mildly emetogenic chemotherapy but are more often used in antiemetic drug combinations.[101,102][Level of evidence: I];[103]

Steroids are given orally or intravenously before chemotherapy and may be repeated. Dosages and administration schedules are selected empirically. Dexamethasone is often the treatment of choice for N&V in patients receiving radiation to the brain, as it also reduces cerebral edema. It is administered orally or intravenously in the dose range of 8 mg to 40 mg (pediatric dose, 0.25–0.5

mg/kg).[104,105] Methylprednisolone is also administered orally or intravenously at doses and schedules that vary from 40 mg to 500 mg every 6 to 12 hours for up to 20 doses.[102,106]

Dexamethasone is also used orally for delayed N&V. Long-term corticosteroid use, however, is inappropriate and may cause substantial morbidity, including the following:[107-109]

- 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).[110] As previously shown with metoclopramide, numerous studies have demonstrated that dexamethasone potentiates the antiemetic properties of 5-$HT_3$ receptor–blocking agents.[107,111] If administered intravenously, dexamethasone may be given over 10 to 15 minutes because rapid administration may cause sensations of generalized warmth, pharyngeal tingling or burning, or acute transient perineal and/or rectal pain.[112-115]

## Benzodiazepines

Benzodiazepines, such as lorazepam and alprazolam, are valuable adjuncts in the prevention and treatment of anxiety and the symptoms of anticipatory N&V associated with chemotherapy, especially with the highly emetogenic regimens given to children.[107-109] Benzodiazepines have not demonstrated intrinsic antiemetic activity as single agents, so they are adjuncts to other antiemetic agents in antiemetic prophylaxis and treatment.[116] Benzodiazepines presumably act on higher CNS structures, the brainstem, and spinal cord, and they produce anxiolytic, sedative, and anterograde amnesic effects. In addition, these drugs markedly decrease the severity of EPS, especially akathisia, associated with dopaminergic receptor antagonist antiemetics.

The adverse effects of lorazepam include sedation, perceptual and vision disturbances, anterograde amnesia, confusion, ataxia, and depressed mental

acuity.[117];[118][Level of evidence: I];[119,120] Alprazolam has been shown to be effective when given in combination with metoclopramide and methylprednisolone.[19]

## Olanzapine

Olanzapine is an antipsychotic in the thienobenzodiazepine drug class that blocks multiple neurotransmitters: dopamine at $D_1$, $D_2$, $D_3$, and $D_4$ brain receptors; serotonin at 5-$HT_{2a}$, 5-$HT_{2c}$, 5-$HT_3$, and 5-$HT_6$ receptors; catecholamines at alpha-1 adrenergic receptors; acetylcholine at muscarinic receptors; and histamine at $H_1$ receptors.[121] Common side effects include the following:[122,123]

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

- Dizziness.

Olanzapine's activity at multiple receptors, particularly at the $D_2$ and 5-$HT_3$ receptors that appear to be involved in N&V, suggests that it may have significant antiemetic properties.[124][Level of evidence: II] Subsequent studies have shown its effectiveness as a CINV antiemetic.[125,126][Level of evidence: II] A large study [127][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.

A randomized, double-blind, phase III trial evaluated olanzapine versus placebo in addition to standard antiemetics for the prevention of CINV associated with highly emetogenic chemotherapy.[20][Level of evidence: I] Chemotherapy-naïve patients receiving either (1) cisplatin at least 70 $mg/m^2$ of body surface area (BSA) with or without

additional agents or (2) doxorubicin 60 mg/$m^2$ of BSA with cyclophosphamide 600 mg/$m^2$ of BSA were randomly assigned to receive olanzapine 10 mg orally on days 1 through 4 or matching placebo with guideline-directed antiemetics. The antiemetic regimen included an NK-1 antagonist (fosaprepitant or aprepitant), 5-$HT_3$ receptor antagonist (palonosetron, granisetron, or ondansetron), and dexamethasone 12 mg on day 1, followed by 8 mg orally daily on days 2 through 4. Patients were stratified by sex, chemotherapy regimen, and the specific 5-$HT_3$ receptor antagonist chosen. The primary endpoint, no nausea, was defined as a score of 0 on the visual analogue scale of 0 to 10 and assessed at three time points postchemotherapy:

- Early, 0 to 24 hours.
- Later, 25 to 120 hours.
- Overall, 0 to 120 hours.

The percentage of patients experiencing no nausea was significantly higher in the olanzapine group than in the placebo group at the early (74% vs. 45%; *P* = .002), later (42% vs. 25%; *P* = .002), and overall time points (37% vs. 22%; *P* = .002). CR rate and freedom from clinically significant nausea (a score lower than 3 on the visual analog scale of 0–10) were also significantly improved with the addition of olanzapine at all time points. Patients receiving olanzapine reported increased sedation from baseline on day 2, which resolved on days 3 through 5. Based on these data and additional clinical trials, olanzapine appears to be safe and effective in controlling acute and delayed CINV in patients receiving highly emetogenic and moderately emetogenic chemotherapy.[128,129]

## Other Pharmacological Agents

### *Cannabis*

The plant *Cannabis* contains more than 60 different types of cannabinoids, or components

that have physiological activity. The most popular, and perhaps the most psychoactive, is delta-9-tetrahydrocannabinol (delta-9-THC).[130] There are two FDA-approved *Cannabis* products for CINV:

- Dronabinol (a synthetic delta-9-THC), as prophylaxis for CINV, 5 mg/m$^2$ 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, for CINV that has failed to respond to other antiemetics, 1 to 2 mg orally twice a day.

With respect to CINV, *Cannabis* products probably target cannabinoid-1 and cannabinoid-2 receptors, which are in the CNS.[131]

Much of the research on agents in this class, conducted in the late 1970s and 1980s, compared nabilone, dronabinol, or levonantradol to older antiemetic agents that targeted the dopamine

receptor, such as prochlorperazine (Compazine) and metoclopramide (Reglan).[132-136] This group of studies demonstrated that cannabinoids were as effective as dopaminergic antiemetics for moderately emetogenic chemotherapy or were more effective than placebo.[130] Side effects included euphoria, dizziness, dysphoria, hallucinations, and hypotension.[130] Despite earlier reports of efficacy, in at least one study, patients did not significantly prefer nabilone because of the side effects.[132]

Since the 1990s, research in N&V has elucidated newer and more physiological targets, namely 5-$HT_3$ and NK-1 receptors. Subsequently, 5-$HT_3$ and NK-1 receptor antagonists have become standard prophylactic therapy for CINV. Few studies have investigated the role of *Cannabis* extract and cannabinoids with these newer agents, so only limited conclusions can be drawn. In published trials, however, *Cannabis* extract and cannabinoids have not demonstrated more efficacy than 5-$HT_3$

receptor antagonists, and synergistic or additive effects have not been fully investigated.[137,138]

In summary, *Cannabis* and cannabinoids' role in the prevention and treatment of CINV is not fully known. Discussions with patients about their use may include responses to available agents, known side effects of *Cannabis*, and an assessment of the risks versus benefits of this therapy.[139] For more information, see Cannabis and Cannabinoids.

## Ginger

There are conflicting data on the efficacy of ginger for prophylaxis of CINV. 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). Patients experienced some level of nausea (as measured on an 11-point scale) caused by their current chemotherapy regimen, despite standard prophylaxis with a 5-$HT_3$ receptor

antagonist. Patients began taking ginger or placebo capsules 3 days before each chemotherapy treatment and continued them for 6 days. For average nausea severity, 0.5 g of ginger was significantly better than placebo. For maximum nausea severity, both 0.5 g and 1 g were significantly better than placebo. Effects for delayed N&V were not significant. This trial did not control for emetogenicity of the chemotherapy regimens. Adverse events were infrequent and were not severe.[23]

Conversely, data on ginger used to prevent N&V have not been as promising. A randomized, double-blind, placebo-controlled study evaluated the use of ginger 160 mg per day in patients receiving high-dose cisplatin (>50 mg/$m^2$). Patients (N = 251) were assigned to receive either ginger or placebo. The incidence of delayed nausea, intercycle nausea, and anticipatory nausea did not differ between the two treatment arms.[140]

## Multiday Chemotherapy

Regimens that include chemotherapy doses on multiple sequential days (multiday chemotherapy) present a unique challenge to preventing CINV because after the first dose of chemotherapy, nausea may be both acute and delayed. Although there is no standard antiemetic regimen for multiday chemotherapy, a corticosteroid and a 5-$HT_3$ receptor antagonist should be given with each day of highly and moderately emetogenic chemotherapy.[7,141] Evidence demonstrates benefit for the addition of an NK-1 antagonist to highly and moderately emetogenic multiday chemotherapy.[2,7,13,141] The choice of antiemetic drugs and their schedule should be matched to the emetogenicity of the individual chemotherapy agents and their sequence. In addition, the length of delayed nausea varies and will depend on the emetogenicity of the last day's chemotherapy.

Dexamethasone is scheduled on each day of a multiday chemotherapy regimen and for 2 to 3 days after if there is a risk of delayed nausea. Additional dexamethasone is not necessary if the chemotherapy regimen contains a corticosteroid. It is not known whether dexamethasone 20 mg given each day of a 5-day cisplatin regimen provides additional antiemetic benefit, and it may add toxicity.[13,142] Therefore, an alternative dexamethasone schedule (20 mg on days 1 and 2, followed by 8 mg twice daily on days 6 and 7, and 4 mg twice daily on day 8), based on the timing of CINV and to reduce the total steroid dose, has been studied in patients receiving 5-day cisplatin regimens.[12,13]

Standard antiemetic prophylaxis includes a 5-$HT_3$ receptor antagonist given before the first chemotherapy dose each day of a multiday chemotherapy regimen.[2,7,13,141] No 5-$HT_3$ receptor antagonist is favored over other agents in the class for multiday chemotherapy.

Palonosetron is a 5-$HT_3$ receptor antagonist with a longer half-life and higher receptor-binding affinity than other members in its class, allowing it to be given less frequently.[71] A prospective, uncontrolled trial demonstrated that palonosetron, as a single IV dose with dexamethasone 20 mg before two 3-day chemotherapy regimens, resulted in an 80% CR.[143] Palonosetron was also studied with dexamethasone as prophylaxis for a 5-day cisplatin-based regimen for germ cell tumors.[12] When palonosetron plus dexamethasone was given on days 1, 3, and 5, 51% of patients experienced no emesis on days 1 to 5, and 83% experienced no emesis on days 6 to 9.

Alternative methods of 5-$HT_3$ receptor antagonist delivery have been studied. Granisetron as a 7-day continuous transdermal patch was compared with daily oral granisetron in patients receiving multiday chemotherapy in a double-blind, phase III, noninferiority study.[63] The patch

demonstrated complete control in 60% of patients, while the oral formulation did so in 65% of patients, achieving noninferiority.

The NK-1 antagonist aprepitant and its IV formulation, fosaprepitant, have been studied with multiday chemotherapy in dosing schedules that differ from their FDA-approved schedules. A nonrandomized trial evaluated the use of aprepitant, granisetron, and dexamethasone for CINV prophylaxis with 3- and 5-day highly and moderately emetogenic chemotherapy.[144] Aprepitant was given at 125 mg orally before the first dose of chemotherapy, then 80 mg orally on each day of chemotherapy and for 2 following days (total, 5–7 days). CR was seen in 57.9% and 72.5% of patients receiving highly and moderately emetogenic chemotherapy, respectively. Similarly promising results were found in a subsequent single-arm trial looking at a 7-day oral aprepitant regimen with dexamethasone and a 5-$HT_3$

receptor antagonist for 5-day cisplatin-based chemotherapy.[145]

A randomized, double-blind, placebo-controlled crossover trial of aprepitant, a 5-$HT_3$ receptor antagonist, and dexamethasone was conducted in patients receiving 5-day cisplatin-based chemotherapy for germ cell tumors.[86] Oral aprepitant 125 mg was given on day 3, followed by oral aprepitant 80 mg daily on days 4 to 7. More patients achieved CR with aprepitant than with placebo, 42% versus 13% ($P < .001$). IV fosaprepitant 150 mg given on days 3 and 5 was studied in a small phase II trial evaluating its use with a 5-$HT_3$ receptor antagonist and dexamethasone in 5-day cisplatin-based chemotherapy.[146] Preliminary results showed a CR rate of 28.1%, lower than results of the oral aprepitant trial conducted by the same institution.

## High-Dose Chemotherapy With Stem Cell Transplant

Prevention of emesis during high doses of chemotherapy, with or without total-body irradiation, continues to be a challenging area of patient care.[147] Current guidelines primarily address single-day therapies. In addition, while emesis prevention for the multiple days of chemotherapy or radiation therapy used in this setting is based on single-day experiences, additional research is needed to improve symptom control for these patients.[147] This has led to the addition of NK-1 antagonists to the daily dosing of a serotonin antagonist plus dexamethasone.[147-149] Additional evidence is needed to determine optimal combinations, as CR rates range as low as 30%.[149] Also, experience has primarily been with aprepitant. The newer NK-1 antagonists may offer additional benefit.

Overall, these antiemetic combinations are well tolerated, with most side effects involving the dexamethasone component. In addition, while drug interactions were originally a concern, they

do not appear to be clinically significant.[150] Also, emesis is controlled to a much greater extent than is nausea, which continues to be challenging for many patients.[147,151] Finally, a randomized phase III trial studied the use of aprepitant, granisetron, and dexamethasone for the prevention of CINV in multiple myeloma patients receiving high-dose melphalan with autologous stem cell transplant. A statistically positive benefit, without an increase in side effects, was seen in patients who received the three-drug regimen.[148]

## Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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## Nonpharmacological Management of Nausea and

# Vomiting

Nonpharmacological strategies are also used to manage nausea and vomiting (N&V). These strategies include the following:

- Dietary alterations. For more information, see the Behavioral strategies for symptom management section in Nutrition in Cancer Care.
- Hypnosis.
- Acupuncture. For more information, see Acupuncture.
- 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 N&V (ANV). They are the recommended treatments for this classically conditioned response. For more information, see the Treatment of ANV section.

# Radiation-Induced Nausea and Vomiting

Radiation therapy (RT) is an important cause of nausea and vomiting (N&V) in patients with cancer. Observational studies suggest that some degree of N&V occurs in 80% of patients undergoing RT.[1] Risk factors for developing N&V are known. Radiation-induced N&V (RINV) worsen quality of life, leading to treatment delays and cancelled appointments and compromising cancer control.[2,3]

## Epidemiology

Two large prospective observational studies provide information on the frequency of RINV and antiemetic measures. The Italian Group for Antiemetic Research in Radiotherapy analyzed the incidence of RINV in 1,020 patients receiving various kinds of RT.[4] Overall, 28% of patients reported nausea, vomiting, or both. The median time to the first episode of vomiting was 3 days. Antiemetic drugs were administered to 17% of the patients, including 12% treated prophylactically and 5% given rescue therapy. In a second cohort of 368 patients receiving RT, the overall incidence rate for nausea was 39% and for vomiting, 7%.[5] Nausea was more frequent in patients receiving RT to the lower abdomen or pelvis (66%), compared with patients receiving RT to the head-and-neck area (48%). Antiemetics during RT are underprescribed.[6]

## Pathophysiology of RINV

The pathophysiology of RINV is incompletely understood. Serotonin, substance P, and

dopamine are neurotransmitters involved in radiation-induced emesis.[7] RINV bears a close similarity to chemotherapy-induced N&V (CINV). The effectiveness of serotonin antagonists in RINV supports a role for serotonin in radiation-induced emesis.[7] Substance P antagonists have not been used in RINV as extensively as in CINV. Preclinical work suggests a role for substance P in RINV.[8] Substance P antagonists are only beginning to be studied for RINV. Substance P may play a role in prolonged N&V after the administration of RT.

## Risk Stratification

The incidence and severity of RINV are determined by:

- Radiation site.
- Volume.
- Fractionation schedule.
- Single and total dose.

The most important factor appears to be the radiation field. The risk of N&V for a patient being treated with RT depends on multiple other factors in addition to the emetogenicity of the specific RT regimen. Patient-specific factors include the following:[3]

- Simultaneous administration of chemotherapy.
- Age.
- Gender.
- Alcohol consumption.
- Anxiety.
- Previous experience of RINV or CINV.

## Prevention and Treatment of RINV

The body of literature describing treatments for RINV is much smaller than for CINV.[9] Most of the studies were for patients with moderate- to high-risk features for RINV.

## Antiemetic therapy: Prevention and treatment of N&V

Several studies show the superiority of serotonin antagonists for the prophylaxis of RINV.[10-15] For example, ondansetron and dolasetron have shown superiority over placebo or metoclopramide. Dosing of the serotonin antagonists has been single-dose pretreatment or for consecutive days (up to 5–7 days total). Most studies have been conducted in patients at moderate to high risk of RINV.

Recommended dosing is ondansetron 8 mg, regardless of schedule given.[3] Granisetron dosing is 2 mg orally per day.[3] A recent meta-analysis covering nine clinical trials showed differing rates of control when emesis versus nausea is considered. Compared with placebo, fewer patients had residual emesis (40% vs. 57%; relative risk [RR], 0.7), and fewer patients required rescue medication (6.5% vs. 36%; RR, 0.18).[16] The control of nausea seems to be more difficult. Most

patients developed RT-induced nausea despite treatment (70% vs. 83% with placebo; RR, 0.84).[17] In summary, these trials show that patients receiving upper-abdomen irradiation are more likely to control RINV with 5-hydroxytryptamine-3 (5-$HT_3$) receptor antagonists than metoclopramide, phenothiazines, or placebo.[10-15]

The adverse effects of 5-$HT_3$ receptor antagonists are generally mild, consisting mainly of headache, constipation, and asthenia.[18] Randomized trials in RINV have examined the use of different 5-$HT_3$ receptor antagonists, but there are no data comparing them and no consensus on optimal dosing for RINV.[19] A systematic review of 25 randomized and nonrandomized trials revealed that 5-$HT_3$ receptor antagonists were most commonly administered for the entire duration of a course of RT. Optimal duration and timing of 5-$HT_3$ use before, during, and after RT administration needs to be determined.[20] With regard to palonosetron, the appropriate dosing

and frequency in the RINV setting are still unclear, with once-weekly dosing possible when the drug is combined with other agents.[21]

## Corticosteroids

Corticosteroids are an attractive therapeutic antiemetic option because of their widespread availability and low cost. For short-term use, the side effects are few and do not outweigh the benefit of these agents. One randomized trial showed that dexamethasone was significantly more effective than placebo in patients receiving RT to the upper abdomen.[22] Combining corticosteroids with a 5-$HT_3$ receptor antagonist was assessed in a well-designed randomized trial, in which a 5-day course of dexamethasone plus ondansetron was compared with ondansetron plus placebo in 211 patients who received RT to the upper abdomen.[23] During the first 5 days, there was a statistically nonsignificant trend toward complete control of nausea (50% vs. 38% with placebo) and vomiting (78% vs. 71%), which

was the primary objective of the trial. The effects of dexamethasone extended beyond the initial 5-day period, and significantly more patients had complete control of emesis over the entire course of RT (23% vs. 12% with placebo), a secondary objective of the trial. The addition of dexamethasone has a modest effect on RINV and is potentially a useful addition to a 5-$HT_3$ receptor antagonist in this setting.[23]

## Neurokinin-1 (NK-1) receptor antagonists

NK-1 receptor antagonists have an established role in the management of CINV; however, no studies have evaluated their impact solely on the risk of RINV. Although preclinical data indicate that RINV is mediated in part by substance P,[8] recommendation of these agents is premature, and NK-1 receptor antagonists are not included in the antiemetic guidelines for RINV.[3] A phase III, randomized, placebo-controlled trial compared an NK-1 receptor antagonist, fosaprepitant, combined with palonosetron and dexamethasone, with

palonosetron and dexamethasone alone in the prevention of N&V in patients who received concomitant RT and cisplatin.[21][Level of evidence: I] Patients received fractionated radiation therapy with weekly cisplatin, 40 mg/m$^2$. All patients received dexamethasone on the same schedule: 16 mg on day 1, 8 mg twice a day on day 2, 4 mg twice a day on day 3, and 4 mg once on day 4. More patients who received the three-drug regimen reached a complete response (65.7% for the fosaprepitant group vs. 48.7% for the placebo group).

Fosaprepitant has also been compared with olanzapine for the prevention of N&V in patients with head and neck or esophageal cancer who received RT concurrently with highly emetogenic chemotherapy.[24] For those who received olanzapine, palonosetron, and dexamethasone (OPD), dosing was as follows: dexamethasone 20 mg and palonosetron 0.25 mg intravenously (IV) on day 1 of chemotherapy, and olanzapine 10 mg

on days 1 to 4 of chemotherapy. For those who received fosaprepitant, palonosetron, and dexamethasone (FPD), dosing was as follows: dexamethasone 12 mg, palonosetron 0.25 mg IV, and fosaprepitant 150 mg IV on day 1 of chemotherapy, followed by dexamethasone 4 mg bid on days 2 to 3 of chemotherapy. Complete response was similar between the two groups, with a rate of 76% overall in the OPD arm and 74% overall in the FPD arm. This suggests that NK-1 receptor antagonists may play a role in patients receiving highly emetogenic chemotherapy.[24]

### Other agents

Older, less-specific antiemetic drugs, such as prochlorperazine, metoclopramide, and cannabinoids, have shown limited efficacy in the prevention or treatment of RINV, although they may have a role in treating patients with milder symptoms and as rescue agents.[25]

## Duration of Prophylaxis

The appropriate duration of antiemetic prophylaxis for patients receiving fractionated RT is not clear. There have been no randomized trials using 5-$HT_3$ receptor antagonists that compared a 5-day course of treatment with a more protracted course.[7] A systematic review that included 25 randomized and nonrandomized trials revealed that 5-$HT_3$ receptor antagonists were most commonly administered for the entire duration of a course of RT.[20]

## Rescue Therapy

Studies suggest the benefit of 5-$HT_3$ receptor antagonists once nausea or vomiting occurs, but there are no trials specifically in this setting.[26] The emerging role of olanzapine in breakthrough emesis in patients with CINV has not been studied in RINV.[27]

## Guidelines and Patient Management

For patients at high risk of developing RINV, prophylaxis with a 5-$HT_3$ receptor antagonist is

recommended in the clinical practice guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) and American Society of Clinical Oncology (ASCO). Based on results from patients receiving highly emetogenic chemotherapy, the addition of dexamethasone to the 5-$HT_3$ receptor antagonist is suggested. The antiemetic clinical practice guidelines from both MASCC and ASCO also recommend that patients receiving moderately emetogenic RT be given with a 5-$HT_3$ receptor antagonist, with or without a short course of dexamethasone.[7] There are no fully published comparative clinical trials on the use of NK-1 receptor antagonists in preventing RINV; therefore, its use cannot be recommended.

Antiemetic dosing suggestions for the prevention of RINV are summarized in Table 6.

## Table 6. Antiemetic Dosing for Radiation Therapy[a]

| Drug Category | Antiemetic | Dose |
|---|---|---|
| Serotonin (5-$HT_3$) receptor antagonists | Granisetron | 2 mg PO daily |
| | Ondansetron | 8 mg PO or 0.15 mg/kg IV daily |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; IV
prn = as needed; RT = radiation therapy; TBI = total-b
day.

[a]Adapted from Roila et al.[3] and Hesketh et al.[28]

| Drug Category | Antiemetic | Dose |
|---|---|---|
| | Palonosetron | 0.25 mg IV or 0.5 mg PO |
| | Dolasetron | 100 mg PO only |
| Corticosteroids | Dexamethasone | 4 mg PO or IV |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; IV
prn = as needed; RT = radiation therapy; TBI = total-b
day.

[a]Adapted from Roila et al.[3] and Hesketh et al.[28]

| Drug Category | Antiemetic | Dose |
|---|---|---|
| Dopamine receptor antagonists | Metoclopramide | 20 mg PO |
| | Prochlorperazine | 10 mg PO or IV |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; IV
prn = as needed; RT = radiation therapy; TBI = total-b
day.

[a]Adapted from Roila et al.[3] and Hesketh et al.[28]

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## Pediatric Chemotherapy-Induced Acute Nausea and Vomiting

# Pediatric Guidelines for Acute Nausea and Vomiting (N&V)

Chemotherapy-induced N&V (CINV) is an important problem in the pediatric population. As in adults, nausea in children is more of a problem than vomiting. Parents of children who received active antineoplastic therapy in Ontario, Canada, identified nausea as the fourth most prevalent and bothersome treatment-related symptom.[1] Current approaches to prevent CINV are based on an accurate description of the potential of antineoplastic therapies to cause N&V. Current recommendations, based on published guidelines, [2] include patients aged 1 month to 18 years who are about to receive their first-ever course of antineoplastic therapy. These recommendations focus on the prevention of acute CINV (i.e., within 24 hours of administration of an antineoplastic agent).

Guidelines define optimal control of acute CINV as no vomiting, no retching, no nausea, no use of

antiemetic agents other than those given for CINV prevention, and no nausea-related change in the child's usual appetite and diet. This level of CINV control is to be achieved on each day that antineoplastic therapy is administered and for 24 hours after administration of the last agent in the antineoplastic therapy cycle.

## Emetic Risk

In children receiving antineoplastic agents who were not given antiemetic prophylaxis or who were given ineffective prophylaxis, expected rates of complete CINV control were as follows:[2]

- High emetic risk, less than 10%.
- Moderate emetic risk, 10% to less than 30%.
- Low emetic risk, 30% to less than 90%.
- Minimal emetic risk, more than 90%.

The expected rate of complete CINV control in children receiving antiemetic prophylaxis (5-

hydroxytryptamine-3 [5-$HT_3$] receptor antagonist with or without dexamethasone) is more than 70% to 80%.[2] Each chemotherapy agent carries an inherent risk of emesis, which is the first issue to consider when planning chemotherapy treatment. For more information about preventing acute or delayed CINV, see Table 5.

## Acute Chemotherapy-Induced Nausea and Vomiting—Antiemetic Prophylaxis

### Highly emetogenic chemotherapy

Guidelines [2,3] recommend that children aged 6 months and older who are receiving antineoplastic agents of high emetic risk that are not known or suspected to interact with aprepitant receive aprepitant, a 5-$HT_3$ receptor antagonist, and dexamethasone. Children older than 6 months who cannot receive dexamethasone should receive a 5-$HT_3$ receptor antagonist plus aprepitant. Children who cannot receive

aprepitant should receive a 5-$HT_3$ receptor antagonist plus dexamethasone.[4][Level of evidence: IV]

## Moderately emetogenic chemotherapy

Children receiving antineoplastic agents of moderate emetogenicity should receive ondansetron, granisetron, or palonosetron plus dexamethasone. Children aged 6 months and older and whose antineoplastic agents do not interact with aprepitant and who cannot receive dexamethasone should receive a 5-$HT_3$ receptor antagonist plus aprepitant.[3,4][Level of evidence: IV]

## Low emetogenic chemotherapy

Children receiving antineoplastic agents of low emetogenicity should receive a 5-$HT_3$ receptor antagonist.[3]

## Minimal emetogenic potential

Children receiving antineoplastic agents of minimal emetogenicity should receive no routine prophylaxis.[3]

## Other Antiemetic Modalities

Current consensus is that the following modalities may be effective in children receiving antineoplastic agents:[2]

- Acupuncture.
- Acupressure.
- Guided imagery.
- Music therapy.
- Progressive muscle relaxation.
- Psychoeducational support and information.

In addition, virtual reality may convey some benefit. Other recommendations (low level of evidence) include the following:

- Eating smaller, more-frequent meals.

- Reducing food aromas and other stimuli with strong odors.
- Avoiding foods that are spicy, fatty, or highly salty.
- Taking antiemetics before meals so that the effect is present during and after meals.
- Using measures and foods (e.g., “comfort foods”) that previously helped minimize nausea.

Despite a lack of strong evidence, most experts think that these recommendations are unlikely to result in undesirable effects or to adversely affect quality of life, and they may convey benefit.[2]

## Antiemetics

Prophylaxis with a 5-$HT_3$ receptor antagonist alone leads to poor CINV control in pediatric patients receiving antineoplastic agents of moderate and high emetic risk. A synthesis of three studies that evaluated alternative antiemetic agents

(chlorpromazine and metoclopramide) in children receiving highly emetogenic chemotherapy observed a complete CINV control rate of 9% (95% confidence interval: 0, 20).[2] When corticosteroids are contraindicated, it is recommended that nabilone or chlorpromazine be administered together with ondansetron or granisetron to children receiving highly emetogenic chemotherapy. Metoclopramide is a third option for children receiving moderately emetogenic chemotherapy. Corticosteroids combined with a serotonin antagonist are recommended for patients receiving highly and moderately emetogenic chemotherapy.[5]

Antiemetic dosing suggestions for pediatric patients are summarized in Table 7.

## Table 7. Pediatric Antiemetic Dosing

| Drug Category | Medication | |
|---|---|---|
| Phenothiazines | Chlorpromazine | 0.5 m<br>q6h; r<br>to 1 m<br>q6h; r<br>dose: |
| | Prochlorperazine | 9–13 l<br>PO qd<br>maxir<br>7.5 m |
| | | 13–18<br>PO bi |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; l
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | maxir<br>10 mg |
| | | 18–39<br>tid or<br>maxir<br>15 mg |
| | Promethazine | Age ><br>mg/kg<br>6h; m<br>dose: |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| Substituted benzamides | Metoclopramide | Mode<br>emet<br>chem<br>mg/k<br>once<br>prech<br>then (<br>mg/k<br>q6h |
| Serotonin (5-$HT_3$) receptor antagonists | Granisetron | 40 µg<br>40 µg<br>maxir<br>mg/d |
| | Ondansetron | Age 0<br>mg/k |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | mg/m<br>prech<br>then<br>highly<br>or q1<br>mode<br>emet<br>chem |
| | | Low e<br>chem<br>0.3 m<br>(10 m<br>once<br>prech |
| | | Maxir<br>dose: |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1;
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | maxir<br>16 mg |
| | Palonosetron | Age 1<br>µg/kg<br>dose: |
| Substance P antagonists (NK-1 receptor antagonists) | Aprepitant | Capsu<br>y: 125<br>prech<br>day 1,<br>qd x2 |

$5\text{-HT}_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | Suspe<br>mo–1<br>kg): 3<br>prech<br>day 1,<br>mg/kg |
| | Fosaprepitant | Age 1<br>mg |
| Corticosteroids | Dexamethasone | Highly<br>chem<br>mg/m |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | |
| | | Mode<br>emet<br>chem<br>BSA ≤<br>q12h |
| | | BSA ><br>q12h |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | Maxir<br>mg/d |
| | Methylprednisolone | 4–10 |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; B
intramuscular; IV = intravenous; NK-1 = neurokinin-1;
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| Benzodiazepines | Lorazepam | Antici<br>0.05 r<br>(maxi<br>mg/d<br>bedti<br>befor<br>chem<br>and o<br>prech |
| | | Break<br>0.02–<br>mg/kg<br>(maxi<br>q6h p |

$5\text{-HT}_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| Atypical antipsychotics | Olanzapine | 0.1–0.<br>mg/kg<br>maxir |
| Other pharmacological agents | Dronabinol | Age 6<br>mg/m<br>prech |
| | Nabilone | Age > |

$5\text{-}HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; BS
intramuscular; IV = intravenous; NK-1 = neurokinin-1; I
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

| Drug Category | Medication | |
|---|---|---|
| | | <18 k<br>q12h |
| | | 18–3(<br>q12h |
| | | >30 k<br>12h |
| | | Maxir<br>0.06 r |

5-$HT_3$ = 5-hydroxytryptamine-3; bid = twice a day; B
intramuscular; IV = intravenous; NK-1 = neurokinin-1;
sublingual; tid = 3 times a day.

[a]Palonosetron prescribing information lists the pedia

## Multiagent, single-day chemotherapy regimens

Experience in pediatrics and guidelines recommend basing the emetogenicity of combination antineoplastic regimens on that of the agent of highest emetic risk.[20] The emetogenicity of the antineoplastic combinations in the following list appears to be higher than would be appreciated by assessment of the emetic risk of the individual agents.[21]

### *High Level of Emetic Risk (>90% Frequency of Emesis in Absence of Prophylaxis)*

- Cyclophosphamide + anthracycline.
- Cyclophosphamide + etoposide.
- Cytarabine (150–200 $mg/m^2$) + daunorubicin.
- Cytarabine (300 $mg/m^2$) + etoposide.
- Cytarabine (300 $mg/m^2$) + teniposide.
- Doxorubicin + ifosfamide.

- Doxorubicin + methotrexate (5 g/m$^2$).
- Etoposide + ifosfamide.

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# Pediatric Delayed Nausea and Vomiting

The nature and prevalence of delayed nausea and vomiting (N&V) in children after administration of antineoplastic agents have not been well described.[1] Additionally, most pediatric chemotherapy regimens are given over multiple days, making the onset and duration of risk of delayed versus acute N&V unclear.

Research on chemotherapy-induced N&V (CINV) in children has been limited in part by the lack of assessment tools and the subjective nature of nausea. In the pediatric population, vomiting is more easily recognizable and measurable than nausea.[1] Difficulties in assessing nausea in young children may contribute to the common perception that young children experience CINV less frequently than older children. In addition, caregivers may have a higher tolerance for vomiting in young children and may miss detecting

nausea.[1] In view of these limitations, studies often use dietary intake to assess the extent of nausea.

Several investigators have attempted to determine the prevalence of delayed N&V in the pediatric population. One early study suggested a low incidence.[2] A large study assessed the nature and prevalence of delayed CINV in children.[1] Nausea was self-assessed daily using a numeric scale reflecting the effect of nausea on activities and a faces scale for children aged 3 to 6 years. Diet was also assessed daily. Results showed a 33% rate of delayed vomiting in patients who received cyclophosphamide, cisplatin, or carboplatin and an 11% rate in those who received other antineoplastic agents. No antiemetics were given on 412 (79%) of 522 study days. Nevertheless, on 381 (93%) of those 412 study days, patients were completely free from vomiting. Antiemetics were most often given as single agents (ondansetron, on 54 study days; dimenhydrinate,

on 17 study days; dexamethasone, on 6 study days). Diet was not affected. The authors concluded that antineoplastic-induced delayed N&V may be less prevalent in children than in adults.[1] The high percentage of children who did not experience delayed vomiting may reflect a lack of significant emetogenic potential among many of the regimens in the study. In 100 of 174 chemotherapy cycles, no antiemetics were administered. In addition, there was no characterization of antiemetic response in moderate and severe chemotherapy regimens.

Another study evaluated the incidence of delayed N&V in pediatric patients receiving moderately and highly emetogenic chemotherapy as well as premedications (ondansetron alone or with dexamethasone, depending on a treatment's emetogenic potential).[3] Investigators measured nausea severity and duration, vomiting severity, the number of vomiting episodes, interference with daily activities, and assessment of appetite.

The authors found that delayed N&V occurred with both moderately and highly emetogenic chemotherapy regimens, but that the severity of N&V varied. In addition, toddlers had better antiemetic control than older children, which may be the result of anxiety differences between the age groups. The reasons for toddler patients' greater complete control are unclear but are consistent with a previous study of N&V control rates in children.[4] Anxiety and patient perception may be important contributors to N&V in older children; a relationship between control of acute N&V and the occurrence of delayed N&V was found.

Another study suggested a higher incidence of delayed N&V than was previously found in a pediatric population.[5] In 40 pediatric cancer patients receiving chemotherapy, N&V was measured from the child’s perspective using the Adapted Rhodes Index of Nausea and Vomiting for Pediatrics; from the primary caregiver’s

perspective using the Adapted Rhodes Index of Nausea and Vomiting for Parents; and from the nurses' perspective using the National Cancer Institute Nausea and Vomiting Grading Criteria. The highest frequency of nausea occurred in the delayed period, with 60% of patients (n = 24) reporting delayed nausea. The authors concluded that CINV occurred throughout the chemotherapy course, with delayed N&V occurring most frequently and with greater severity and distress. Delayed N&V in the pediatric population requires further study.

Because well-designed studies on the prevention of delayed N&V in children are not available, the best available evidence comes from adult data and a pediatric clinical practice guideline.[6][Level of evidence: IV]; [7]

## Delayed Chemotherapy-Induced Nausea and Vomiting—Antiemetic Prophylaxis

## Highly emetogenic chemotherapy

Palonosetron is the preferred 5-hydroxytryptamine-3 (5-$HT_3$) receptor antagonist in the acute phase in patients at high risk of delayed CINV. Guidelines recommend that children who can receive aprepitant and dexamethasone continue to do so during the delayed phase. If dexamethasone cannot be used, aprepitant should be continued. If aprepitant cannot be used, dexamethasone should be continued. If olanzapine was started during the acute phase, it should be continued during the delayed phase.[6][Level of evidence: IV]

In a phase III, double-blind, randomized controlled trial, 128 patients aged 3 to 18 years receiving highly emetogenic chemotherapy were randomly assigned to receive intravenous ondansetron and dexamethasone plus olanzapine or placebo on days 1 and 2. More patients in the olanzapine group had complete control of vomiting in the delayed phase (73% vs. 48%; *P* = .005), although

there was no difference in control in the acute phase or overall. More patients in the placebo group required rescue medications for vomiting than in the olanzapine group (29% vs. 14%; *P* = .025). Grade 1/2 sedation was greater in the olanzapine group than in the placebo group (46% vs. 14%).[8]

## Moderately emetogenic chemotherapy

In the delayed phase, children receiving antineoplastic agents of moderate emetogenicity who received a 5-$HT_3$ receptor inhibitor and dexamethasone in the acute phase should consider dexamethasone during the delayed phase.

Children receiving a 1-day regimen of antineoplastic agents of moderate emetogenicity who received a 5-$HT_3$ receptor inhibitor and fosaprepitant or aprepitant in the acute phase should continue oral aprepitant in the delayed phase. Children receiving a multiday regimen of

antineoplastic agents of moderate emetogenicity who received a 5-$HT_3$ receptor inhibitor and fosaprepitant or aprepitant in the acute phase should consider not using oral aprepitant in the delayed phase.

Children receiving a 5-$HT_3$ receptor inhibitor with olanzapine during the acute phase should consider continuing olanzapine during the delayed phase.[6][Level of evidence: IV]

## Low emetogenic chemotherapy

Children receiving antineoplastic agents of low emetogenicity should not receive routine prophylaxis during the delayed phase.[6][Level of evidence: IV]

## Minimal emetogenic potential

Children receiving antineoplastic agents of minimal emetogenicity should not receive routine prophylaxis during the delayed phase.[6][Level of evidence: IV]

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# Pediatric Anticipatory Nausea and Vomiting

Patients with cancer who have received chemotherapy may experience nausea and vomiting (N&V) when anticipating further chemotherapy. Study differences in methodology, timing, and assessment instruments; small samples; and a focus on nausea or vomiting but not both has led to difficulties in capturing the prevalence of anticipatory N&V (ANV) in children. Accurate prevalence is also stymied by using parent or caregiver proxy reports of nausea and nonvalidated nausea assessment tools.

In patients receiving 5-hydroxytryptamine-3 (5-$HT_3$) receptor antagonists and corticosteroids as antiemetic agents, approximately one-third of adults experienced ANV, while 6% to 11% reported anticipatory vomiting.[1] A study of children in the pre–5-$HT_3$ receptor antagonist era reported anticipatory nausea in 23 (29%) of 80 children and

anticipatory vomiting in 16 (20%) of 80 children who had received 11 cycles of antineoplastic therapy, on average, before evaluation.[2] In the post–5-$HT_3$ receptor antagonist era, the reported prevalence of anticipatory nausea in children has ranged from 0% to 59%.[3] Similar to observations in adult patients, the reported prevalence of anticipatory nausea is always higher than that of anticipatory vomiting in children, although one study reported an equivalent prevalence (5 [26%] of 19 patients) for these conditions.[4]

This section focuses on the management of ANV in children aged 1 month to 18 years who are receiving antineoplastic medication. Optimal control of ANV is defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for the prevention or treatment of chemotherapy-induced N&V (CINV), and no nausea-related change in the child's usual appetite and diet. This level of ANV control is to be achieved during the 24 hours before

administration of the first antineoplastic agent of the upcoming planned antineoplastic cycle.

## Approaches to Prevent ANV in Children

ANV appears to be a conditioned response to CINV experienced in the acute phase (24 hours after administration of chemotherapy) and delayed phase (more than 24 hours after and within 7 days of administration of chemotherapy).[3] The anxiety and distress attendant to CINV reinforce the conditioned response.[3] It follows, then, that a higher rate of complete control of acute and delayed CINV would result in lower rates of ANV. Adherence to evidence-based recommendations for CINV prevention has been shown to substantially improve complete control of acute CINV.[5]

Optimized control of acute and delayed CINV may help minimize exposure to the negative stimuli required for conditioning to occur. Consensus

recommendations call for antiemetic interventions to be based on published guidelines for the prevention of acute CINV in children receiving antineoplastic agents,[6,7] including antineoplastic agent–naïve patients. Once antineoplastic therapy has been initiated, the selection of antiemetic interventions should be informed by evidence-based guidelines and tailored to the patient's CINV control and any adverse effects associated with antiemetic agents.

## Interventions to Control ANV in Children

### Hypnosis

Hypnosis has been defined as an intervention that "provides suggestions for changes in sensation, perception, cognition, affect, mood, or behavior."[8] Two trials evaluated the role of hypnosis in controlling ANV in children. One study recruited 54 children aged 5 to 17 years who had reported experiencing anticipatory nausea,

anticipatory vomiting, or both in a previous study and who were about to receive at least two identical antineoplastic treatment courses.[9] On average, children were 15.8 months (range, 0.5–118 months) from their cancer diagnosis at the time of the study. The control group had received antineoplastic therapy for much longer than the other two groups (29.5 months vs. 8 or 11.5 months).

Although it is not possible to precisely ascertain the emetogenicity of the antineoplastic therapy these children received, it appears that most received highly emetogenic treatment. The antiemetic agents taken for prophylaxis were not reported, but children's antiemetic regimens were unchanged during the trial. The severity of N&V was assessed through semistructured interviews. Children were randomly assigned to receive one of three possible interventions: hypnosis training (imagination-focused therapy), active cognitive distraction (relaxation), or contact with a therapist

(control). The authors reported a significant improvement in complete control of anticipatory vomiting in the group who received hypnosis training (12 [57%] of 21 patients at baseline vs. 18 [86%] of 21 patients after hypnosis training; *P* < .05). Complete control of anticipatory nausea increased from 5 (24%) of 21 patients at baseline to 8 (38%) of 21 patients after hypnosis training.[9]

Another study evaluated hypnosis as a means of preventing ANV in 20 children aged 6 to 18 years who were naïve to chemotherapy.[10] Controls were matched for age (±3 years) and the emetogenicity of their antineoplastic treatment. Insufficient information is available to determine the emetogenicity of the antineoplastic regimens. Children randomly assigned to receive hypnosis did not receive antiemetic prophylaxis but did receive antiemetic agents as needed. Children in the control group received standard antiemetic prophylaxis for 4 to 6 hours after antineoplastic therapy. Ondansetron was given to more children

in the control group (7 of 10 patients) than in the hypnosis group (3 of 10 patients).

Children randomly assigned to receive hypnosis were taught self-hypnosis during the initial antineoplastic treatment, while children in the control group spent equivalent time in conversation with a therapist. Researchers used a daily structured interview with the children to assess ANV at 1 to 2 months, and at 4 to 6 months after diagnosis. At the time of first assessment, children who had been taught self-hypnosis reported significantly less anticipatory nausea than did the control group, although the incidence was not reported. The rate of anticipatory vomiting was identical in each group (1 of 10 patients). By the time of the second assessment, there was no difference between the groups in the rate of anticipatory nausea. The rate of anticipatory vomiting between the groups was also similar (hypnosis, 0 of 10 patients vs. control, 2 of 10 patients).[10]

## Pharmacological interventions

Studies of pharmacological interventions for ANV have been conducted only in adults and are limited to benzodiazepines. Because patients who experience ANV have been observed to be more anxious than patients who do not experience ANV, [11] anxiolytics have been studied. Studies in adults have evaluated benzodiazepines as a treatment for ANV.[12,13] In one randomized trial, adult patients with cancer received a placebo or lorazepam 2 mg by mouth the night before antineoplastic treatment, the morning of treatment, and at bedtime for the next 5 days during 180 antineoplastic treatment courses containing cisplatin.[12] Patients also received metoclopramide 2 mg/kg per dose, clemastine, and dexamethasone for antiemetic prophylaxis. At the time of randomization, approximately two-thirds of patients were naïve to antineoplastic agents. ANV was defined as nausea, vomiting, or both that occurred within 12 hours before antineoplastic therapy or 1 hour after the start of

antineoplastic therapy. A significantly higher proportion of treatments with lorazepam were associated with complete ANV control, compared with the control group (52% vs. 32%; $P < .05$). Few adverse effects occurred; 76% of the patients who received lorazepam and 32% of the controls had mild sedation.

Women with breast cancer who were naïve to antineoplastic treatment were enrolled in a double-blind placebo-controlled trial comparing the incidence of ANV after relaxation training and either alprazolam (n = 29) or placebo (n = 28). Alprazolam 0.25 mg or placebo was given twice daily by mouth for 6 to 12 months. Triazolam was also given as needed to patients in both study arms to manage insomnia. The proportion of patients who experienced complete control of anticipatory nausea and anticipatory vomiting before the fourth antineoplastic treatment was similar in both study arms (26% vs. 25% and 4% vs. 0%, respectively). Diazepam 5 mg twice daily was

given to 29 adult cancer patients with ANV for 3 days before each of four consecutive antineoplastic treatment courses.[13] Thirteen patients (45%) experienced complete ANV control at some time over the four antineoplastic treatment courses.

## Conclusions

While the improvement in complete control of ANV provided by psychological interventions such as hypnosis or systematic desensitization may not be dramatic, these interventions may benefit individual patients with minimal risk. For this reason, one guideline development panel recommends that such interventions be offered to age-appropriate patients who experience ANV where the expertise and resources exist to deliver them.[6]

Despite the lack of evidence supporting the use of benzodiazepines to treat ANV in children, guidelines based on clinical experience

recommend using lorazepam for ANV in children.[14] The recommended initial dose was based on current pediatric dosing recommendations, with the usual adult dose as the maximum dose.[15] This dose should be titrated to the needs of each child, with dose lowering recommended for excessive sedation.

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## Latest Updates to This Summary (03/10/2025)

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Editorial changes were made to this summary.

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