

Chemotherapy-Induced Nausea and Vomiting: Prevention, Detection, and Treatment—How Are We Doing?

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Chemotherapy-induced nausea and vomiting (CINV) has been with us for as long as cytotoxic chemotherapy has been used to treat cancer [1]. As it was 20 years ago, CINV is still among the most troubling adverse effects of cancer treatment that patients cite most often [2, 3]. In the past decade, more effective antiemetic medications were introduced and widely adopted. These serotonin (5-HT₃) receptor antagonists are considered safe and work alone or in combination with corticosteroids (eg, dexamethasone) or other agents. Most recently, neurokinin-1 (NK-1) receptor antagonists, a new class of antiemetic, have been studied. One such drug (aprepitant [Emend]) has been approved for use in combination with other antiemetics [4].

Despite the availability of effective antiemetic regimens and guidelines for their use, cancer patients are not receiving optimal care in terms of preventing CINV. Study findings [5] indicate that actual clinical practice is lagging behind the guidelines for adoption and use of prophylactic antiemetics. In fact, the incidence of CINV, especially at home on days 2–5 after initiation of chemotherapy, has not changed remarkably since 1985 [6, 7].

Focusing on CINV is therefore important, for several reasons. First, CINV is a frequent occurrence and negatively affects patients' treatment experience. Second, clinical practice is inconsistent where prophylactic treatment is concerned. And third, CINV is often preventable; that is, there is room for improvement in clinical outcomes, as well as patients' quality of life [8]. The purpose of this supplement is to review the incidence of CINV, increase awareness of how it affects patients immediately after treatment and in the 2–5 days after chemotherapy, describe treatment approaches as outlined in current guidelines, and examine the types of treatments available, including 5-HT₃ receptor

Abstract As cancer chemotherapy has led to better medical outcomes, patients' concerns about quality of life and adverse effects have become increasingly important. Chemotherapeutic regimens have improved and are more finely targeted than in the past, but chemotherapy-induced nausea and vomiting (CINV) remains a major obstacle and affects patients' satisfaction with treatment. Despite the development of effective antiemetic therapies and practice guidelines recommending their use, clinical practice lags behind. Patients continue to be undertreated when receiving moderately or highly emetogenic chemotherapy while, perhaps, being overtreated when receiving mildly emetogenic chemotherapy. An understanding of the physiologic and psychological processes that lead to CINV has improved. Different neurotransmitters may trigger acute versus delayed emesis, whereas psychological factors appear to predominate in anticipatory nausea. This supplement will examine current clinical practice to explore where prophylactic treatment for CINV is lagging, determine the role of psychological triggers, and discuss treatment approaches that are supported by existing practice guidelines. In addition, new approaches to treatment, such as neurokinin-1 antagonists, acupuncture, and acustimulation, will be discussed.

antagonists, NK-1 antagonists, and non-pharmacologic approaches.

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Three Phases of CINV

To understand CINV better, it is important to recognize its three distinct phases: acute, delayed, and anticipatory (Figure 1) [8].

The acute form of CINV is the most well-recognized form. It is also known as posttreatment

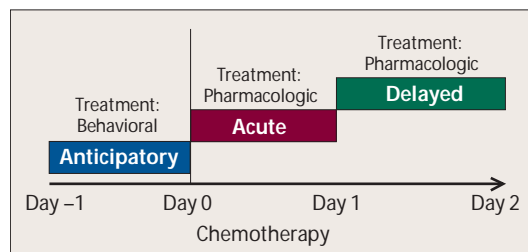


Figure 1 Timing and Treatment of Three Distinct Phases of CINV

From ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery [8].

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CINV. Acute CINV is usually defined as nausea and/or vomiting within the first 24 hours after administration of cancer chemotherapy [8].

Delayed CINV is usually defined as nausea or vomiting that begins after the first 24 hours because of administration of chemotherapy. Delayed CINV may last for as long as 120 hours after chemotherapy administration [8].

Anticipatory CINV occurs before the second or later course of chemotherapy. Anticipatory CINV is a learned or conditioned response to poorly managed CINV during previous courses of chemotherapy. As a learned response, anticipatory CINV has a strong psychological component and does not respond well to antiemetic prophylaxis or treatment. However, it has been shown to respond to behavioral interventions [8]. The most effective approach to preventing anticipatory CINV is to prevent nausea and vomiting associated with the patient's earlier courses of chemotherapy.

Incidence of CINV

In the placebo arms of a series of controlled clinical studies [8], 98% of patients who received cisplatin-based chemotherapy developed acute emesis, and 61% developed delayed emesis. Patients reported that their nausea and vomiting were most severe from 48 to 72 hours after they received cisplatin chemotherapy [8]. In a 1985 study, Kris et al [6] reported that 38% of patients experienced acute vomiting after receiving cisplatin chemotherapy, and 61% of patients reported vomiting on days 2–3 after receiving cisplatin, despite treatment with metoclopramide and dexamethasone at the time that cisplatin was administered. From cisplatin administration through 120 hours later, between 24% and 78% of patients reported nausea; the highest incidence of nausea, like that of vomiting, was from 48 to 72 hours after chemotherapy [6]. In a recent study [7] of patients receiving moderately emetogenic chemotherapy, 47% experienced acute nausea and 28% acute vomiting, despite that most patients (84%) received a 5-HT₃ receptor antagonist in combination with a corticosteroid to prevent CINV. In addition, 57% of patients experienced nausea and 41% vomiting on days 2–5 after administration of chemotherapy [7]. The incidence of delayed CINV depends on the type of chemotherapy used, and the emetogenic potential of chemotherapy agents is one of the factors to be considered when decisions about prophylactic antiemetics are made (Table 1).

Table 1

Incidence of Emesis on Days 2 and 3 Following Chemotherapy

	CISPLATIN	FAC	CMF	CARBOPLATIN
Day 2	40%	> 50%	25%	10%–20%
Day 3	61%	< 20%	< 10%	NA

FAC = 5-fluorouracil, Adriamycin (doxorubicin), and cyclophosphamide; CMF = cyclophosphamide, methotrexate, and 5-fluorouracil; NA = data not available.

From Martin [9].

Regardless of the regimen used, delayed CINV presents a more difficult treatment challenge than does acute CINV. Agents that are highly effective in preventing acute vomiting are less effective in preventing delayed vomiting. A review [10] of three clinical studies compared the serotonin-antagonist ondansetron (Zofran) with the dopamine-antagonist metoclopramide for the prevention of delayed emesis associated with non-cisplatin-based chemotherapy. The study results found that 34% (n = 152) of patients treated with metoclopramide experienced emesis on day 2 and 16% (n = 139) on day 3. Among patients treated with ondansetron, 17% (n = 149) experienced emesis on day 2 and 11% (n = 135) on day 3 [10].

The relationship between acute and delayed CINV is not completely understood, but the control of acute CINV appears to minimize the development of severe, delayed CINV [11]. Furthermore, control of acute CINV minimizes the risk of a patient developing anticipatory CINV before subsequent courses of chemotherapy [11]. When patients whose acute CINV was completely controlled were treated with dexamethasone plus ondansetron, 92% had complete control of delayed CINV. Among patients who experienced acute CINV, only 41% had complete control of delayed CINV [12].

Effects of CINV on Quality of Life

Overall, between 70% and 80% of patients who receive cancer chemotherapy experience nausea and/or vomiting [13]. Almost 60% experience nausea after their first course of chemotherapy, and about 30% experience vomiting [14]. These episodes of nausea and/or vomiting vary in severity but may significantly affect patients' lives. In particular, CINV that occurs during the 3-day period after chemotherapy, when the patient is at home, has a negative effect on a patient's ability to care for himself or herself. Patients may have difficulty

preparing or eating meals, performing household tasks, or enjoying other daily activities (Figure 2) [15]. Furthermore, the experience of CINV may lead patients to postpone or withdraw from subsequent courses of chemotherapy, with negative effects on the management of their disease [13].

Controlling CINV is an important component of maintaining a patient's quality of life during cancer treatment. When CINV is not fully controlled, health-related quality of life suffers [16–18], and uncontrolled CINV continues as an adverse effect of treatment that most concerns patients [3]. In a 1997 survey by de Boer-Dennert et al [3], cancer patients ranked (from greatest concern to less concern) nausea, loss of hair, and vomiting as the three adverse effects that most distressed them. Assessments of health-related quality of life have been shown to associate CINV with significant ($P < 0.05$ to $P < 0.0001$) worsening of scores in cognitive function, global quality of life, fatigue, anorexia, insomnia, and dyspnea [16]. Osoba et al [16] suggested that patients who score significantly lower on quality-of-life functional measures or significantly higher on quality-of-life symptom measures before receiving moderately or highly emetogenic chemotherapy are more likely to experience vomiting afterward. After receiving moderately or highly emetogenic chemotherapy, patients who experienced vomiting showed significantly worse scores on most physical and symptom measures than did patients who had no vomiting (Table 2) [17]. Among these patients, the experience of one or two episodes of vomiting was as detrimental to health-related quality of life as more severe vomiting on all measurements except anorexia and global quality of life. This suggests that complete control of CINV is necessary to significantly improve

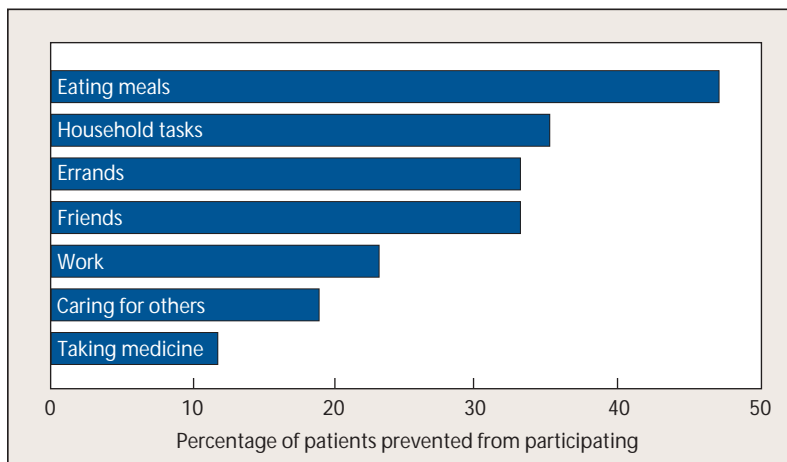


Figure 2 Consequences of Chemotherapy-Induced Emesis on Daily Activities

Results of a follow-up telephone interview in which patients were asked whether chemotherapy-induced emesis had prevented them from performing certain daily activities. From Lindley et al [15].

patients' quality-of-life perceptions [16]. Similarly, Rusthoven et al [18] found that CINV contributed to most, but not all, of the measured deterioration in health-related quality of life in the 6 days after treatment with moderately emetogenic chemotherapy. In their study [18], severe vomiting peaked on day 2 (52%) and day 3 (33%), although a large percentage (50%–100%) of patients reported "a little" vomiting on each day except day 2 (24%).

Preventing or minimizing CINV can improve patients' health-related quality of life after cancer chemotherapy. Other studies have reviewed whether quality-of-life outcomes differ based on the antiemetic prophylaxis that is used. In a study [19] of the efficacy and quality-of-life outcomes

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Table 2
Relationship of Mean Function Scores and Risk of Vomiting

FUNCTION DOMAIN	MEAN PRE-CHEMOTHERAPY SCORES ^a IN PATIENTS WITH		P	MEAN CHANGE ^b FROM PRE-CHEMOTHERAPY TO DAY 8		P
	NO VOMITING	VOMITING		NO VOMITING	VOMITING	
Physical	78.7	70.3	0.001	-6.7	-9.7	0.20
Role	75.1	59.7	0.001	-10.4	-7.3	0.39
Emotional	70.1	67.1	0.20	5.0	1.4	0.15
Cognitive	83.8	82.4	0.47	1.8	-7.6	0.0001
Social	75.7	60.8	0.0001	-3.0	-7.6	0.11
Global quality of life	62.9	53.7	0.0001	-4.4	-13.8	0.0001

^a Higher scores indicate better function. ^b Minus sign denotes worsening from pre-chemotherapy to day 8. Adapted from Osoba et al [17]; used with permission.

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with ondansetron or metoclopramide, 183 women undergoing moderately or highly emetogenic chemotherapy for breast cancer were evaluated over six courses of chemotherapy. All of the women received intravenous (IV) dexamethasone (16 mg) plus either IV ondansetron (8 mg; $n = 93$) or IV metoclopramide (60 mg; $n = 90$) before chemotherapy. Over the next 5 days, the women took either 8 mg of ondansetron three times a day or 20 mg of metoclopramide three times a day. Women who took ondansetron had significantly ($P < 0.001$) less emesis and nausea after the first course of chemotherapy and better maintenance of emetic control over six courses of chemotherapy, compared with women who took metoclopramide. The Rotterdam Symptom Checklist was used to assess health-related quality of life. It uses a 4-point scale to evaluate various aspects of patients' lives, with 0 representing an optimal outcome and 3 representing the worst outcome. After the first course of treatment and throughout the trial (Figure 3), patients who received ondansetron scored significantly better on the psychological subscale (ie, irritability, worry, depression, nervousness, loneliness, tension, anxiety, desperation) than did patients receiving metoclopramide [19].

Morrow et al [14] showed that control of CINV during a patient's first course of treatment positively affects quality of life and future treatment courses. Their study was done with 1,413 patients, of whom 839 (59%) developed nausea and 404 (29%) developed vomiting after the first course of chemotherapy. Approximately 72% of patients who

vomited after their first course of chemotherapy went on to vomit after at least one subsequent course, and 31% vomited after every subsequent course. The exact opposite was true of those who did not vomit after their first treatment; 76% continued to be free of vomiting during all subsequent treatment courses. In addition, 13% of patients who experienced vomiting after their first treatment had at least one episode of anticipatory vomiting before subsequent treatments, compared with 5% of the patients who did not vomit after their first course of chemotherapy [14].

Clinical Reality vs Caregiver Perception

Practice guidelines from the American Society of Clinical Oncology (ASCO), the American Society of Health-System Pharmacists (ASHP), the Multinational Association for Supportive Care in Cancer (MASCC), and others have been developed to help standardize the use of antiemetic prophylaxis with chemotherapy [8, 20–22]. These efforts have raised awareness of the continuing presence of CINV; still, problems with undertreatment persist.

In 2002, Grunberg et al [7] reported the results of a survey conducted among physicians and nurses at six oncology centers. The survey asked them to estimate the frequency of acute and delayed CINV among patients in their own practices receiving moderately emetogenic chemotherapy. Patients who were receiving such chemotherapy were then asked to complete a 5-day nausea/vomiting diary and a day-6 Functional Living Index–Emesis (FLIE) questionnaire. The latter assessed the impact of CINV on the patients' daily lives. All of the patients received antiemetic prophylaxis with a 5-HT₃ receptor antagonist, and 84% received corticosteroids.

The results [7] showed a dichotomy between physicians' and nurses' perceptions of CINV and patients' actual experiences. The oncology staff estimated that during the first 24 hours after the initial course of chemotherapy, 69% of patients would have no nausea and 83% would have no vomiting. However, 53% of patients had no nausea and 72% no vomiting. The staff estimated that 76% of patients would have no delayed nausea and 91% no delayed vomiting. Here, the discrepancy was larger; in fact, only 43% of patients had no delayed nausea and 59% no delayed vomiting. Further, 59% of patients reported that nausea and 25% reported that vomiting had significantly affected

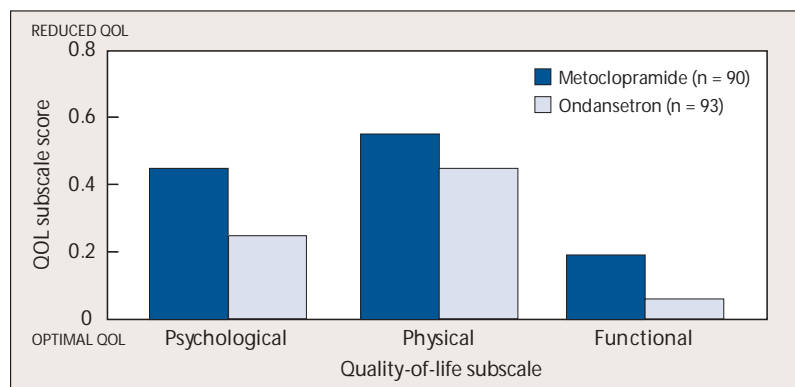


Figure 3 Mean Quality-of-Life (QOL) Scores After Six Courses of Chemotherapy for Breast Cancer in 183 Women

Patients who received ondansetron scored significantly better ($P < 0.001$) on the psychological subscale. For the other subscales (physical and functional), no significant difference was observed between ondansetron or metoclopramide. Adapted from Soukop et al [19]; used with permission.

their daily activities (based on FLIE score) during the study period.

These results suggest that the incidence and impact of CINV are underestimated by oncology physicians and nurses [7]. More recently, a study of 322 chemotherapy-naïve patients found that despite appropriate use of antiemetic prophylaxis, 73% reported delayed nausea on days 2–5 after their first treatment course, including 18% who did not develop nausea until day 3 or later. More than half described their nausea as of moderate or greater intensity [23].

De Angelis et al [5, 24] conducted two studies to evaluate the effect of guidelines on practice. In the first study, they interviewed physicians at 26 oncology centers before and after the MASCC guidelines were released in 1998 [24]. Some of the centers also received a visit from a local expert, whose goal was to increase awareness of the guidelines, approximately 3 months before release of the guidelines. The results showed that publication of the guidelines had a positive effect on the use of antiemetic prophylaxis for acute and delayed emesis. Use of prophylaxis for acute CINV associated with cisplatin administration increased from 76% before to 92% after publication of the guidelines. Prophylaxis for acute CINV associated with use of moderately emetogenic chemotherapy increased from 42% before to 69% after publication of the guidelines. Use of prophylaxis for delayed CINV differed somewhat. After the guidelines, 71% of patients treated with cisplatin and 50% of those treated with moderately emetogenic chemotherapy received antiemetic prophylaxis, compared with 53% and 34%, respectively, before the guidelines. These results suggest that between 29% and 50% of patients treated with moderately emetogenic chemotherapy still did not receive the recommended prophylaxis for delayed CINV. Centers that received a visit from a local expert increased their use of antiemetic prophylaxis for acute CINV associated with cisplatin to 100% and for delayed CINV from 8.7% to 42.9%.

In 2003, De Angelis et al [5] revisited the question of whether the publication of guidelines affects clinical practice. They reviewed the antiemetic prophylaxis prescribed for delayed emesis in 2,393 consecutive patients undergoing various forms of chemotherapy ($n = 437$ for cisplatin; $n = 1,065$ for other moderately-highly emetogenic chemotherapy; $n = 607$ for intermediately emetogenic chemotherapy; and $n = 215$ for low

emetogenic chemotherapy) to determine the number of patients treated according to guidelines [5]. They found that only 29% of patients receiving cisplatin and 13% of patients receiving moderately-highly emetogenic chemotherapy were treated with the recommended combination of a 5-HT₃ receptor antagonist plus corticosteroids, and 18% and 7%, respectively, were treated with the alternatively recommended combination of corticosteroids plus benzamides. Thus, only 47% of patients treated with cisplatin and 20% of patients treated with other moderately-highly emetogenic chemotherapy received recommended prophylaxis for delayed CINV. For intermediate emetogenic and low emetogenic chemotherapy regimens, in which guidelines recommend no prophylaxis for delayed emesis, 54% and 69%, respectively, were treated according to guidelines. These findings continue to indicate that prophylaxis for delayed vomiting is underused for patients receiving cisplatin or moderately-highly emetogenic chemotherapy and overused for patients receiving chemotherapy regimens with little or no emetogenic potential [5].

Physiology of CINV

Chemotherapy-induced nausea and vomiting are distinct components and must be assessed independently. Nausea is defined as a subjective, unpleasant feeling characterized by flushing, tachycardia, and an awareness of the urge to vomit. Because it is subjective, nausea is the most difficult symptom for physicians to assess. Visual analog scales are often used so that patients can indicate their level of distress.

Vomiting is characterized by the forced expulsion of stomach contents through the combined actions of the abdominal muscles, diaphragm, and the opening of the gastric cardia [8]. Vomiting is triggered by afferent impulses to the vomiting center, located in the lateral reticular formation of the medulla, from the chemoreceptor trigger zone (CTZ) or from afferent fibers located in the gastrointestinal tract, cerebral cortex, and vestibular apparatus. In general, vomiting triggered by drugs or chemical agents is mediated through the CTZ [25].

Many pathways and neurotransmitter receptors are involved in CINV. The dopamine-2 (D₂) and serotonin-3 (5-HT₃) receptors have long been known to play a major role; new research suggests a significant role, particularly in delayed CINV, for NK-1 receptors as well [26]. Histamine and mus-

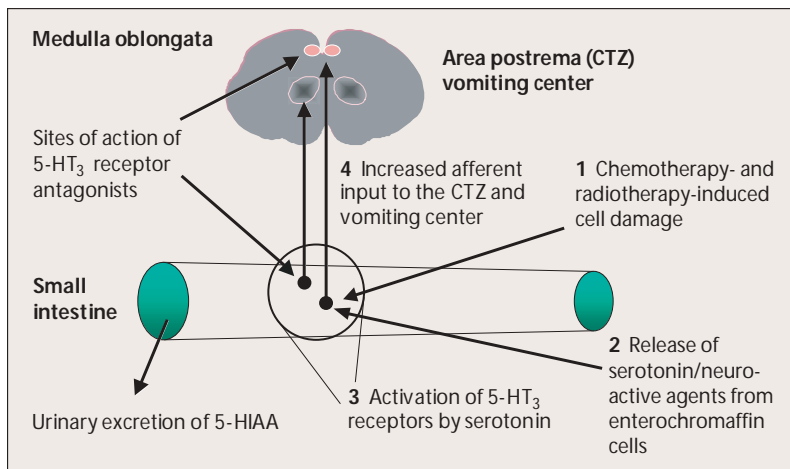


Figure 4 Proposed Pathways of Chemotherapy-Induced Emesis and Sites of Action of 5-HT₃ Receptor Antagonist Antiemetics

From ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery [8]. Adapted from Hesketh and Gandara [28]; used with permission.

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carinic receptors have lesser roles but are prominent in vomiting associated with motion sickness [8, 27]. Chemotherapy is known to induce emesis, in part, by causing enterochromaffin cells lining the gastrointestinal tract to release serotonin in response to cell damage (Figure 4). Serotonin binds to vagal afferent 5-HT₃ receptors in the gastrointestinal tract, which send impulses to the vomiting center. The CTZ has an important role in chemotherapy-induced emesis because it lies outside the blood-brain barrier, which makes it accessible to circulating emetogenic substances. Studies of this model show that patients who receive cisplatin-based chemotherapy transiently have increased levels of the serotonin by-product 5-HIAA, which correlate with emesis [8, 10, 28].

Antiemetics that are highly effective in treating acute emesis, such as 5-HT₃ receptor antagonists, have a lower efficacy in preventing delayed emesis. Based on this reduced efficacy, it has been theorized that additional neurotransmitter receptors, such as NK-1 receptors, may be involved in delayed emesis attributed to chemotherapy [26]. For example, after cisplatin-based chemotherapy is administered, serotonin serum levels peak at approximately 6 hours, correlating with acute chemotherapy-induced emesis, but do not peak again at 48 hours, which is the time of greatest risk for delayed chemotherapy-induced emesis [8].

Substance P is a peptide neurotransmitter that binds preferentially to the NK-1 receptor.

Neurokinin-1 receptors densely populate the intestinal tract and the nucleus tractus solitarius of the brain. The action of substance P at the NK-1 receptors in the nucleus tractus solitarius is final common pathway in the vomiting response. Chemotherapy drugs cause serotonin to be released, with downstream effects in the vomiting center. Substance P is co-localized with serotonin in intestinal enterochromaffin cells and is released in response to the increased release of serotonin. However, substance P is also released directly in response to the toxic effects of chemotherapy drugs on the CTZ [26, 29].

The two-phase release of substance P may contribute to the phases of CINV. The acute phase appears to be mediated by serotonin and substance P. In the delayed phase, although serotonin is still present, substance P appears to be the primary mediator [26, 29]. The lack of a universally accepted experimental model for delayed emesis has impeded research in this area.

Risk Factors for CINV

Risk factors for CINV fall into patient-related and treatment-related categories. Patient-related risk factors include age younger than 50 years, female sex, history of light alcohol use (heavier drinkers have less emesis), a prior history of nausea and/or vomiting associated with pregnancy or motion sickness, increased anxiety, a history of CINV with prior exposure to chemotherapy, and low social functioning [8, 30, 31]. The risk of developing CINV increases with the number of risk factors present [31]. Treatment-related risk factors include the emetogenicity of the chemotherapy regimen used (eg, types of drugs, dosages, and combinations versus sequential administration) [8]. To further explore these treatment-related factors, a definition of emetic potential must be formulated. Koeller et al [32] devised a system to grade the overall emetic potential of chemotherapy drugs that will be discussed in this supplement (Table 3). Table 4 lists different chemotherapy drugs and ranks them by emetic potential. Variables that contribute to nausea and vomiting may not be independent. Morrow et al [34] proposed a bio-behavioral model that incorporates the psychological and physical aspects of CINV. Rather than focusing on one aspect to the exclusion of the other, both aspects should be considered [34].

Table 3**Emetic Risk of Chemotherapy**

EMESIS RISK	ACUTE CINV ^a	DELAYED CINV ^a
High	++	++
Moderate	++	+
Low	+	-
Minimal	-	-

^a Plus signs indicate the degree of potential for acute or delayed emesis; minus signs indicate little or no potential. Adapted from Koeller et al [32]; used with permission.

PATTERNS OF EMESIS VARY AMONG TREATMENT REGIMENS

Cisplatin-based chemotherapy shows a biphasic pattern of emesis when prophylactic antiemetic treatment is unavailable. Patients experience an initial peak of emesis 4–5 hours after receiving cisplatin-based chemotherapy, which then subsides. A second phase of emesis begins between 21 and 24 hours after cisplatin-based chemotherapy and is most intense on days 2 to 3 [9]. This contrasts with the typical pattern of emesis observed with cyclophosphamide or carboplatin (Paraplatin) regimens. With these regimens (and no antiemetic prophylaxis), emesis peaks in severity a few hours after treatment and then gradually subsides. Still, 35%–60% of patients will experience vomiting on day 2 after treatment with 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC), and about 80% will experience emesis on day 2 after treatment with

cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (Table 1) [9].

Treatment of Acute and Delayed CINV

Four major classes of antiemetic agents are used to treat the acute and delayed phases of CINV: corticosteroids, D₂ receptor antagonists, 5-HT₃ receptor antagonists, and NK-1 receptor antagonists.

Corticosteroids, typified by the agent dexamethasone, are widely used to control CINV. Their antiemetic mechanism of action is unclear, but they may work through prostaglandin antagonism, tryptophan depletion, or changes in the permeability of the cerebrospinal fluid to serum proteins [35]. At equivalent doses, several different corticosteroids are equally safe and effective. Dexamethasone has the advantage of being available in many dosage formulations. When used in combination with 5-HT₃ receptor antagonists to prevent acute CINV, corticosteroids add 20%–25% to the response rate [8]. For preventing delayed CINV, corticosteroids and 5-HT₃ receptor antagonists both have antiemetic efficacy. The adverse effects of corticosteroids used to prevent CINV are primarily gastrointestinal upset, anxiety, and insomnia [8]. Unless contraindicated, corticosteroids should be part of any regimen for prevention of delayed CINV [8].

Dopamine-2 receptor antagonists include butyrophenones (eg, droperidol), phenothiazines (eg, prochlorperazine), and substituted benzamides, of which metoclopramide is most widely recommend-

Table 4**Chemotherapy Drugs Ranked by Emetic Potential^a**

HIGH (> 90%; LEVEL 5)	MODERATE (30%–90%; LEVELS 3 AND 4)	LOW (10%–30%; LEVEL 2)	MINIMAL (< 10%; LEVEL 1)
Carmustine (> 250 mg/m ²)	Cyclophosphamide (< 1,500 mg/m ²)	Aldesleukin (interleukin-2)	Methotrexate (< 100 mg/m ²)
Cisplatin	Carmustine (< 250 mg/m ²)	Doxorubicin (< 20 mg/m ²)	Bleomycin
Cyclophosphamide (> 1,500 mg/m ²)	Doxorubicin	Methotrexate (> 100 mg/m ²)	Capecitabine
Dacarbazine (> 500 mg/m ²)	Cisplatin (< 50 mg/m ²)	Fluorouracil (< 1,000 mg/m ²)	Rituximab
Lomustine (> 60 mg/m ²)	Epirubicin	Mitoxantrone (< 12 mg/m ²)	Vincristine
Mechlorethamine	Cytarabine (> 1 g/m ²)	Gemcitabine	Trastuzumab
Pentostatin	Idarubicin	Temozolomide	Vinblastine
Streptozocin	Irinotecan	Mitomycin	Vinorelbine (IV)
Dactinomycin	Ifosfamide	Etoposide (PO)	Etoposide/teniposide (IV)
	Melphalan	Paclitaxel	
	Hexamethylamine (PO)	Asparaginase	
	Procarbazine (PO)	Thiotepa	
	Carboplatin	Cytarabine (< 1 g/m ²)	
	Mitoxantrone (> 12 mg/m ²)	Topotecan	
	Cyclophosphamide (PO)	Docetaxel	

^a Rankings assume the absence of effective prophylactic antiemetic treatment.

From ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery [8], Koeller et al [32], and Hesketh et al [33]. Adapted from Koeller et al [32]; used with permission.

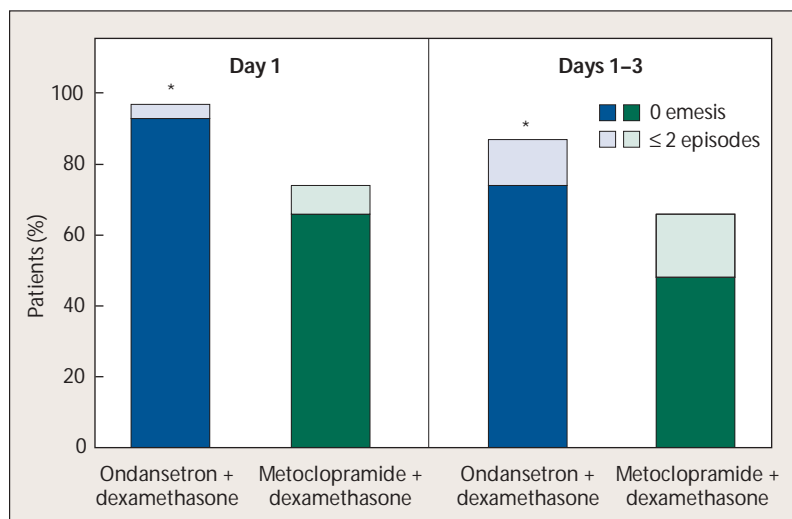


Figure 5 Prophylaxis of Acute and Delayed CINV

Efficacy and safety were compared in two groups of women. The first group (n = 95) received 8 mg of ondansetron IV (plus 20 mg of dexamethasone) on day 1, followed by 8 mg of ondansetron PO twice daily on days 2 and 3. The second group (n = 94) received 60 mg of metoclopramide IV (plus 20 mg of dexamethasone IV) on day 1, followed by 20 mg of metoclopramide PO twice daily on days 2 and 3. Patients in the ondansetron treatment group took one placebo tablet to maintain the blinding in the study. Significantly more patients ($P < 0.001$) given ondansetron had complete (0 emesis; 93%) or major (≤ 2 episodes of emesis; 4%) control. Corresponding percentages for metoclopramide were 66% and 8%. $P < 0.001$. Adapted from du Bois et al [37]; used with permission.

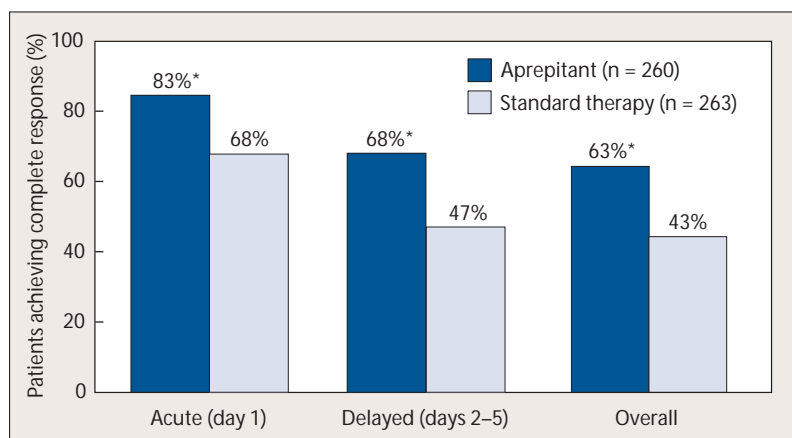


Figure 6 Prophylaxis of Acute and Delayed CINV: Adjuvant Aprepitant Versus Standard Therapy

Results of a multicenter, randomized, double-blinded, placebo-controlled study on patients treated with cisplatin-based chemotherapy. One group of patients (standard therapy group; n = 263) received 32 mg of ondansetron IV and 20 mg of dexamethasone PO on day 1, followed by 8 mg of dexamethasone PO twice daily on days 2-4. Another group of patients (aprepitant group; n = 260) received 125 mg of aprepitant PO, 32 mg of ondansetron IV, and 12 mg of dexamethasone PO on day 1, followed, on days 2 and 3, by 80 mg of aprepitant PO and 8 mg of dexamethasone PO once daily and, on day 4, by 8 mg of dexamethasone PO. After 5 days, 63% of patients in the aprepitant treatment group had a complete response, compared with 43% in the standard therapy group. Complete response was defined as no emesis and no rescue therapy during the 5 days after chemotherapy. $P < 0.001$ vs standard therapy. Adapted from Poli-Bigelli et al [39]; used with permission.

ed [8, 36]. These agents work centrally to block dopamine receptors in the CTZ and the vomiting center (Figure 5). Adverse effects associated with D_2 receptor antagonists include sedation, CNS depression, restlessness, and extrapyramidal symptoms. Diarrhea is common with metoclopramide [8].

The 5-HT₃ receptor antagonists have the unique benefit of acting at central and peripheral sites by binding to 5-HT₃ receptors found in the CTZ and afferent pathways of the gastrointestinal tract. At present, four 5-HT₃ receptor antagonists are approved for use in the United States: dolasetron (Anzemet), granisetron (Kytril), ondansetron, and palonosetron (Aloxi) (IV only). At equivalent doses, these agents are equally safe and effective for CINV [35, 38]. Oral and IV doses can generally be used interchangeably, depending on patients' needs. The most common adverse effects of these agents are mild headache, constipation, and asymptomatic prolongation of ECG intervals [8, 38].

The NK-1 receptor antagonists are a new class of drugs, of which aprepitant is the only approved agent. Aprepitant, in combination with other antiemetics, is approved for prevention and control of CINV [4]. It crosses the blood-brain barrier to block NK-1 receptors and augments the antiemetic efficacy of 5-HT₃ receptor antagonists and dexamethasone, particularly in the setting of delayed CINV (Figure 6) [39]. The most common adverse effects in clinical studies were diarrhea, dizziness, nausea, mild anorexia, and drug interactions via inhibition and induction of the CYP3A4 enzyme pathway [40].

ACUPRESSURE AND ACUSTIMULATION

Acupressure and acustimulation for the prevention of CINV have been investigated in preliminary clinical trials [41, 42]. In a small study (n = 27) comparing active stimulation of the pericardium-6 point, using an acustimulation wrist band, sham stimulation, or no stimulation, results were equivocal but suggested that acustimulation was more effective than sham or no stimulation in minimizing the severity of delayed nausea [41]. A larger study (n = 739) compared acustimulation with acupressure and no stimulation. Acupressure significantly ($P < 0.05$) reduced acute nausea, compared with no acupressure or stimulation, but no differences in effect were seen for delayed nausea or vomiting. A sex difference was noted. Men using acustimulation, but not acupressure, experi-

enced significantly ($P < 0.05$) less nausea and vomiting than control patients, whereas there were no differences between groups for women [42]. More research is needed before these approaches can be reliably recommended.

Breakthrough Emesis

Breakthrough emesis is defined as emesis that occurs despite the use of optimal prophylactic antiemetic treatment. It is difficult to assess the incidence and impact of breakthrough emesis because there are no studies that differentiate between emesis resulting from inadequate prophylaxis and emesis that truly fits the “breakthrough” definition [43]. If emesis occurs despite optimal prophylaxis, treatment with the same medications is unlikely to be effective, and rescue agents from a different pharmacologic class should therefore be tried. If emesis occurs despite proper dosing of dexamethasone plus a 5-HT₃ receptor antagonist, the addition of a D₂ antagonist during the next cycle of chemotherapy may increase antiemetic coverage [43].

Current Practice Guidelines

Several major organizations have developed practice guidelines, including ASCO, ASHP, and MASCC (Tables 5 and 6) [8, 20, 21]. These groups recommend using a 5-HT₃ receptor antagonist in combination with a corticosteroid to prevent acute emesis. Recommendations for prevention/treatment of delayed emesis vary somewhat between groups. ASCO recommends a corticosteroid alone or with a 5-HT₃ receptor antagonist or metoclopramide. ASHP recommends a corticosteroid plus a 5-HT₃ receptor antagonist, and MASCC recommends a corticosteroid or 5-HT₃ receptor antagonist or a corticosteroid plus a 5-HT₃ receptor antagonist. To help streamline and synthesize these recommendations, one group composed of representatives from each organization proposed the treatment approach shown in Table 7 [32, 43].

Role of Healthcare Givers in the Management of CINV

Perhaps as important as adequate prescription of antiemetic prophylaxis is the detection of prophylactic failures. This is best accomplished through telephone or other follow-up evaluation of patients on days 2–5. Patients should be asked specific questions about symptoms of nausea, retching, and/or vomiting. Although telephone follow-

Table 5

Prevention of Delayed Emesis in Highly or Moderately Emetogenic Chemotherapy

	CISPLATIN	NON-CISPLATIN
ASCO	Corticosteroid + (5-HT ₃ receptor antagonist <i>or</i> metoclopramide)	Corticosteroid <i>or</i> corticosteroid + (5-HT ₃ receptor antagonist <i>or</i> metoclopramide)
ASHP	Corticosteroid + (5-HT ₃ receptor antagonist <i>or</i> metoclopramide)	5-HT ₃ receptor antagonist + corticosteroid
MASCC	Corticosteroid + (5-HT ₃ receptor antagonist <i>or</i> metoclopramide)	Corticosteroid <i>or</i> 5-HT ₃ receptor antagonist <i>or</i> 5-HT ₃ receptor antagonist + corticosteroid

ASCO = American Society of Clinical Oncology [20]; ASHP = American Society of Health-System Pharmacists [8]; MASCC = Multinational Association of Supportive Care in Cancer [21]

Table 6

Adult Dosage Recommendations for Intravenous 5-HT₃ Receptor Antagonists in Highly/Moderately Emetogenic Chemotherapy

AGENT ^a	ASCO	ASHP	MASCC
Ondansetron	8 mg or 0.15 mg/kg	8 mg	8 mg
Granisetron	1 mg or 10 µg/kg	10 µg/kg	10 µg/kg
Dolasetron	100 mg or 1.8 mg/kg	100 mg or 1.8 mg/kg	1.8 mg/kg
Dexamethasone	20 mg	20 mg	Remains to be determined

^a All agents are administered as a single daily dose.

ASCO = American Society of Clinical Oncology [20]; ASHP = American Society of Health-System Pharmacists [8]; MASCC = Multinational Association of Supportive Care in Cancer [21]

Table 7

Prevention/Treatment Options Based on Emetic Category

EMESIS RISK ^a	ACUTE CINV (DAY 1)	DELAYED CINV (DAY 2+)
High	5-HT ₃ receptor antagonist + dexamethasone	Dexamethasone + (metoclopramide <i>or</i> 5-HT ₃ receptor antagonist)
Moderate	5-HT ₃ receptor antagonist + dexamethasone	Dexamethasone + (metoclopramide <i>or</i> 5-HT ₃ receptor antagonist)
Low	Dexamethasone <i>or</i> D ₂ antagonists	None
Minimal	None	None

^a See Tables 3 and 4.

Adapted from Koeller et al [32] and Aapro [43]; used with permission.

up is ideal, patients can also be taught to use a diary to record their symptoms during this time [44]. The oncology staff should initiate this type of follow-up review, because patients often wait until their next visit to report delayed nausea and/or vomiting. Nonetheless, reports of delayed CINV with a prior course of chemotherapy should make aggressive antiemetic prophylaxis a priority for subsequent courses of chemotherapy.

Grunberg

Chemotherapy-Induced Nausea and Vomiting

When assessing patients with CINV, nausea and vomiting should be assessed separately. The severity and duration of nausea should be noted, along with the number of episodes of vomiting and the duration of vomiting (and retching, if present). Patients should be specifically interviewed about how well CINV has been controlled [8].

A useful tool for CINV assessment is the Morrow Assessment of Nausea and Emesis (MANE). It uses a self-report format and asks separate questions to identify acute, delayed, and anticipatory CINV and to assess the frequency and severity of each [45].

The staff also has an important role in educating patients about their chemotherapy and its probable adverse effects. Informing patients that antiemetic prophylaxis is likely to prevent or minimize CINV may reduce the likelihood of CINV developing. Hickok et al [46] showed that women who expect to have nausea and/or vomiting associated with cancer chemotherapy are significantly ($P < 0.001$) more likely to develop anticipatory nausea than women who do not expect to have CINV. This finding was supported by a 2003 study of breast cancer patients [47]. Those who expected to develop posttreatment (ie, acute) nausea generally did. The single factor that most influenced their expectations was past experience with CINV [47]. This study also reinforced the importance of controlling acute nausea and vomiting at the beginning of cancer chemotherapy.

ROLE OF PATIENTS AND FAMILIES

As Grunberg et al [7] have shown, many oncology professionals continue to underestimate the incidence of acute and delayed CINV. Patients can certainly help to raise their healthcare givers' awareness by proactively reporting symptoms and distress when they occur, rather than waiting until their next office visit. By reporting on the incidence of delayed CINV when it happens, patients are more likely to give accurate assessments. Time and other concerns tend to minimize these experiences if not reported until the next office visit.

Family relationships have been shown to affect patients' adjustments to cancer chemotherapy, and this is particularly true of younger adult and female patients [48]. Younger adults reported significantly longer durations of acute nausea and increased severity of anticipatory nausea if there were greater intrafamily conflicts. Among women, increased conflict within the family correlates with

an increased severity of anticipatory nausea. Interventions that have proven effective in helping patients and families through chemotherapy include cognitive behavioral therapy, increases in general social support (eg, the size of the social network), and the Multiple Family Discussion Group, a program that encourages the consideration of multiple points of view [48].

Summary

Despite the availability of effective antiemetics to prevent CINV, nearly 60% of patients experience nausea and 30% experience vomiting in the days after their first course of cancer chemotherapy [14]. Chemotherapy-induced nausea and vomiting in its acute, delayed, and anticipatory phases remains one of the most problematic treatment-related adverse effects for cancer patients and exerts a negative effect on their quality of life and ability to cope with their disease.

One barrier is inadequate use of prophylactic antiemetics for patients receiving moderately or highly emetogenic chemotherapy [5], which points to a need to increase physicians' awareness of current guidelines, such as those from ASCO, ASHP, and MASCC. Another barrier to the elimination of CINV is underestimation of the incidence of delayed CINV [7]. Healthcare professionals and patients must be more aggressive in detecting and reporting delayed CINV. A third barrier has been the lesser efficacy of antiemetic prophylaxis in preventing delayed CINV, perhaps reflecting the roles of different neurotransmitters in the acute and delayed phases of CINV. The addition of NK-1 receptor antagonists to antiemetic regimens may help overcome this barrier.

Identifying health-related quality-of-life risk factors before a patient's first course of chemotherapy, together with clinical assessment of patient and treatment risk factors, may help define the group of patients most likely to develop CINV. Use of corticosteroids plus 5-HT₃ receptor antagonists, as recommended for acute and most delayed CINV associated with moderately or highly emetogenic chemotherapy, plus NK-1 antagonists where appropriate, must be emphasized. Alternative remedies also deserve further investigation. Although improvement still needs to be made in preventing CINV, more tools are now available than previously. With proper use, these tools can minimize this debilitating adverse effect of cancer chemotherapy.

References

1. Borison HL, Brand ED, Orkand RK. Emetic action of nitrogen mustard (mechlorethamine hydrochloride) in dogs and cats. *Am J Physiol* 1958;192:410-416.
2. Coates A, Abraham S, Kaye SB, et al. On the receiving end—patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol* 1983;19:203-208.
3. de Boer-Dennert M, de Wit R, Schmitz PI, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer* 1997;76:1055-1061.
4. Emend (aprepitant capsules). Prescribing information. Whitehouse Station, NJ: Merck & Co. Inc.; March 2003. Available at: http://www.fda.gov/cder/foi/label/2003/21549_Emend_lbl.pdf. Accessed November 4, 2003.
5. De Angelis V, Roila F, Sabbatini R, et al, for the Italian Group for Antiemetic Research. Cancer chemotherapy (CT)-induced delayed emesis: antiemetic prescriptions in clinical practice. In: Program/Proceedings of the 39th Annual Meeting of the American Society of Clinical Oncology; May 31-June 3, 2003; Chicago, Ill. Abstract 2971.
6. Kris MG, Gralla RJ, Clark RA, et al. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. *J Clin Oncol* 1985;3:1379-1384.
7. Grunberg SM, Hansen M, Deuson R, Mavros P. Incidence and impact of nausea/vomiting with modern antiemetics: perception vs. reality. In: Program/Proceedings of the 38th Annual Meeting of the American Society of Clinical Oncology; May 18-21, 2002; Orlando, Fla. Abstract 996.
8. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. *Am J Health Syst Pharm* 1999;56:729-764.
9. Martin M. The severity and pattern of emesis following different cytotoxic agents. *Oncology* 1996;53(suppl 1):26-31.
10. Schmoll HJ. The role of ondansetron in the treatment of emesis induced by non-cisplatin-containing chemotherapy regimens. *Eur J Cancer Clin Oncol* 1989;25(suppl 1):S35-S39.
11. Markman M. Progress in preventing chemotherapy-induced nausea and vomiting. *Cleve Clin J Med* 2002;69:609-610, 612, 615-617.
12. The Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med* 2000;342:1554-1559.
13. National Comprehensive Cancer Network. NCCN antiemesis practice guidelines. *Oncology* 1997;11:57-89.
14. Morrow GR, Roscoe JA, Hickok JT, et al. Initial control of chemotherapy-induced nausea and vomiting in patient quality of life. *Oncology* 1998;12(suppl 4):32-37.
15. Lindley CM, Hirsch JD, O'Neill CV, Transau MD, Gilbert CS, Osterhaus JT. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res* 1992;1:331-340.
16. Osoba D, Zee B, Warr D, et al. Effect of postchemotherapy nausea and vomiting on health-related quality of life. *Support Care Cancer* 1997;5:303-313.
17. Osoba D, Zee B, Warr D, Kaizer L, Latreille J, Pater J. Quality of life studies in chemotherapy-induced emesis. *Oncology* 1996;53(suppl 1):92-95.
18. Rusthoven JJ, Osoba D, Butts CA, Yelle L, Findlay H, Grenville A. The impact of postchemotherapy nausea and vomiting on quality of life after moderately emetogenic chemotherapy. *Support Care Cancer* 1998;6:389-395.
19. Soukop M, McQuade B, Hunter E, et al. Ondansetron compared with metoclopramide in the control of emesis and quality of life during repeated chemotherapy for breast cancer. *Oncology* 1992;49:295-304.
20. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol* 1999;17:2971-2994.
21. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. *Ann Oncol* 1998;9:811-819.
22. National Comprehensive Cancer Network. Practice guidelines in oncology. Available at: http://www.nccn.org/physician_gls/f_guidelines.html. Accessed December 15, 2003.
23. Hickok JT, Roscoe JA, Morrow GR, King DK, Atkins JN, Fitch TR. Nausea and emesis remain significant problems of chemotherapy despite prophylaxis with 5-hydroxytryptamine-3 antiemetics: a University of Rochester James P. Wilmut Cancer Center Community Clinical Oncology Program study of 360 cancer patients treated in the community. *Cancer* 2003;97:2880-2886.
24. De Angelis V, Roila F, Patoia L, et al. Impact on antiemetic prescriptions of the Consensus Conference (CC) and of an expert's visit to oncological centers. In: Program/Proceedings of the 36th Annual Meeting of the American Society Clinical Oncology; May 20-23, 2000; New Orleans, La. Abstract 2386.
25. Mitchell EP, Schein PS. Gastrointestinal toxicity of therapeutic agents, in Perry MC, Yarbrow JW (eds): *Toxicity of Chemotherapy*. Orlando, Fla: Grune & Stratton 1984:269-285.
26. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer* 2003;39:1074-1080.
27. Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. *N Engl J Med* 1993;329:1790-1796.
28. Hesketh PJ, Gandara DR. Serotonin antagonists: a new class of antiemetic agents. *J Natl Cancer Inst* 1991;83:613-620.
29. Stahl SM. The ups and downs of novel antiemetic drugs, part 1: substance P, 5-HT, and the neuropharmacology of vomiting. *J Clin Psychiatry* 2003;64:498-499.
30. Balfour JA, Goa KL. Dolasetron: a review of its pharmacology and therapeutic potential in the management of nausea and vomiting induced by chemotherapy, radiotherapy, or surgery. *Drugs* 1997;54:273-298.
31. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L. Determinants of postchemotherapy nausea and vomiting in patients with cancer: Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1997;15:116-123.
32. Koeller JM, Aapro MS, Gralla RJ, et al. Antiemetic guidelines: creating a more practical treatment approach. *Support Care Cancer* 2002;10:519-522.
33. Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;15:103-109.
34. Morrow GR, Roscoe JA, Hickok JT, Andrews PLR, Matteson S. Nausea and emesis: evidence for a biobehavioral perspective. *Support Care Cancer* 2002;10:96-105.
35. Kovac AL. Benefits and risks of newer treatments for chemotherapy-induced and postoperative nausea and vomiting. *Drug Saf* 2003;26:227-259.
36. Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs* 2000;59:213-243.
37. du Bois A, McKenna CJ, Andersson H, et al. A randomised, double-blind, parallel-group study to compare the efficacy and safety of ondansetron (GR38032F) plus dexamethasone with metoclopramide plus dexamethasone in the prophylaxis of nausea and emesis induced by carboplatin chemotherapy. *Oncology* 1997;54:7-14.
38. Aloxi (palonosetron HCl injection). Prescribing information. Bloomington, Minn: MGI Pharma Inc; July 2003.
39. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al, for the Aprepitant Protocol 054 Study Group. Addition of the neurokinin-1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting: results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer* 2003;97:3090-3098.
40. Van Belle S, Lichinitser MR, Navari RM, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. *Cancer* 2002;94:3032-3041.

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41. Roscoe JA, Morrow GR, Bushunow P, Tian L, Matteson S. Acustimulation wristbands for the relief of chemotherapy-induced nausea. *Altern Ther Health Med* 2002;8:56–57, 59–63.
42. Roscoe JA, Morrow GR, Hickok JT, et al. The efficacy of acupressure and acustimulation wristbands for the relief of chemotherapy-induced nausea and vomiting: a University of Rochester Cancer Center Community Clinical Oncology Program multicenter study. *J Pain Symptom Manage* 2003;26:731–742.
43. Aapro MS. How do we manage patients with refractory or breakthrough emesis? *Support Care Cancer* 2002;10:106–109.
44. Rhodes VA, Johnson MH, McDaniel RW. Nausea, vomiting, and retching: the management of the symptom experience. *Semin Oncol Nurs* 1996;11:256–265.
45. Morrow GR. Methodology in behavioral and psychosocial cancer research: the assessment of nausea and vomiting: past problems, current issues, and suggestions for future research. *Cancer* 1984;53(suppl 10):2267–2280.
46. Hickok J, Roscoe JA, Morrow GR. The role of patients' expectations in the development of anticipatory nausea related to chemotherapy for cancer. *J Pain Symptom Manage* 2001;22:843–850.
47. Montgomery GH, Bovbjerg DH. Expectations of chemotherapy-related nausea: emotional and experiential predictors. *Ann Behav Med* 2003;25:48–54.
48. Kim Y, Morrow GR. Changes in family relationships affect the development of chemotherapy-related nausea symptoms. *Support Care Cancer* 2003;11:171–177.