Antiemetic Therapy in Patients Receiving Cancer Chemotherapy

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Purpose/Objectives: To examine the currently available antiemetic medications and review their uses in the treatment of chemotherapy-induced nausea and vomiting (N&V).

Data Sources: Published articles and book chapters.

Data Synthesis: N&V is a common yet potentially serious side effect of chemotherapy. Nurses must understand the physiology of N&V, its impact on patients, and the proper use of antiemetic medications to effectively manage this problem. Antiemetic medications vary in mechanism of action, indications for use, and adverse effects.

Conclusions: Nurses are in a position to identify patients who are at risk for N&V and to manage their care using accepted practice guidelines.

Implications for Nursing: Although practice guidelines have been established, the nurse's role in assessment and implementation of care is critical in the prevention and management of chemotherapy-induced N&V.

Key Points . . .

- Nausea and vomiting (N&V) is one of the most distressing and potentially serious side effects of chemotherapy, with physical, psychological, emotional, and treatment-related consequences.
- N&V may be classified as anticipatory, acute, delayed, or persistent; each category requires a different approach to treatment.
- Because N&V can be triggered by multiple pathways, selection of the most appropriate antiemetic medication and route of administration is extremely important.
- Nurses are in a unique position to assess the potential for N&V, its effects on patients, and the effectiveness of antiemetic therapy.

Nausea and vomiting (N&V) is one of the most distressing and potentially serious side effects of chemotherapy. Without antiemetic therapy, 60%–80% of patients receiving chemotherapy experience significant N&V. Despite advances in the understanding and treatment of chemotherapy-induced N&V, approximately 40%–60% of patients continue to experience this side effect (Bender et al., 2002; Eckert, 2001).

The goal of antiemetic therapy is to prevent or reduce the incidence and intensity of N&V related to chemotherapy. However, research indicates that N&V often is underassessed by oncologists and oncology nurses (Bender et al., 2002). Although newer antiemetic medications are far more effective than previous generations of drugs, these medications do not work for all patients. Once an antiemetic regimen has been prescribed, many practitioners assume that patients' N&V has been relieved; this may prevent practitioners from gaining a true understanding of the incidence and impact that this condition has on patients receiving cancer chemotherapy.

The use of complementary and alternative treatments for chemotherapy-induced N&V has received much attention during the past decade; however, a discussion of these modalities is beyond the scope of this article.

Goal for CE Enrollees:

To further enhance nurses' knowledge regarding antiemetic therapy in patients receiving cancer chemotherapy.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe the risk factors and the four classifications of nausea and vomiting with chemotherapy.
2. Discuss the treatment options available for nausea and vomiting with chemotherapy.
3. Discuss the nursing implications in the care of patients who experience nausea and vomiting with chemotherapy.

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Digital Object Identifier: 10.1188/03.ONF.259-271

Impact on Patients

The effects of N&V are multidimensional. The physical sequelae perhaps are the most easily recognized. N&V can, in a short time, lead to nutritional deficiencies, dehydration, and electrolyte imbalances. Patients' fear that eating or drinking will trigger another bout of N&V can reduce their intake and result in cachexia and dehydration. Dehydration can be exacerbated by severe or prolonged vomiting resulting in loss of fluid volume and is associated with electrolyte imbalances, including hypokalemia, hyponatremia, hypomagnesemia, and hypochloremia (Bender et al., 2002). The combination of inadequate intake and excessive output from vomiting in patients who already are compromised by cancer or its treatment puts patients at an even higher risk for life-threatening complications.

N&V also has a psychological impact on patients. Fear of N&V has been shown by researchers to be a major concern for patients with cancer (Kraut & Fauser, 2001). This fear has been associated with patient distress, disruption of normal social and work routines, and impaired quality of life (Rittenberg, 2002). Other studies have demonstrated that patients who experience N&V report increased anxiety and depression, as well as lower levels of cognitive functioning (Kraut & Fauser).

Poorly controlled N&V also can cost patients and the healthcare system money and other resources. Patients who experience N&V lose time at work, reducing their income. Those who suffer from the effects of dehydration and cachexia often require hospitalization to manage these complications, resulting in increased costs for drug therapy and nursing care (Pendergrass, 1998).

The complications related to nutritional deficiencies, electrolyte imbalances, and dehydration can result in reduced doses of chemotherapy medications, making them less effective. These complications may cause treatment to be delayed, thus reducing the likelihood that the cancer can be brought under control. Fear of N&V may be so extreme that patients may refuse further, potentially lifesaving treatments (Campos et al., 2001; Pendergrass, 1998).

A large, international, multicenter study was conducted to determine the monetary value that patients place on improved quality of life and control of N&V (Dranitsaris et al., 2001). The researchers surveyed 245 patients with cancer in seven cancer centers to rate the value they placed on medications that would reduce their risk for N&V in incremental levels. They found that patients were willing to pay for a medication that would reduce their risk for N&V by even 5%, indicating that they placed a high value on avoiding these incidents as a major factor in quality of life. They also found that these patients would be willing to pay more money for a medication that would reduce their risk for vomiting from a baseline risk of 30% to a risk of 0% than for one that would reduce their risk from the baseline to 10%. Although the researchers measured several variables, including a history of emesis and previous uncontrolled N&V associated with chemotherapy, they found that the only variable that affected the patients' willingness to pay for an effective antiemetic was income: Patients with higher incomes were willing to pay more for the medication than those with lower incomes.

Physiology

Several researchers have suggested that the mechanisms behind N&V may be different (Campos et al., 2001; Dranitsaris et al., 2001; Eckert, 2001; Roscoe, Morrow, Hickok, & Stern, 2000). Nausea is a subjective sensation in the back of the throat or the stomach that is accompanied by changes in the parasympathetic nervous system; it may or may not result in vomiting. Vomiting, in contrast, is the forceful ejection of the contents of the stomach, duodenum, and jejunum through the mouth. Whereas nausea is subjective, vomiting is completely objective and observable. Control of nausea usually is considered by patients to be far more important than control of vomiting, in contrast to the usual perception of physicians and nurses (Roscoe et al.).

The physiology of N&V has been examined by numerous researchers. The primary mediator of chemotherapy-induced N&V is believed to be the chemoreceptor trigger zone (CTZ), located on the floor of the fourth ventricle of the brain. The CTZ lies outside the blood-brain barrier, and therefore can be stimulated by serotonin and other neurotransmitters in the blood and cerebrospinal fluid. Once it is stimulated, the CTZ acts on the vomiting center in the lateral reticular formation of the medulla oblongata. The vomiting center also may be triggered by vagal nerve stimulation from the pharynx and gastrointestinal tract, the vestibular apparatus, or the cerebral cortex (Bender et al., 2002; Itano & Taoka, 1998; Pendergrass, 1998).

When chemotherapy agents are administered, they are believed to affect the CTZ and vomiting center via multiple pathways. They may stimulate the CTZ directly through blood transmission, which, in turn, releases neurotransmitters (primarily dopamine) that stimulate the vomiting center. Chemotherapy agents also may damage the enterochromaffin cells in the small intestinal mucosa, which triggers the release of serotonin, believed to be one of the principal mediators of the vomiting reflex (Gralla et al., 1998; Wilkes, Ingwersen, & Barton-Burke, 2000). Serotonin binds to receptors in the gut, which stimulates vagal nerve impulses to the CTZ. The CTZ, in turn, stimulates the vomiting center, which activates a number of responses that manifest as N&V, such as decreased gastric motility and tone, increased salivation, light-headedness, difficulty swallowing, and rhythmic retching that usually precedes vomiting (National Comprehensive Cancer Network [NCCN], 2001; Pendergrass, 1998). More recent research is examining the role of substance P, a tachykinin found in the neurons of the area of the brain surrounding the CTZ and the vomiting center, in the physiology of N&V (Campos et al., 2001).

Contributing Factors

Risk factors for N&V may be related to patients' diseases, their treatments, or specific situations (Itano & Taoka, 1998). Disease-related factors include tumors of the central nervous system that stimulate the CTZ or vomiting center; gastrointestinal obstruction; infection; food toxins; metabolic imbalances, including hyperglycemia, hypercalcemia and hyponatremia; and renal and hepatic dysfunction.

Treatment-related risk factors include the emetic potential of the chemotherapy agent (see Table 1), damage to the enterochromaffin cells of the gastrointestinal tract by treatment agents (e.g., chemotherapy, radiation therapy, surgery), stimulation of the CTZ by treatment agents, and medication and nutritional supplement side effects (Itano & Taoka, 1998).

Combination chemotherapy administration presents a particular challenge to the management of N&V. Few studies

Table 1. Emetogenic Potential of Chemotherapy Agents

Emetogenic Potential	Drug Name	
Very high (> 90%)	Cisplatin	Mechlorethamine[a]
	Cytarabine[a]	Melphalan
	Dacarbazine	Streptozocin
High (60%–90%)	Actinomycin-D	Idarubicin
	Busulfan[a]	Ifosfamide[a]
	Carboplatin[a]	Interleukin-2
	Carmustine	Lomustine
	Cyclophosphamide	Methotrexate[a]
	Daunorubicin[a]	Plicamycin
	Denileukin diftitox	Procarbazine
	Doxorubicin[a]	Semustine
	Epirubicin[a]	
	Hexamethyl-melamine[a]	
Moderate (30%–60%)	5-Fluorouracil[a]	Interleukin
	11-Irinotecan	Mitomycin[a]
	Asparaginase	Mitoxatrone
	Docetaxel	Paclitaxel[a]
	Etoposide[a]	Retinoids
	Gemcitabine[a]	Teniposide[a]
	Gemtuzumab	Topotecan
	Interferons	
Low (10%–30%)	2-Chlorodeoxy-adenosine[a]	Levamisole
	6-Mercaptopurine	Mercaptopurine
	Bacillus Calmette-Guerin	Rituximab
	Bleomycin[a]	Tamoxifen[a]
	Capecitabine	Thioguanine[a]
	Chlorambucil[a]	Trastuzumab
	Doxorubicin liposomal	Vindesine
	Fludarabine[a]	Vinblastine
	Flutamide	Vinorelbine
	Hydroxyurea	
Very low (< 10%)	Daclizumab	Pentostatin
	L-Phenylalanine mustard	Vincristine

[a] Emetogenic potential of drugs depends on the dose and the route of administration. In general, higher doses are more emetogenic than lower doses.

Note. Based on information from Brown et al., 2001; Gralla et al., 1999; Itano & Taoka, 1998; National Comprehensive Cancer Network, 2001.

have examined the use of antiemetic medications in this situation. Although some evidence supports the suggestion that combinations of chemotherapy of the same emetogenic potential category have an additive effect that would warrant use of a higher level of antiemetic therapy, results of studies have not been consistent (Gralla et al., 1999; Pendergrass, 1998). Currently, experts suggest using the antiemetic medication regimen appropriate for the chemotherapy agent with the highest emetogenic potential, although the number of treatment days may be reduced (Gralla et al., 1999).

Factors related to patients' situations may be more difficult to quantify. Tension, stress, and anxiety related to the disease and its treatment are expected responses but can provoke N&V. Noxious stimuli, such as strong odors, also may trigger this response. Conditioned responses may occur, leading to the development of anticipatory N&V (Gralla et al., 1999; Itano & Taoka, 1998).

Types

N&V may be classified as anticipatory, acute, delayed, or persistent (Otto, 2001). Each of these classifications is associated with distinct characteristics that influence the ways they are treated.

Anticipatory N&V: Anticipatory N&V occurs prior to the administration of chemotherapy, and about 25% of patients receiving chemotherapy experience this type (Itano & Taoka, 1998). Anticipatory N&V is defined most often in terms of classical conditioning and is linked to the association of the unpleasant side effects of chemotherapy with neutral stimuli (Bender et al., 2002).

Several risk factors have been associated with the development of anticipatory N&V (Eckert, 2001). Patients with four or more of these risk factors were found to be significantly more likely to experience anticipatory N&V after the first cycle of chemotherapy than those with fewer risk factors. The researchers found that no single risk factor was as clearly associated with anticipatory N&V as the combination of two or more risk factors. These risk factors included severe post-treatment nausea, a history of motion sickness, and completion of more than one chemotherapy cycle. Factors with a lesser association included age less than 45 years, female gender, and a history of low chronic alcohol use. Some studies have found that a high level of anxiety promoted the development of anticipatory N&V (Bauduer, 1999; Eckert, 2001), whereas others found no such link (Hickok, Roscoe, & Morrow, 2001). The type of cancer being treated was found to have no association with the occurrence of anticipatory N&V (Eckert).

Hickok et al. (2001) studied 63 female patients with cancer undergoing chemotherapy to determine how pretreatment expectations regarding N&V influenced the development of anticipatory N&V. They found that 32% of the subjects expected to feel nausea after their chemotherapy. After the first cycle of chemotherapy treatment, 55% of the women who expected to experience nausea did so, whereas none of those who were certain that they would not feel nausea experienced it. These findings suggest that the expectations may play a larger role than classical conditioning in the development of anticipatory N&V.

Prevention of post-therapy N&V is the most effective way to deter anticipatory N&V (Gralla et al., 1999). As demonstrated by Hickok et al. (2001), patients' expectations play a significant role in anticipatory N&V; therefore, education, including a realistic yet optimistic overview of possible side effects of chemotherapy, may be the best nursing intervention for this problem.

Once it occurs, anticipatory N&V usually is unresponsive to current antiemetic agents and therefore is very difficult to treat (Eckert, 2001). Behavioral modification therapy and systematic desensitization to the triggering stimuli may be required to manage this type of N&V (Gralla et al., 1999) but may not be available widely in most clinical or hospital settings (Hickok et al., 2001).

Acute N&V: Acute N&V occurs within 24 hours of chemotherapy administration and is mediated through the autonomic nervous system, which triggers the release of neurotransmitters in the gastrointestinal tract, the CTZ, and the vomiting center (Itano & Taoka, 1998). It usually peaks five to six hours after the administration of the treatment agent (NCCN, 2001).

Although the emetogenic potential of the chemotherapy agent is the primary risk factor for acute N&V, other factors

may play a role. These include a history of poor control of N&V with previous chemotherapy administrations, female gender, a history of motion sickness, age under 50 years, and low chronic alcohol intake (Gralla et al., 1999; Hickok et al., 2001). Chronic alcohol intake of less than 100 grams per day (100 grams is equivalent to approximately six ounces of hard liquor, 30 ounces of wine, or six to seven beers) for a period of years has been associated with a significantly lower risk of acute N&V, although the mechanism of this is not fully understood (Gralla et al., 1999).

The currently accepted standard treatment regimen for acute N&V is a serotonin receptor antagonist combined with a corticosteroid (Campos et al., 2001); these drugs will be discussed more fully later in this article.

Delayed N&V: Delayed N&V occurs in about 40%–50% of patients receiving chemotherapy (Dranitsaris et al., 2001). The symptoms occur 24–48 hours after chemotherapy has been administered but may persist up to seven days (NCCN, 2001); delayed N&V tends to be less intense than acute N&V (Eckert, 2001). The risk factors for developing delayed N&V are the same as those for acute N&V but also include poor control of acute N&V (Gralla et al., 1999). Although some chemotherapy agents, such as cyclophosphamide, epirubicin, and carboplatin, are known to cause delayed emesis, many agents have not been studied for this side effect (Gralla et al., 1999; Italian Group for Antiemetic Research, 2000).

Treatment for delayed N&V currently includes the combination of a corticosteroid with a serotonin receptor antagonist or metoclopramide (Campos et al., 2001); however, this therapy is controversial because of the high cost of the drugs and the lack of consistently proven benefits (Valley, 2000). Although serotonin receptor antagonists combined with a corticosteroid protect up to 90% of patients from acute emesis, this treatment is less effective in delayed emesis, with only a 40%–60% response rate (Italian Group for Antiemetic Research, 2000).

A large, multicenter, randomized study of 705 patients with cancer receiving moderately emetogenic chemotherapy examined the efficacy of dexamethasone (a corticosteroid) versus ondansetron (a serotonin receptor antagonist) combined with dexamethasone in the treatment of delayed N&V (Italian Group for Antiemetic Research, 2000). Subjects were divided into groups according to risk. Those in the low-risk group had experienced no vomiting and no moderate-to-severe nausea in the 24 hours after chemotherapy administration and were given either a placebo, dexamethasone, or dexamethasone plus ondansetron. Patients in the high-risk group had experienced symptoms in the 24 hours after chemotherapy administration and were given either dexamethasone or dexamethasone plus ondansetron.

The researchers found that, in the low-risk group, dexamethasone alone and the combination of dexamethasone plus ondansetron were significantly better than the placebo in controlling delayed N&V. They found no statistically significant differences between patients who received dexamethasone alone and those who were given dexamethasone plus ondansetron in protection from moderate-to-severe nausea, vomiting, or both. In the high-risk group, the combination of dexamethasone plus ondansetron was not significantly more effective in preventing these symptoms than dexamethasone alone (Italian Group for Antiemetic Research, 2000).

In a similar study, researchers examined the use of dexamethasone in combination with granisetron (a serotonin receptor antagonist) to prevent delayed N&V (Latreille et al., 1998). This multicenter, blinded study randomized 447 patients receiving highly emetogenic chemotherapy to receive either dexamethasone and granisetron for seven days or dexamethasone and granisetron on day one followed by placebo for days two through seven. Latreille et al. found no significant differences in the two study arms, suggesting that the use of these agents for delayed N&V may not be warranted.

Persistent N&V: Persistent N&V occurs despite efforts to control acute and delayed episodes (Itano & Taoka, 1998). With this type of N&V, the treatment regimen should be reviewed to ensure that the best medications available for the particular situation are being used, based on evaluation of each patient's risk factors for N&V, the emetogenic potential of the chemotherapy agent, and concurrent medication use (Gralla et al., 1999). Patients at risk for breakthrough or persistent N&V should be provided with antiemetics on an as-needed basis (American Society of Health-System Pharmacists [ASHP], 1999). Increasing the dose of the current antiemetic agent to the maximum accepted level may be indicated. The addition of an antianxiety agent or combining a dopamine receptor antagonist with a serotonin receptor antagonist also may be recommended (ASHP).

Antiemetic Therapy

Because N&V can be triggered by multiple pathways, effective antiemetic therapy requires medications that work by different mechanisms. Current recommendations suggest that combinations of medications work better than monotherapy and scheduled dosing is superior to as-needed administration. Selection of an appropriate medication, dosing schedule, and route of administration is determined by thorough assessments of patients. Table 2 summarizes the classes and types of antiemetic medications currently used for the treatment of chemotherapy-induced N&V.

Serotonin Receptor Antagonists

In 1991, when serotonin receptor antagonists were introduced for the treatment of chemotherapy-induced N&V, about half of patients receiving chemotherapy also were administered these drugs; by 1995, they were used in 90% of patients receiving chemotherapy (Roscoe et al., 2000). These medications, especially when used in combination with corticosteroids, significantly reduced the severity of N&V in patients who received moderately or highly emetogenic chemotherapy (Gralla et al., 1998; Pendergrass, 1998), resulting in fewer complications of uncontrolled N&V and improved quality of life (Valley, 2000). However, some researchers suggested that the frequency of N&V is not significantly reduced by serotonin receptor antagonists (Eckert, 2001).

In general, serotonin receptor antagonists exert their activity by preventing the serotonin released by the enterochromaffin cells in the gastrointestinal tract from binding to receptors in the gut and the CTZ (Anastasia, 2000; Gralla et al., 1999). Because these medications are well absorbed in the intestines and begin to immediately affect the serotonin receptors there, researchers suggested that the oral route of administration is equal or superior to the IV route in effectiveness (Gralla et al., 1999).

Serotonin receptor antagonists currently available in the United States include ondansetron hydrochloride, granisetron hydrochloride, and dolasetron mesylate. Ondansetron was the first of these agents approved for use in the treatment of chemotherapy-induced vomiting (Dranitsaris et al., 2001). This drug

Table 2. Antiemetic Agents

Agent	Indications	Mechanism of Action	Pharmacokinetics	Nursing Considerations	Recommended Dosing
Serotonin receptor antagonists: ondansetron, granisetron, dolasetron	Acute nausea related to moderately to highly emetogenic chemotherapy	Selectively block the stimulation of serotonin release and the effects of serotonin, both centrally (in the chemoreceptor trigger zone [CTZ] and vomiting center) and peripherally (in the gastrointestinal [GI] tract)	**Peak plasma levels:** given orally (PO), 1–2.1 hours; given via IV, immediate **Half-life:** given PO, 3.1–8.1 hours; given via IV, 3.5–4.7 hours	Side effects include headache, diarrhea, and hypotension. Occasionally, dolasetron and ondansetron may cause acute, usually reversible, echocardiogram changes.	**Ondansetron hydrochloride (HCl):** 8 mg PO 30 minutes before chemotherapy, then 4 and 8 hours after chemotherapy; then 8 mg PO three times a day for 1–2 days **Granisetron HCl:** 10 mcg/kg via IV (over five minutes) 30 minutes before chemotherapy; or 1 mg PO twice a day given 1 hour before chemotherapy, then 12 hours later; or 2 mg PO every day 1 hour before chemotherapy **Dolasetron mesylate:** 100 mg PO 1 hour before chemotherapy; or 1.8 mg/kg via IV 30 minutes before chemotherapy; or 100 mg via IV (over 30 seconds) 30 minutes before chemotherapy
Corticosteroids: dexamethasone, methylprednisolone	In combination with serotonin receptor antagonists for acute and delayed emesis associated with moderately to highly emetogenic chemotherapy; OR in combination with a substituted benzamide or phenothiazine for moderately emetogenic chemotherapy; OR alone in patients receiving moderately emetogenic chemotherapy	Unclear; may be because of the release of endorphins or to prostaglandin antagonism	**Onset:** 12–27 hours given PO; within minutes given via IV **Duration:** up to 1 week **Half-life:** 78–210 minutes	Usually is contraindicated in patients receiving biotherapy Dose should be tapered if used for more than several days. Careful monitoring is required in patients with diabetes mellitus. Dexamethasone is the corticosteroid most often used for control of delayed nausea and vomiting. Side effects include anxiety, insomnia, acne, and appetite changes. Long-term use may result in Cushinoid syndrome, psychosis, seizure, and other adverse effects.	**Dexamethasone:** 20 mg via IV or PO before chemotherapy for prevention of acute nausea and vomiting; for delayed nausea and vomiting, 8 mg twice a day for 2–3 days, then 4 mg twice a day for 1–2 days, then discontinue. **Methylprednisolone:** 40 mg–125 mg IV before chemotherapy
Substituted benzamides: metoclopramide	Alone OR in combination with a corticosteroid for control of acute nausea and vomiting caused by moderately emetogenic chemotherapy; OR alone for delayed nausea and vomiting	At lower doses, antagonizes the dopamine receptors in the CTZ and the GI tract; at higher doses, also acts as a serotonin receptor antagonist	**Onset:** Given PO, 30–60 minutes; given via IV, 1–3 minutes **Duration:** 1–2 hours **Half-life:** 5–6 hours	Associated with a high incidence of extrapyramidal effects, especially in younger patients; should be given with diphenhydramine to minimize these effects IV administration is associated with significant cardiovascular side effects, including hypotension, bradycardia, and tachycardia. Side effects include dystonia, akathisia, diarrhea, sedation, and dry mouth.	**Metoclopramide:** 10–20 mg PO or 2–3 mg/kg via IV before chemotherapy and 2 hours after chemotherapy.

(Continued on next page)

Note. All doses listed are for adults. Based on information from American Society of Health-System Pharmacists, 1999; Brown et al., 2001; Gralla et al., 1999; Skidmore-Roth, 2002; Spratto & Woods, 2002.

Table 2. Antiemetic Agents *(Continued)*

Agent	Indications	Mechanism of Action	Pharmacokinetics	Nursing Considerations	Recommended Dosing
Phenothiazines: prochlorperazine, perphenazine	Acute nausea and vomiting associated with moderately emetogenic chemotherapy; OR in combination with a corticosteroid for delayed nausea and vomiting; OR in combination with other agents in persistent nausea and vomiting	Acts primarily in the CTZ as a dopamine$_2$ receptor antagonist; also decreases vagal nerve stimulation of the vomiting center.	**Onset:** given PO, 30–40 minutes; given rectally (PR), 60 minutes; given IV, 3–5 minutes **Duration:** 3–4 hours for immediate release dose; 10–13 hours for extended release dose	Associated with a high risk of extrapyramidal symptoms, especially in younger patients; may be given with diphenhydramine to minimize these effects. Side effects include dystonia, sedation, photosensitivity, orthostatic hypotension, and akathisia.	**Prochlorperazine:** 10–20 mg PO every 3–4 hours; 15–30 mg extended release spansule PO every 12 hours; 25 mg PR every 4–6 hours; 10–30 mg via IV every 3–4 hours **Perphenazine:** 1–5 mg via IV every 4–6 hours; may be given as a continuous IV infusion at a rate not greater than 1 mg/minute; 4 mg PO every 4–6 hours; maximum of 15 mg per 24 hours (outpatient) or 30 mg per 24 hours (inpatient)
Butyrophenones: droperidol, haloperidol	Acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy	Blocks dopamine$_2$ receptors in the CTZ and vomiting center; also decreases stimulation of the vomiting center via the vestibular pathway.	**Onset:** given PO 30–60 minutes; given IV or IM (intramuscularly, 3–10 minutes **Half-life:** 12–38 hours	Associated with extrapyramidal symptoms, especially in younger patients; may give with diphenhydramine to minimize these effects Use with caution in patients with cardiac disorders. Side effects include dystonia, akathisia, sedation, tachycardia, and hypotension.	**Droperidol:** 2.5–10 mg via IV every 3–4 hours; 0.5–2.5 mg via IV every 3–4 hours **Haloperidol:** 2–5 mg PO every 4 hours; 0.5–2 mg via IV or IM every 2–6 hours
Cannabinoids: dronabinol	Moderately emetogenic chemotherapy Not a first-line antiemetic medication	Unclear; the active ingredient in cannabis may inhibit prostaglandin synthesis or indirectly block the vomiting center.	**Onset:** 30–60 minutes **Duration:** 4–6 hours **Half-life:** 25–36 hours	Can produce physical and psychological dependency Side effects include mood changes; drowsiness; impaired perception, sensory function, and coordination; tachycardia; hypotension; and appetite stimulation.	**Dronabinol:** 2.5–10 mg PO two or three times a day
Benzodiazepines: alprazolam, lorazepam	Anticipatory nausea and vomiting; in addition to other agents to treat persistent nausea and vomiting Not a true antiemetic, but may be useful as an adjunct to antiemetic medications	Antiemetic activity unclear; reduce anxiety by potentiating the activity of gamma-amino butyric acid in the brain	**Onset:** given PO, 30 minutes; given IM, 15–30 minutes; given IV, 5–15 minutes **Duration:** 24–48 hours **Half-life:** 12–15 hours	Side effects include sedation, dizziness, and orthostatic hypotension.	**Alprazolam:** 0.25–0.5 mg PO two or three times a day **Lorazepam:** 1–3 mg PO or sublingually every 4–6 hours; 0.5–2.5 mg IV or IM every 4–6 hours

Note. All doses listed are for adults. Based on information from American Society of Health-System Pharmacists, 1999; Brown et al., 2001; Gralla et al., 1999; Skidmore-Roth, 2002; Spratto & Woods, 2002.

is approved for use with moderately emetogenic chemotherapy agents and usually is given twice daily beginning 30 minutes before chemotherapy administration and continuing for one or two days after completion of the therapy (Anastasia, 2000).

Researchers suggest that granisetron may be the most effective for the prevention of acute N&V caused by moderately or highly emetogenic chemotherapy (Bauduer, 1999). It usually is given as a single dose prior to chemotherapy.

Several researchers have compared the efficacy of granisetron to that of ondansetron. A double-blind study of 1,085 patients receiving chemotherapy randomized subjects to receive either granisetron 2 mg orally plus an IV placebo or ondansetron 32 mg via IV plus an oral placebo; use of dexamethasone or methylprednisolone was permitted as needed (Perez et al., 1998). The researchers found no significant differences between the two groups in the proportion of patients who attained total control of emesis during the first 24 or 48 hours after treatment.

In another study of 1,053 patients receiving highly emetogenic chemotherapy, patients were given either granisetron 2 mg orally or ondansetron 32 mg via IV; again, corticosteroids were permitted as needed (Gralla et al., 1998). The researchers found that the serotonin receptor antagonists were equally effective in controlling chemotherapy-induced N&V in this population.

Dolasetron, the most recently released serotonin receptor antagonist, has been found to have a shorter time to maximum concentration and a higher bioavailability than ondansetron or granisetron. Hydrolasetron, its active metabolite, is 50 times more potent in serotonin receptor antagonist activity than dolasetron. It usually is given in a single dose within one hour of chemotherapy administration (Valley, 2000).

Serotonin receptor antagonists have the advantages of a high rate of efficacy in the prevention of acute N&V, the option of oral or IV dosing, and fewer side effects than other types of antiemetics (Anastasia, 2000; Dranitsaris et al., 2001; Gralla et al., 1998, 1999). Side effects include headache, constipation, diarrhea, and transient, asymptomatic transaminase increases (Anastasia; Gralla et al., 1999). Dolasetron and ondansetron have been associated with mild prolongations in the cardiac QT interval several hours after administration (Anastasia; Valley, 2000). In addition, whether these drugs are effective in the prevention or treatment of delayed N&V is unclear (Latreille et al., 1998).

Corticosteroids

Corticosteroids, including dexamethasone and methylprednisolone, are used widely in the treatment of acute, delayed, and persistent chemotherapy-induced N&V. Although the exact mechanism of action of these drugs is not fully understood, they are believed to inhibit prostaglandin activity that promotes emesis. They also may change cellular permeability peripherally and in the CTZ, as well as stimulate the release of endorphins that cause appetite stimulation and a sense of well-being (Pendergrass, 1998; Perez, 1998).

Treatment guidelines recommend that corticosteroids be combined with serotonin receptor antagonists for the treatment of acute N&V (Gralla et al., 1999). This combination increases the complete response rate by 9%–40% compared to the use of serotonin receptor antagonists as monotherapy (Perez, 1998). Other studies have demonstrated that corticosteroids given in combination with other antiemetic agents, such as metoclopramide, improved the effectiveness of both drugs (Gralla et al., 1999). Advantages of corticosteroids include their wide availability in a range of dosage formulations, low cost, and oral or IV administration routes (Gralla et al., 1999).

Some researchers have questioned the use of corticosteroids in patients with cancer, expressing concern about the possibility of further immune suppression in patients who already are immunocompromised by disease or cancer treatment (Perez, 1998). Other concerns include use of corticosteroids in patients who may need careful monitoring to identify exacerbations of their underlying comorbid disease such as diabetes, hypertension, or psychosis, and the possibility of metastatic progression promoted by steroid use in patients with solid tumors (Pendergrass, 1998). Use of corticosteroids in patients receiving biotherapy for cancer is contraindicated (Brown et al., 2001). Most studies of corticosteroids in the treatment of acute or delayed emesis suggest that doses of 20 mg or less be given in divided doses twice daily for two to five days, with dose tapering (Gralla et al., 1999), so that the risk of corticosteroid-related complications are minimal.

Substituted Benzamides

Metoclopramide is the only substituted benzamide in use for the control of N&V in the United States. In addition to increasing gastric motility, metoclopramide acts as an antagonist for the dopamine$_2$ receptors at low doses; at higher doses, the drug also blocks serotonin receptors, although it is slightly less selective in this activity than the serotonin receptor antagonist drugs (Gralla et al., 1999; Pendergrass, 1998). Extrapyramidal side effects, including acute dystonic reactions, akathisia, and sedation, are associated with metoclopramide use (Gralla et al., 1999). In one study, 12% of patients treated with metoclopramide developed extrapyramidal side effects compared to 0% of patients treated with dolasetron (Valley, 2000). IV administration has been linked to cardiovascular side effects, particularly hypotension, tachycardia, and bradycardia (Thongprasert, 2000). The incidence of these effects increases with higher doses and in young adults and children (Pendergrass, 1998). Although the effects can be managed by premedication with diphenhydramine, extrapyramidal reactions are considered a dose-limiting toxicity (Gralla et al., 1999; Pendergrass; Thongprasert).

Phenothiazines

Phenothiazines such as prochlorperazine and perphenazine are used primarily for management of N&V associated with minimally or moderately emetogenic chemotherapy (Pendergrass, 1998). They act by blocking the dopamine$_2$ receptors.

Like metoclopramide, the phenothiazines are associated with extrapyramidal side effects, including sedation, postural hypotension, akathisia, and dystonic reactions. The use of high doses of phenothiazines is contraindicated, especially in children, because of these reactions (Pendergrass, 1998). These medications have the advantages of lower cost and oral or IV dosing options.

Butyrophenones

Butyrophenones act by blocking the dopamine$_2$ receptors active in the promotion of N&V (Gralla et al., 1999). These drugs, including droperidol and haloperidol, are used primarily to manage postoperative N&V and prevent anticipatory N&V associated with minimally emetogenic chemotherapy administration (Pendergrass, 1998).

The side effects of butyrophenones may be severe and include sedation, postural hypotension, akathisia, and dystonic reactions. Tolerance may develop with long-term dosing. These factors limit these drugs' usefulness in the management of chemotherapy-induced N&V (Pendergrass, 1998).

Cannabinoids

Although tetrahydrocannabinol, the active ingredient in marijuana, has been found to have antiemetic activity in patients receiving moderately emetogenic chemotherapy, it seldom is used as first-line antiemetic therapy (Pendergrass, 1998). The antiemetic effects of this compound in its pharmaceutical form, dronabinol, are less than that of metoclopramide or the serotonin receptor antagonists (Gralla et al., 1999).

A review of clinical trials testing the antiemetic efficacy and side effects of cannabinoids found that most patients preferred the inhaled form of the drug to the oral form (Tramer et al., 2001). The information consolidated from 30 randomized studies also indicated that although cannabinoids may have some use in controlling emesis, they are significantly more toxic, especially to elderly patients. Side effects include dizziness, sedation, hypotension, hallucinations, paranoia, and dysphoria (Gralla et al., 1999; Pendergrass, 1998; Tramer et al.). The severity of these side effects is so intense that it may lead to patients' withdrawal from treatment (Tramer et al.).

Benzodiazepines

Because they are highly effective in relieving anxiety, benzodiazepines may be useful in the prevention and management of anticipatory N&V (Pendergrass, 1998). Drugs in this class include alprazolam and lorazepam.

Although benzodiazepines have low antiemetic activity, they are considered to be useful as adjuncts to other antiemetic medications (Gralla et al., 1999; Pendergrass, 1998). However, a multicenter, randomized study of 225 patients compared the efficacy of granisetron alone to granisetron and alprazolam in the prevention of acute N&V after chemotherapy (Bauduer, 1999). The researchers found no significant differences in the control of these symptoms, suggesting that the use of a benzodiazepine does not improve the effectiveness of serotonin receptor antagonists in management of acute chemotherapy-induced N&V.

Neurokinin-1 Receptor Antagonists

Research currently is under way to investigate the use of neurokinin-1 receptor antagonists in chemotherapy-induced N&V. These agents block the activity of substance P, one of the neurotransmitters active in the emetogenic process (Dranitsaris et al., 2001; Pendergrass, 1998). Clinical studies indicate that neurokinin-1 receptor antagonists may be useful in the treatment of acute and delayed N&V (Pendergrass).

Several studies have examined the use of neurokinin-1 receptor antagonists in the control of acute chemotherapy-induced N&V. A double-blind, multicenter, parallel group study of 351 patients compared the effects of the neurokinin-1 receptor antagonist MK-869 in various combinations with granisetron and dexamethasone prior to and after highly emetogenic chemotherapy (Campos et al., 2001). They found that the group that received the combination of granisetron, dexamethasone, and MK-869 achieved significantly better control of acute N&V. Another study of 159 patients investigated the use of neurokinin-1 receptor antagonists combined with granisetron and dexamethasone (Navari et al., 1999). These researchers found that administration of all three drugs improved the control of acute N&V.

Neurokinin-1 receptor antagonists also may be useful in the control of delayed N&V. In one study, 63% of patients who received the neurokinin-1 receptor antagonist had no delayed symptoms, whereas only 29% of those who did not receive this treatment had no delayed N&V (Campos et al., 2001). Other studies have found that even a single dose of a neurokinin-1 receptor antagonist provided protection from delayed N&V (Navari et al., 1999; Rittenberg, 2002). This suggests that neurokinin-1 receptor antagonists may be valuable because few effective medications currently exist for this side effect.

The side effects of neurokinin-1 receptor antagonists include constipation, diarrhea, abdominal pain, headache, hiccups, asthenia, and anorexia (Campos et al., 2001). Phase III clinical trials of MK-869 currently are being conducted.

Combination Therapy

The current recommendations for the management of chemotherapy-induced N&V suggest that combining antiemetic agents will provide the best protection while minimizing adverse effects. This strategy is effective because N&V develops along multiple pathways; using medications that affect these different pathways will provide better control of the symptoms.

Expert panels, including the American Society of Clinical Oncology (Gralla et al., 1999), ASHP (1999), and NCCN (2001), have developed guidelines to assist clinicians in choosing the most effective medications for each type of N&V. See Table 3 for a summary of these guidelines.

Routes of Administration

Although most antiemetic medications are equally effective when given orally or via IV (ASHP, 1999; Gralla et al., 1999), the route of administration selected for a particular drug regimen can influence patients' compliance (Kraut & Fauser, 2001). To be most effective, a medication regimen should be convenient and cost effective and result in minimal adverse effects. Current research efforts are being directed toward developing improved drug delivery systems that will enhance medications' therapeutic effects as well as patient compliance.

Oral

Oral medication administration is preferred over most other routes because it is simple, convenient for most patients, and generally lower in cost than other methods (Anastasia, 2000). Fast-dissolving formulations are being developed for many medications, including antiemetics, which will further simplify medication administration (Kraut & Fauser, 2001).

The oral route may not be acceptable for all patients, however. Those who have severe stomatitis or esophagitis secondary to cancer treatment may not be able to swallow pills or capsules easily. Impaired gastrointestinal absorption may alter the metabolism of the drug, making it less effective. Nausea, vomiting, and diarrhea may make it difficult for patients to take oral medications or keep them in the gastrointestinal tract long enough to be absorbed properly (Kraut & Fausner, 2001).

Transmucosal

Rapidly dissolving tablets and films are being developed for use in patients who cannot swallow oral medications.

Table 3. Summary of Clinical Practice Guidelines for Treatment of Chemotherapy-Induced Nausea and Vomiting

Indication	American Society of Clinical Oncology	National Comprehensive Cancer Network	American Society of Health-System Pharmacists
Anticipatory nausea and vomiting (N&V)	1. Use the most active antiemetic regimen appropriate for the chemotherapy being given to prevent N&V. 2. If anticipatory N&V occurs, treat with behavioral therapy and systematic desensitization.	1. Prevention by use of effective antiemetic therapy before the first cycle of chemotherapy 2. If anticipatory N&V occurs a. Behavioral modification therapy b. May add anxiolytic medications prior to each treatment c. May add more potent antiemetic medications to the regimen	–
Acute N&V			
• High or very high emetogenic potential	Serotonin receptor antagonist plus a corticosteroid 1. Medications in each class may be used interchangeably at equivalent doses. 2. Medications in each class have equivalent activity given orally or via IV. 3. Single doses are preferred.	Serotonin receptor antagonist plus a corticosteroid 1. A benzodiazepine may be added if needed. 2. May be given orally or via IV.	Serotonin receptor antagonist plus a corticosteroid 1. Medications in each class may be used interchangeably at equivalent doses. 2. Oral and IV routes of administration are equivalent.
• Moderate emetogenic potential	Corticosteroid 1. May be used interchangeably at equivalent doses. 2. Has equivalent activity given orally or via IV. 3. Single doses are preferred.	Corticosteroid, phenothiazine, or substituted benzamide 1. A benzodiazepine may be added if needed. 2. Diphenhydramine may be used to minimize adverse effects of the phenothiazines or substituted benzamide. 3. May be given orally or via IV.	Serotonin receptor antagonist plus a corticosteroid 1. Medications in each class may be used interchangeably at equivalent doses. 2. Oral and IV routes of administration are equivalent.
• Low or very low emetogenic potential	No treatment is recommended.	No treatment is recommended.	No treatment is recommended.
• Combination chemotherapy	The antiemetic medication(s) recommended for the agent with the highest level of emetogenic potential should be given.	–	–
Delayed N&V			
• High or very high emetogenic potential	A corticosteroid alone, a corticosteroid plus metoclopramide, or a corticosteroid plus a serotonin receptor antagonist 1. Medications in each class may be used interchangeably at equivalent doses. 2. Medications in each class have equivalent activity given orally or via IV.	A phenothiazine or substituted benzamide 1. A benzodiazepine or butyrophenone may be added if needed. 2. Diphenhydramine may be used to minimize adverse effects of the phenothiazines or substituted benzamide. 3. May be given orally or via IV. 4. If N&V is uncontrolled, consider adjusting the chemotherapy dose or changing chemotherapy agents.	A serotonin receptor antagonist plus a corticosteroid or a phenothiazine plus a corticosteroid
• Moderate or low emetogenic potential	No regular use of antiemetic medication is recommended.	No regular use of antiemetic medication is recommended.	No regular use of antiemetic medication is recommended.
Persistent N&V	1. Re-evaluate risk, antiemetic medications, chemotherapy, tumor, and concurrent disease or medication factors. 2. Ensure that the best regimen is being used for the emetic setting. 3. Consider adding an antianxiety agent. 4. Consider substituting a dopamine receptor antagonist for the serotonin receptor antagonist (or add the dopamine antagonist to the regimen).	A serotonin receptor antagonist plus a butyrophenone or a cannabinoid alone 1. Serotonin receptor antagonists and butyrophenones may be given orally, rectally, or via IV. 2. Cannabinoids may be given orally or rectally.	1. Add an antiemetic agent from another class of medications; in adults, benzodiazepines, corticosteroids, substituted benzamides, cannabinoids, or butyrophenones may be considered. 2. Increase the dose of the antiemetic drug to the maximum in the acceptable dose range. 3. Use a combination of approaches to control N&V.

Note. Based on information from American Society of Health-System Pharmacists, 1999; Gralla et al., 1999; National Comprehensive Cancer Network, 2001.

Prochlorperazine and ondansetron currently are available; other drugs are under investigation for this type of administration. This route is convenient and easy to use and avoids first-pass elimination. However, it requires a special technique to place the tablet or film into the buccal pouch to ensure rapid dissolution and absorption (Kraut & Fauser, 2001).

Rectal

Rectal administration of medication often is used when other routes of administration are not feasible. It has the advantage of being easy to use; however, many patients find this type of administration uncomfortable. Absorption of medications given by this route may be uneven, resulting in peaks and troughs of medication activity (Kraut & Fauser, 2001).

Transdermal

The major obstacle for the transdermal route is the physiochemical properties of the drugs themselves; few thus far have been found to be suitable for transdermal administration, although research is ongoing to investigate the use of lerisetron, a new serotonin receptor antagonist, in this form (Kraut & Fauser, 2001).

Transdermal administration has several advantages. First, transdermal patches are easy to use, resulting in high patient compliance. Second, this route of administration avoids the first-pass effect, allowing higher bioavailability of the medication. Finally, transdermal administration permits stability of serum drug levels, which allows for long-term effect and fewer serious side effects (Kraut & Fauser, 2001).

Because transdermal administration requires time to reach peak serum concentrations, this route is not useful for patients who require acute control of N&V. Those who have dermatologic side effects of cancer therapy also would be unable to use this technique (Kraut & Fauser, 2001).

Intravenous

This method is used most often in the inpatient setting but also may be available in patients' homes through coordination with home infusion agencies. The IV route is useful for patients who require standard, precise doses that can be rapidly metabolized (Kraut & Fauser, 2001). Disadvantages of the IV route of administration include a higher cost for the drugs and the relative complexity of the administration procedure. More nursing time for drug preparation, administration, and port or catheter care add up to a less convenient, more costly alternative (Kraut & Fauser, 2001).

Intranasal

Metoclopramide is the only antiemetic medication currently available in intranasal form in the United States. Pharmacokinetic research indicates that intranasal administration is equal to IV and intramuscular metoclopramide in the control of N&V associated with moderately emetogenic chemotherapy. The drug generally is well tolerated and has achieved high compliance among patients. Intranasal metoclopramide is associated with the same types of systemic side effects as metoclopramide given by any other route (Kraut & Fauser, 2001).

Pulmonary

The inhalant route of administration is considered one of the most promising for improving the absorption and efficacy of many drugs. Inhalation permits rapid onset of drug effect, instant systemic circulation, and higher drug bioavailability. Currently, cannabinoids are the only antiemetic drugs available in the inhaled form, but the use of marijuana as a medication is not legal in all states (Kraut & Fauser, 2001).

Implications for Nurses

Nurses play an important role in the management of chemotherapy-induced N&V. Careful assessment of patients, an understanding of the chemotherapy treatments they are receiving, and knowledge of the types of antiemetic drugs available, their indications and contraindications, and their side effects are key to the proper selection of a nursing care plan.

When caring for patients who are receiving chemotherapy, nurses must assess the patients for potential adverse reactions, including N&V. Such assessment should include a physical examination and a thorough health history.

Physical examination of patients with N&V should include assessment of weight changes and evaluation of laboratory values to identify metabolic imbalances at early stages (Itano & Taoka, 1998). Factors to be addressed in the health history

Table 4. Risk Factors Associated With Nausea and Vomiting

Risk Factor	Comments
Emetogenic potential of the chemotherapy agent	Considered to be the most important predictor of chemotherapy-induced nausea and vomiting (N&V)
Poor control of N&V with prior chemotherapy	Associated with anticipatory, acute, and delayed N&V
Female gender	Although the association is not strong, gender has been linked with anticipatory, acute, and delayed N&V.
Younger age	Age under 45 years has been associated with anticipatory N&V; age under 50 years, with acute N&V.
History of motion sickness	Associated with anticipatory, acute, and delayed N&V
Low chronic alcohol intake	Alcohol intake of less than 100 g per day for a period of years has been associated with lower risk of acute N&V; in general, higher intake is associated with lower risk.
Anxiety about treatment	Most strongly associated with anticipatory N&V; may be difficult to treat
Current infection	Associated with acute, delayed, or persistent N&V
Metabolic imbalances	Hyperglycemia, hypercalcemia, and hyponatremia are common; they can cause N&V or be caused by it.
Food toxins	Associated with damage to enterochromaffin cells in the intestinal tract
Renal or hepatic dysfunction	Associated with acute, delayed, or persistent N&V
Central nervous system disease or injury	Primary tumors, metastasis, or treatment-related injuries that affect the chemoreceptor trigger zone
Gastrointestinal obstruction	Stimulate enterochromaffin cells to release serotonin, which, in turn, stimulates the chemoreceptor trigger zone

Note. Based on information from Bauduer, 1999; Bender et al., 2002; Eckert, 2001; Gralla et al., 1999; Hickok et al., 2001; Itano & Taoka, 1998.

include patients' knowledge of and experience with chemotherapy, their expectations about the treatment, their current health status, and any comorbidities that could contribute to intolerance of the treatment (Bender et al., 2002). Table 4 provides a summary of risk factors associated with the development of acute emesis. Current infections, metabolic imbalances, or comorbidities such as central nervous system disease or injury or gastrointestinal obstruction also can cause N&V (Itano & Taoka, 1998).

The emetogenic potential of the chemotherapy agent is considered by most experts to be the most important factor in predicting N&V (ASHP, 1999; Kraut & Fauser, 2001) and most often is the basis for guidelines for antiemetic therapy. Unfortunately, few studies have examined the potential of many of these agents for causing delayed N&V, how their emetogenic potential changes when they are given in combination, or their effects when given as part of a high-dose chemotherapy regimen (Gralla et al., 1999).

Another consideration is the potency of the antiemetic agent. Well-supported guidelines can assist in this assessment; through multiple clinical trials, researchers have established which agents are useful in various situations. These guidelines suggest that beginning therapy prior to the development of symptoms and continuing the treatment for as long as necessary is an extremely important factor in achieving good control of chemotherapy-induced N&V (NCCN, 2001).

Perhaps the key component in the assessment of patients with chemotherapy-induced N&V is the evaluation of the effectiveness of the antiemetic therapy. As previously discussed, several options are available for treatment: medications with different mechanisms of action, combinations of these medications, and alternate routes of administration. Nurses must remember that guidelines are only guidelines and cannot allow for variation among patients or their individual situations. Nurses play a vital role in observing and assessing patients to adjust their therapies to meet patients' needs.

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References

American Society of Health-System Pharmacists (ASHP). (1999). ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. *American Journal of Health-System Pharmacists, 56,* 729–764.

Anastasia, P.J. (2000). Effectiveness of oral 5-HT_3 receptor antagonists for emetogenic chemotherapy. *Oncology Nursing Forum, 27,* 483–493.

Bauduer, F. (1999). Granisetron plus or minus alprazolam for emesis prevention in chemotherapy of lymphomas. *Leukemia and Lymphoma, 34,* 341–348.

Bender, C.M., McDaniel, R.W., Murphy-Ende, K., Pickett, M., Rittenberg, C.N., Rogers, M.P., et al. (2002). Chemotherapy-induced nausea and vomiting. *Clinical Journal of Oncology Nursing, 6,* 94–102.

Brown, K.A., Esper, P., Kelleher, L.O., Brace O'Neill, J.E., Polovich, M., & White, J.M. (Eds.) (2001). *Chemotherapy and biotherapy guidelines and recommendations for practice.* Pittsburgh, PA: Oncology Nursing Society.

Campos, D., Pereira, J.R., Reinhardt, R.R., Carracedo, C., Poli, S., Vogel, C., et al. (2001). Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with gransetron and dexamethasone or with dexamethasone alone. *Journal of Clinical Oncology, 19,* 1759–1767.

Dranitsaris, G., Leung, P., Ciotti, R., Ortega, A., Spinthouri, M., Liaropoulos, L., et al. (2001). A multinational study to measure the value that patients with cancer place on improved emesis control following cisplatin chemotherapy. *Pharmacoeconomics, 19,* 955–967.

Eckert, R.M. (2001). Understanding anticipatory nausea. *Oncology Nursing Forum, 28,* 1553–1560.

Gralla, R.J., Navari, R.M., Hasketh, P.J., Popovic, W., Strupp, J., Noy, J., et al. (1998). Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *Journal of Clinical Oncology, 16,* 1568–1573.

Gralla, R.J., Osoba, D., Kris, M.G., Kirkbride, P., Hesketh, P.J., Chinnery, L.W., et al. (1999). Recommendations for the use of antiemetics: Evidence-based clinical practice guidelines. *Journal of Clinical Oncology, 17,* 2971–2994.

Hickok, J.T., Roscoe, J.A., & Morrow, G.R. (2001). The role of patients' expectations in the development of anticipatory nausea related to chemotherapy for cancer. *Journal of Pain and Symptom Management, 22,* 843–850.

Italian Group for Antiemetic Research. (2000). Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *New England Journal of Medicine, 342,* 1554–1559.

Itano, J., & Taoka, K. (1998). *Core curriculum for oncology nursing,* (3rd ed.) Philadelphia: Saunders.

Kraut, L., & Fauser, A.A. (2001). Antiemetics for cancer chemotherapy-induced emesis: Potential of alternative delivery systems. *Drugs, 61,* 1553–1562.

Latreille, J., Pater, J., Johnston, D., Laberge, F., Stewart, D., Rusthoven, J., et al. (1998). Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. *Journal of Clinical Oncology, 16,* 1174–1178.

National Comprehensive Cancer Network. (2001). *Nausea and vomiting: Treatment guidelines for patients with cancer, version I.* Washington, D.C.: American Cancer Society and Author.

Navari, R.M., Reinhardt, R.R., Gralla, R.J., Kris, M.G., Hesketh, P.J., Khojasteh, A., et al. (1999). Reduction of cisplatin-induced emesis by a selective neurokinin-1 receptor antagonist. *New England Journal of Medicine, 340,* 190–195.

Otto, S.E. (2001). *Oncology nursing* (4th ed.). St. Louis, MO: Mosby, Inc.

Pendergrass, K.B. (1998). Options in the treatment of chemotherapy-induced emesis. *Cancer Practice, 6,* 276–281.

Perez, E.A. (1998). Use of dexamethasone with 5-HT_3-receptor antagonists for chemotherapy-induced nausea and vomiting. *Cancer Journal, 4*(2), 72–78.

Perez, E.A., Sandbach, J., Reeves, J., Chawla, S., Markman, M., Hainsworth, J., et al. (1998). Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: A multicenter, double-blind, randomized parallel study. *Journal of Clinical Oncology, 16,* 754–760.

Rittenberg, C. (2002). A new class of antiemetic agents on the horizon. *Clinical Journal of Oncology Nursing, 6,* 103–104.

Roscoe, J.A., Morrow, G.R., Hickok, J.T., & Stern, R.M. (2000). Nausea and vomiting remain a significant clinical problem: Trends over time in controlling chemotherapy-induced nausea and vomiting in 1,413 patients treated in community clinical practices. *Journal of Pain and Symptom Management, 20,* 113–121.

Skidmore-Roth, L. (2002). *Nursing drug reference.* St. Louis, MO: Mosby.

Spratto, G.R., & Woods, A.L. (2002). *PDR nurse's drug handbook.* Montvale, NJ: Delmar.

Thongprasert, S. (2000). Efficacy and tolerability of tropisetron in the prevention of cisplatin-induced nausea and vomiting in advanced non-small cell lung cancer. *Acta Oncologica, 39,* 221–224.

Tramer, M.R., Carroll, D., Campbell, F.A., Reynolds, D.J.M., Moore, R.A., & McQuay, H.J. (2001). Cannabinoids for control of chemotherapy-induced nausea and vomiting: Quantitative systematic review. *BMJ, 323,* 1–9.

Valley, A.W. (2000). A review of dolasetron as management of nausea and vomiting in cancer patients. *Journal of Oncology Pharmaceutical Practice, 6*(3 Suppl.), S28–S40.

Wilkes, G.M., Ingwersen, K., & Barton-Burke, M. (2000). *Oncology nursing drug handbook.* Boston: Jones and Bartlett.