ASCO SPECIAL ARTICLE

Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice Guidelines

By Richard J. Gralla, David Osoba, Mark G. Kris, Peter Kirkbride, Paul J. Hesketh, Lawrence W. Chinnery, Rebecca Clark-Snow, David P. Gill, Susan Groshen, Steven Grunberg, James M. Koeller, Gary R. Morrow, Edith A. Perez, Jeffrey H. Silber, and David G. Pfister for the American Society of Clinical Oncology

THE GOAL OF ANTIEMETIC therapy is to prevent nausea and vomiting completely. This goal is achieved for many patients receiving chemotherapy or radiation therapy, and is based on clinical and basic research that has steadily improved the control of emesis over the last 20 years. As therapy has become more effective, it has also become safer, with few side effects associated with the most commonly used regimens. These regimens are convenient for patients to receive and for health care professionals to administer. However, despite improvements, a significant number of patients still experience emesis, and efforts to reduce this side effect of treatment must continue.

As antiemetic usage has grown, the classes of agents available for antiemetic treatment, the number of agents, and the indications for antiemetics have all increased as well. The prevention of delayed emesis and anticipatory emesis is equal in importance to the need to prevent acute chemotherapy- and radiation-induced emesis. Additionally, managing special and difficult emetic problems and selecting the proper antiemetic approach necessitate identification of the patient's emetic risk.

Although the neuropharmacologic basis of emesis is still incompletely understood, the selection of an appropriate antiemetic regimen is possible and can have an impact on several aspects of clinical care. Goals related to the complete control of emesis, ie, no vomiting, include providing care that is convenient for the patient, treatment that reduces hospitalization and time in the ambulatory setting, and therapy that enhances the patient's quality of life. Additionally, practitioners need to be mindful of reducing costs of treatment while achieving these goals.[1-3]

The American Society of Clinical Oncology (ASCO) appreciates these issues and their applicability to the management of patients with cancer. Accordingly, ASCO convened an Expert Panel under the auspices of its Health Services Research Committee to develop recommendations regarding antiemetic therapy (Table 1). This report describes the aims, methods, and results of this Panel's deliberations.

PRACTICE GUIDELINES

Practice guidelines are systematically developed statements to assist the practitioner and patient decisions about appropriate health care for specific clinical circumstances.[4] Good clinical guidelines include considerations of validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.[4]

In formulating recommendations for antiemetic usage, ASCO considered these tenets of guideline development, emphasizing the review of data from controlled clinical trials. The level and grade of evidence can differ; such evidence is rated according to the criteria outlined in Table 2. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. They cannot be considered to be inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

It is also important to note that not all relevant questions regarding emesis in cancer care have been addressed by clinical trials. The antiemetic methods listed in this article have been shown to be beneficial (or not), but additional research in the prevention of emesis is strongly encouraged. In some instances, specific areas of research need are indicated in this article. As ongoing research is completed, helpful results from these trials will be incorporated into updates of these guidelines.

Accordingly, ASCO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each patient's individual circumstances. In addition, these guidelines describe administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative and novel therapies for this symptom in

From the American Society of Clinical Oncology, Alexandria, VA.

Adopted on February 18, 1999, by the American Society of Clinical Oncology.

Address reprint requests to American Society of Clinical Oncology, Health Services Research, 225 Reinekers Lane, Suite 650, Alexandria, VA 22314; email guidelines@asco.org.

0732-183X/99/1709-2971

Table 1. Summary of Guidelines

I. Chemotherapy-Induced Emesis
- A. Acute Emesis (vomiting occurring 0 to 24 hours after chemotherapy)
  - 1. Antiemetic Agents: Highest Therapeutic Index
    - a. Serotonin Receptor Antagonists
      - i. Agent equivalence
        At equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.
      - ii. Drug dosage
        Established, proven doses of all agents are recommended.
      - iii. Drug schedule
        Single doses of antiemetics are effective and preferred for convenience and cost.
      - iv. Route of administration
        At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are less costly and more convenient; for these reasons, they are recommended over intravenous therapy.
    - b. Corticosteroids
      - i. Agent equivalence and route of administration
        At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably.
      - ii. Drug dose and schedule
        Single doses of corticosteroids are recommended.
  - 2. Antiemetic Agents: Lower Therapeutic Index—Dopamine Antagonists, Butyrophenones, Phenothiazines, and Cannabinoids
    For chemotherapy with a high risk of emesis, selective serotonin antagonists (with dexamethosone) are recommended.
  - 3. Antiemetic Agents: Adjunctive Drugs—Benzodiazepines and Antihistamines
    Benzodiazepines and antihistamines are useful adjuncts to antiemetic drugs but are not recommended as single agents.
  - 4. Antiemetic Agents: Combinations of Antiemetics
    It is recommended that serotonin antagonists be given with corticosteroids.
  - 5. Risk Factors for Acute Emesis
    - a. Patient Characteristics
    - b. Chemotherapeutic Agents
    - c. Guidelines
      - i(a). High risk: Cisplatin
        The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.
      - i(b). High risk: noncisplatin
        The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.
      - ii. Intermediate risk
        A corticosteroid is suggested for patients being treated with agents of intermediate emetic risk.
      - iii. Low risk
        It is suggested that for patients being treated with agents of low emetic risk, no antiemetic be routinely administered before chemotherapy.
      - iv. Combination chemotherapy
        It is suggested, that when combination chemotherapy is given, the patient be given antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.
      - v. Multiple consecutive days of chemotherapy
        It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy.
- B. Delayed Emesis (vomiting occurring >24 hours after chemotherapy)
  - 1. Antiemetic Agents
    - a. Single Agents
      - i. Corticosteroids
      - ii. Metoclopramide and serotonin receptor antagonists
    - b. Combinations of Agents
  - 2. Risk Factors for Delayed Emesis
    - a. Patient Characteristics
    - b. Chemotherapeutic Agents
    - c. Guidelines
      - i(a). High risk: cisplatin
        For all patients receiving cisplatin, a corticosteroid plus metoclopramide or plus a 5-HT_3 antagonist is recommended for the prevention of delayed emesis.
      - i(b). High risk: noncisplatin
        A prophylactic corticosteroid as a single agent, a prophylactic corticosteroid plus metoclopramide, and a prophylactic corticosteroid plus a 5-HT_3 antagonist are regimens suggested for the prevention of delayed emesis.
      - ii. Intermediate—low risk
        No regular preventive use of antiemetics for delayed emesis is suggested for patients receiving these chemotherapeutic agents.

Table 1. Summary of Guidelines (Cont'd)

C. Anticipatory Emesis
1. Prevention
Use of the most active antiemetic regimens appropriate for the chemotherapy being given to prevent acute or delayed emesis is suggested. Such regimens must be used with the initial chemotherapy, rather than after assessment of the patient's emetic response to less effective treatment.
2. Treatment
If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested.

D. Special Emetic Problems
1. Emesis in Pediatric Oncology
The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high emetic risk.
2. High-Dose Chemotherapy
A 5-HT_3 antagonist plus a corticosteroid is suggested.
3. Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles
It is suggested that clinicians (1) conduct a careful evaluation of risk, antiemetic, chemotherapy, tumor, and concurrent disease and medication factors, (2) ascertain that the best regimen is being given for the emetic setting, (3) consider adding an antianxiety agent to the regimen, and (4) consider substituting a dopamine receptor antagonist, such as high-dose metoclopramide, for the 5-HT_3 antagonist (or add the dopamine antagonist to the regimen).

II. Radiation-Induced Emesis
A. Risk Factors for Radiation-Induced Emesis
1. Guidelines
a. High Risk: Total Body Irradiation
A serotonin receptor antagonist should be given with or without a corticosteroid before each fraction and for at least 24 hours after.
b. Intermediate Risk: Hemibody Irradiation, Upper Abdomen, Abdominal-Pelvic, Mantle, Cranial Radiosurgery, and Craniospinal Radiotherapy
A serotonin receptor antagonist or a dopamine receptor antagonist should be given before each fraction.
c. Low Risk: Radiation of the Cranium Only, Breast, Head and Neck, Extremities, Pelvis, and Thorax
Treatment should be given on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.

which better treatment is of paramount importance. In that guideline development involves a review and synthesis of the latest literature, practice guidelines also serve to identify important questions for further research and those settings in which investigational therapy should be considered.

Table 2. Levels and Grade of Evidence for Recommendations[280,281]

Level	Type of Evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials have with low false-positive and low false-negative errors (high power).
II	Evidence is obtained from at least one well-designed experimental study. Randomized trials have high false-positive and/or -negative errors (low power).
III	Evidence is obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled, single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence is from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.
V	Evidence is from case reports and clinical examples.
Grade	**Grade for Recommendation**
A	There is evidence of type I or consistent findings from multiple studies of types II, III, and IV.
B	There is evidence of types II, III, and IV, and findings are generally consistent.
C	There is evidence of types II, III, and IV, but findings are inconsistent.
D	There is little or no systematic empirical evidence.

METHODS

A methodology similar to that applied in prior ASCO practice guidelines documentation[5] was used and is described in more detail below.

Expert Panel Composition

The Panel was composed of experts in clinical medicine, clinical research, outcomes/health services research, medical decision-making, and health economics, with a focus on expertise in supportive care and in antiemetics. A patient representative was also included on the Panel. Clinical experts represented all relevant disciplines, including medical oncology, oncology nursing, radiation oncology, pediatric oncology, and oncologic pharmacy practice. A steering committee under the auspices of the Health Services Research Committee chose Panel participants for the clinical practice guideline development process.

Literature Review and Data Collection

Pertinent information from the published literature as of July 1998 was retrieved and reviewed for the creation of these guidelines. MEDLINE (National Library of Medicine, Bethesda, MD) and other databases were searched for pertinent articles. The following keywords or phrases were used: antiemetics, neoplasms, adverse effects, anticipatory + nausea, anticipatory + vomiting, serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, corticosteroids, and metoclopramide. Directed searches were made of the primary articles.

Consensus Development Based on Evidence

The Panel identified topics to be addressed by the guidelines, developed a strategy for completion of the guidelines, and reviewed the literature. The Panel emphasized the inclusion of prospective random-

assignment studies. Phase II trials and clinical reports that evaluated less-well-studied areas of antiemetic treatment were also reviewed. The recommendations made by the Expert Panel are based on current methods of emetic treatment and prevention. The guidelines were circulated in draft form through several iterations, and all members of the Panel had opportunities to comment on the recommendations.

The Panel did not attempt to codify established practice. The experts reviewed the available evidence and added their best clinical judgment to make final recommendations, using standardized language to characterize the strength of the evidence. In accordance with the ASCO Health Services Research Policies and Procedures for guidelines, ''recommendation'' was used when there was level I or II evidence and Panel consensus. ''Suggestion'' was used when there was level III, IV, or V evidence and Panel consensus. ''No guideline possible'' was used when there were no data or the Panel could not reach consensus.

Guidelines and Conflict of Interest

The content of the guidelines and the manuscript were reviewed and approved by the Health Services Research Committee and by the ASCO Board of Directors before dissemination. In addition, several practitioners who had not been directly involved in the development of the guidelines were asked to assess the clarity and utility of the document. All participants in the guideline development process complied with the ASCO policy on conflict of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict.[6]

Revision Dates

At annual intervals, the Panel chairpersons and two Panel members designated by the chairpersons will determine the need for revisions to the guidelines based on an examination of current literature. The entire Panel will be reconvened every 3 years to discuss potential changes, or more frequently if new information suggests that more timely modifications may be warranted. Where appropriate, the Panel will recommend the revised guideline to the Health Services Research Committee and the ASCO Board for review and approval.

Definition of Terms

For cisplatin, high risk is defined as emesis that has been documented to occur in more than 99% of patients. For the high-risk, noncisplatin group, the incidence of emesis is in the 30% to greater than 90% range. Chemotherapeutic agents in the intermediate-risk category induce emesis in 10% to 30% of patients. A less than 10% risk of emesis in patients receiving chemotherapeutic drugs was categorized as low risk.

I. CHEMOTHERAPY-INDUCED EMESIS

In discussing evidence for the control of emesis, it is necessary to outline definitions of control. Emesis, or vomiting, is usually measured by counting the number of vomiting episodes and is the most important end point. With currently available agents, complete control of emesis, ie, no vomiting, is achievable in the majority of patients in the first 24 hours and in approximately 45% of patients during the first 5 to 7 days of chemotherapy. Studies have documented that the complete control end point is a highly accurate and reliable measure.[7-9] The validity of this measure is demonstrated by the fact that complete control of vomiting correlates highly with patients' perception of emesis and with patients' satisfaction with their emetic control.

In contrast, the mechanisms responsible for mediating nausea are less well explained.[10] Nausea, or the perception that emesis may occur, can be judged only by the patient. Various questionnaires, using either visual analog or categorical scales, are in widespread use.[9,11,12] The incidence of nausea correlates well with the incidence of vomiting[13]; however, chemotherapy-induced nausea occurs at a greater frequency than vomiting. Many large random-assignment trials have shown that complete control rates for vomiting are higher than those for the complete control of nausea.[14,15]

The concept of total control (no vomiting or nausea) is attractive; however, recent large studies have indicated that the total control rate is essentially identical to the complete nausea control rate. It seems that this additional category does not provide further useful information.[14,15]

Lesser control rates, such as major control (zero to two or one to two emetic episodes) or minor control (three to five emetic episodes), have been useful in the past and may still have some value in particularly difficult emetic situations. However, the panelists reached consensus in advising the use of complete control rates for the evaluation of most emetic situations and for use in the guideline development process.

A. Acute Emesis
(Vomiting Occurring 0 to 24 Hours After Chemotherapy)

1. Antiemetic Agents: Highest Therapeutic Index

Two classes of agents are in this category, the serotonin receptor antagonists and corticosteroids (Table 3).[16-37] Both classes are highly effective, with few significant side effects when used appropriately, and can be given safely in combination when indicated. These agents have been largely responsible for the ease of use and high effectiveness of antiemetics in clinical practice.

a. Serotonin Receptor Antagonists. The issues of agent equivalence, drug dosage, drug schedule, and route of administration are discussed separately below. Specific guidelines for differing acute emetic risk settings are given in a later section.

i. *Agent equivalence*:

Guideline: At equivalent doses, serotonin receptor antagonists have equivalent safety and efficacy and can be used interchangeably based on convenience, availability, and cost.

Level of Evidence: I.

Grade of Recommendation: A.

There are currently four agents of this class commercially available in many countries: dolasetron, granisetron, ondansetron, and tropisetron. Other, similar agents are available in

Table 3. Antiemetic Agents, Doses, and Administration Schedule

Antiemetic Agent (trade name)	Dose Range	Schedule (for acute chemotherapy-induced emesis, unless otherwise noted)	Evidence (type and grade)
Agents with highest therapeutic index			
Serotonin receptor antagonists			
Dolasetron (*Anzemet*)	100 mg or 1.8 mg/kg IV	One time, before chemotherapy	I, A
Dolasetron (*Anzemet*)	100 mg PO	One time, before chemotherapy	II, A
Granisetron (*Kytril*)	1 mg or 0.01 mg/kg IV	One time, before chemotherapy	I, A
Granisetron (*Kytril*)	2 mg PO	One time, before chemotherapy	I, A
Ondansetron (*Zofran*)	8 mg or 0.15 mg/kg IV	One time, before chemotherapy	I, A
Ondansetron (*Zofran*)	Oral doses vary (12-24 mg/d) (8 mg doses usually used in delayed or RT emesis)	One time, before chemotherapy (two to three times daily in delayed or RT emesis)	II, B
Tropisetron (*Navoban*)	5 mg IV	One time, before chemotherapy	III, B
Tropisetron (*Navoban*)	5 mg PO	One time, before chemotherapy	III, B
Corticosteroids			
Dexamethasone (*Decadron*)	20 mg IV	One time, before chemotherapy	II, B
Methylprednisolone (*Medrol*)	40 mg to 125 mg	One time, before chemotherapy	V, D
Agents of lower therapeutic index			
Dopamine receptor antagonists			
Metoclopramide (*Reglan*)	2 mg/kg to 3 mg/kg IV	Before chemotherapy and 2 hours after chemotherapy	I, A
Metoclopramide (*Reglan*)	20 mg to 0.5 mg/kg PO for delayed emesis or RT	Two to four times a day for delayed emesis	IV, D
Prochlorperazine (*Compazine*)	10 mg to 30 mg IV	Every 3 to 4 hours	II, B
Prochlorperazine (*Compazine*)	10 to 20 mg PO	Every 3 to 4 hours	III-IV, C

individual countries or are under investigation. The majority of multiple, randomized, well-controlled studies with sufficient patients to precisely estimate differences in treatment have demonstrated that these agents have equivalent antiemetic activity and safety.[38-50] There was unanimity among the Panel members for this conclusion.

These agents exert their activities by the same mechanism, antagonism of the type 3 serotonin (5-hydroxytryptamine [5-HT_3]) receptor.[51-57] They are all highly selective with high affinities for this receptor.[58-60] All clinically relevant antiemetic actions are mediated in this way by these agents. These agents also share the same low side-effect pattern, with mild headache, transient asymptomatic transaminase elevations, and constipation being among the most commonly reported adverse events.[17,18,20,23]

The overall conclusion is based on the excellent evidence available for granisetron, ondansetron, and, more recently, dolasetron. The studies with tropisetron are less rigorous (level of evidence: II; grade of recommendation: B), but the Panel found that they are sufficient to allow the confidence in the above-stated conclusion.

ii. *Drug dosage*:

Guideline: Established, proven doses of all agents are recommended.

Level of Evidence: I.

Grade of Recommendation: A.

Many studies have addressed the question of establishing the ideal doses for these agents. Dolasetron, granisetron, and ondansetron are the best-studied agents in terms of dose-finding[38,40,45,48,61-77]; few studies have carefully examined tropisetron dosing. With excellent safety profiles through large dosing ranges, toxicity has not been the criterion for determining dosage. It is clear that too low a dose can be found for these agents, with attenuated activity observed at less than optimal doses (listed in Table 3).[65,67,73,74,78] Panel members concurred that it is likely that a threshold effect exists. Once all relevant receptors are saturated, higher doses do not enhance any aspect of activity. Two corollaries are also important: sufficient doses must be given to ensure maximum efficacy. Most Panel members agreed that the dose will be the same in all antiemetic settings in which a serotonin receptor antagonist is required. The Panel unanimously concluded that the lowest fully effective dose for each of the agents should be used.

As mentioned above, the question of ideal dose has been best studied with dolasetron, granisetron, and ondansetron. A lesser degree of evidence is found for tropisetron,[79,80] but the conclusion reached was the same.

iii. *Drug schedule*:

Guideline: Single doses of antiemetics are effective and are preferred for convenience and cost.

Level of Evidence: I.

Grade of Recommendation: A.

Several recent studies have examined the issue of multiple antiemetic doses compared with a single administration. The latter approach, if equally effective, enhances convenience and adherence. A single-dose regimen using the lowest fully

effective dose can provide economic benefit and the potential for the fewest side effects. Large, randomized studies with granisetron,[80] dolasetron,[81] and ondansetron[66,67,82] have indicated the equivalence of single-dose schedules of these agents when compared with multiple-dose regimens of the same agents. Dolasetron has been largely explored as a single-dose agent; however, with the exception of one study,[47] its single-dose activity is equivalent to single doses of ondansetron,[45,46,48] confirming the utility of this schedule for all three agents. The Panel was unanimous in concluding that single-dose regimens are as active as multiple-dose schedules.

Tropisetron has generally been used in single-dose schedules, with few formal dosing comparisons.[44,49,79,83,84] The level of evidence is less regarding this agent, but the Panel's conclusion was the same.

iv. *Route of administration*:

Guideline: At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are less costly and more convenient; for those reasons, they are recommended over intravenous therapy.

Level of Evidence: I.

Grade of Recommendation: A.

Intravenous and oral routes have been studied with these agents. Most of the conclusions concerning drug equivalence, dosage, and schedules are based on intravenous administration. An emerging body of formal trials is now becoming available concerning the oral route compared with the intravenous in the administration of various serotonin receptor antagonists. All of these agents have undergone pharmacologic testing. Excellent absorption is found with all agents: reports indicate 50% to 80% bioavailability with these drugs.[85] Because 5-HT_3 receptors are found in the enterochromaffin cells in the gut, with vagal afferent fibers in this area,[86] it has been suggested that oral administration may be particularly appropriate for these agents.

Large, randomized studies have shown that, in the settings of both highly emetogenic chemotherapy and chemotherapy of intermediate emetogenicity, a single dose of oral granisetron demonstrates similar efficacy when compared with a single intravenous dose of ondansetron.[14,15] Only extremely small differences were found; these differences were even smaller when both agents were combined with corticosteroids. Oral dolasetron was tested in patients receiving chemotherapy of intermediate emetogenicity[25,47,87,88] and cisplatin,[89] and in comparison with intravenous ondansetron, in a large randomized study.[47] Again, similar efficacy was reported. Both ondansetron[90-95] and tropisetron[79] are known to be active when given orally; however, studies have not been as formalized with the oral form of these drugs. The Panel reached consensus that oral and intravenous routes are similar in efficacy, especially when given in combination with corticosteroids,[33] but the level of evidence is somewhat less for this conclusion than it is for those reported above.

b. Corticosteroids. Corticosteroids also have a high therapeutic index when used for acute chemotherapy-induced emesis. They are among the most frequently used antiemetics, with single-agent use being appropriate in low-risk settings. They are especially valuable when given in combination with serotonin receptor antagonists in patients receiving highly emetogenic chemotherapy[20,33,35,96-105] (this is covered in more detail in a later section). Issues of equivalence and route of administration, as well as drug dose and schedule, are discussed together.

i. *Agent equivalence and route of administration*:

Guideline: At equivalent doses, corticosteroids have equivalent safety and efficacy and can be used interchangeably.

Level of Evidence: IV and Expert Consensus.

Grade of Recommendation: C.

The corticosteroids most frequently studied for use as antiemetics have been dexamethasone[106-111] and methylprednisolone.[112-118] Some reports have used prednisone.[119] Although efficacy has been reported with these agents, there have been no comparison trials. Dexamethasone has the advantages of being available in many dosage formulations and accessible in generic forms in many countries.

There are no formal trials comparing oral with parenteral corticosteroids. Knowledge of acceptable bioavailability and corticosteroid utility in many indications for these agents has encouraged their use in the oral form.

In the absence of comparison studies, most panelists recommended dexamethasone or methylprednisolone because of the published experience with these agents.

ii. *Drug dose and schedule*:

Guideline: Single doses of corticosteroids are recommended.

Level of Evidence: II.

Grade of Recommendation: B.

Some comparison trials have explored these issues.[107] Until recently, these trials have typically been consecutive dose-level investigations rather than randomized studies. Findings suggest that single doses are as effective as multiple-dose schedules. Although few studies have addressed this issue, there is no benefit to starting the corticosteroid the day before chemotherapy.[120] To date, there is no evidence that doses of dexamethasone greater than 20 mg are more effective.[120] A recent randomized study demonstrated improved efficacy and equivalent adverse effects with dexamethasone given at 20 mg (with serotonin antago-

nists) compared with dexamethasone at lower doses.[121] Side effects of single corticosteroid doses are rare, although elevations of serum glucose levels and sleep disturbances occur.[122] The Panel achieved consensus that single-dose regimens are most appropriate.

2. Antiemetic Agents: Lower Therapeutic Index—Dopamine Antagonists, Butyrophenones, Phenothiazines, and Cannabinoids

Guideline: For chemotherapy with a high risk of emesis, selective serotonin antagonists (with dexrazoxane) are recommended.

Level of Evidence: I.

Grade of Recommendation: A.

There are several classes of agents with antiemetic activity that are less efficacious than the serotonin receptor antagonists or corticosteroids. These other agents generally have more side effects because they are less selective than the serotonin receptor antagonists.

Several of these agents are antagonists of dopamine type 2 receptors. Foremost in this group is the substituted benzamide, metoclopramide. At higher doses, however, metoclopramide acts primarily as a serotonin receptor antagonist (Table 3).[123] Antiemetic efficacy with metoclopramide is slightly less than that seen with the selective serotonin receptor antagonists.[120,124-132] Side effects include acute dystonic reactions, akathisia, and sedation.[17,18,20,133,134]

Butyrophenones (such as haloperidol and droperidol)[135-138] and phenothiazines (prochlorperazine and thiethylperazine)[126,139,140] have antiemetic activity mediated by their antidopaminergic actions. Efficacy is generally lower than with metoclopramide.[136] Side effects include dystonic reactions, akathisia, sedation, and postural hypotension (especially with intravenous phenothiazines).[141,142]

Cannabinoids, both as plant extracts (dronabinol) and as semisynthetic agents (nabilone and levonantradol), have been found to have antiemetic activity when used alone[143-150] or in combination with other agents.[151,152] The activity of dronabinol (given in oral doses varying from 2.5 mg per dose to 10 mg/m^2) has been shown to be significantly less than that of metoclopramide in a randomized, double-blinded trial with patients receiving cisplatin.[153] Activity reported for dronabinol in patients receiving methotrexate was not seen by the same investigator testing the agent in patients receiving cyclophosphamide and doxorubicin.[154] Inhalant marijuana has been compared with dronabinol in only one randomized, double-blind trial with patients receiving chemotherapy of intermediate emetic risk.[155] The inhalant and the oral cannabinoids were not effective in either arm of the study. There was no efficacy, side effect, or pharmacologic advantage for either agent or route; however, there was a modest patient preference for the oral dronabinol in this cross-over, blinded trial. These agents cause frequent dizziness, sedation, hypotension, and dysphoria, especially in older adults.[156,157]

The Panel was unanimous in finding that in acute chemotherapy-induced emesis, especially in the high-risk setting, there is no group of patients for whom agents of lower therapeutic index (metoclopramides, phenothiazines, butyrophenones, and cannabinoids) are appropriate as first-choice antiemetic drugs. These agents should be reserved for patients intolerant of or refractory to serotonin receptor antagonists and corticosteroids.

3. Antiemetic Agents: Adjunctive Drugs—Benzodiazepines and Antihistamines

Guideline: Benzodiazepines and antihistamines are useful adjuncts to antiemetic drugs, but are not recommended as single agents.

Level of Evidence: II.

Grade of Recommendation: B.

Benzodiazepines, most commonly lorazepam, have been widely given, both in combination and as single agents.[158-166] Trials, including randomized, blinded studies with lorazepam in combination regimens, have indicated limited antiemetic activity for this agent.[160] However, because of its potent antianxiety effects, lorazepam was believed to be a useful addition to the active antiemetics given in the combination. In general, lorazepam and similar drugs should be viewed as adjunctive agents rather than as useful antiemetics themselves.

Antihistamines have been administered both as antiemetics and as adjunctive agents to prevent dystonic reactions with dopamine antagonists.[120,160] Drugs such as diphenhydramine, hydroxyzine, and benztropine have been the most commonly used agents. Studies have not shown antiemetic activity for these drugs.[120] Diphenhydramine can prevent extrapyramidal reactions[120]; however, because dopamine receptor antagonist agents are no longer first-choice drugs, the role for antihistamines is limited.

4. Antiemetic Agents: Combinations of Antiemetics

Guideline: It is recommended that serotonin antagonists be given with corticosteroids.

Level of Evidence: I.

Grade of Recommendation: A.

Extensive research has shown that combinations of antiemetics are significantly more effective than single agents when used with chemotherapy that is likely to induce emesis. Among the antiemetic agents listed in the highest

therapeutic index category, corticosteroids given in combination with a serotonin receptor antagonist yield the greatest antiemetic protection in repeated, multicenter, randomized studies designed with sufficient numbers of patients to precisely estimate treatment effects.[20,33,62,97-100,104,105,167-169] Side effects are usually low with these combinations. For patients receiving cisplatin or noncisplatin chemotherapy of high emetic risk (as discussed below in Risk Factors for Acute Emesis under High-Risk Cisplatin), these combinations are the regimens of choice. The Panel was unanimous in its recommendation that in these emetic situations, when a serotonin antagonist is indicated, a corticosteroid should also be given unless the use of the latter agent is strongly contraindicated.

Older, well-conducted, randomized trials[131,160] have also demonstrated that corticosteroids given in combination with agents in the lower therapeutic index category, such as metoclopramide, also give superior efficacy when compared with the single agent in high-risk emetic situations. In these situations, however, a large random-assignment trial showed that a serotonin receptor antagonist added to a corticosteroid was superior to a high-dose metoclopramide added to a corticosteroid.[170] The benefit was in terms of both efficacy and fewer side effects.

5. Risk Factors for Acute Emesis

Two major categories predicting risk of acute emesis (emesis occurring in the first 24 hours) or of differences in antiemetic control can be identified. These factors involve patient characteristics and the chemotherapeutic agents.

a. Patient Characteristics. Several patient factors, some confirmed by multivariate analysis, have been shown to predict poor antiemetic control.[18,171-180] These factors include poor control with prior chemotherapy, female sex, a low chronic alcohol intake or history, and younger age. The last factor, age, is a less consistent finding in trials. However, the majority of the panelists indicated that this is a factor to be considered. Chronic alcohol intake can include a prior, rather than a current, history of high alcohol use (frequently defined as the use of more than 100 g of alcohol per day for a period of several years). In general, the higher the alcohol intake history, the lower the emetic risk with chemotherapy. Pre-existing nausea and certain health-related quality-of-life variables, eg, low social functioning and high fatigue scores, may also be predictive factors.[181,182]

b. Chemotherapeutic Agents. Agents should be classified by emetogenic potential, to aid in selection of the appropriate antiemetic. Prospective documentation of the potential of a chemotherapeutic drug to cause emesis has been rigorously established for only a few agents. General categories based on experience rather than on specific data have been useful, but they do not provide precise differentiation among chemotherapy drugs.[7,91,93,183-187] A recent publication has endeavored to establish categories based on data.[188] It has tried to place both single agents and chemotherapy combinations in a classification scheme based on the actual incidence of emesis. Although this approach was encouraged by the Panel, consensus could not be reached because there is no clear evidence of the emetic potential for the majority of chemotherapeutic agents and combinations.

c. Guidelines. To formulate guidelines, a classification based on antiemetic recommendations is needed. Outlined below is the rationale for such a classification by emetic risk of the chemotherapy agent (Table 4, A, B, and C). Table 4 is adapted from other reviews, such as that listed in the Perugia Consensus Conference,[189] and ranks the drugs from highest to lowest risk within each category. It was possible to reach agreement for these treatment-related categories. It was difficult to place in the proper category those agents that seem to be at the borderline between risk categories. These categories are outlined, as follows:

i(a). *High risk – cisplatin*:

Guideline: The combination of a 5-HT_3 antagonist plus a corticosteroid is recommended before chemotherapy.

Level of Evidence: I.

Grade of Recommendation: A.

The literature clearly documents the incidence of emesis with cisplatin.[126,187,190] These data are valuable in antiemetic studies for several reasons: (1) the usefulness of cisplatin in oncology; (2) cisplatin causes emesis in all patients ($>$ 99% risk without active antiemetics); and (3) cisplatin provides a model for antiemetic testing. Trials to date show that if an antiemetic is useful in cisplatin-induced emesis, it will be at least as effective with other chemotherapy drugs.[191]

The risk of emesis with cisplatin ($\geq$ 50 mg/m^2) is universal, but other factors can alter the risk. As the dose of cisplatin increases, the ability to prevent acute and delayed emesis decreases. This observation has placed cisplatin at the top of any classification scheme and often in a category of its own. The treatment guideline for cisplatin is independent of dose or infusion time of the agent.

Because of the careful documentation of cisplatin-induced emesis with numerous well-conducted trials, the Panel was unanimous in its recommendation for treatment. Large, multicenter, randomized trials have shown the rate of complete control of acute emesis (occurring in the first 24 hours) to be approximately 75% (range, 58% to 96%), after high-dose cisplatin using the recommended regimen.[191]

i(b). *High risk – noncisplatin*:

Guideline: Use of a combination of a 5-HT_3 antagonist plus a corticosteroid before chemotherapy is recommended.

Level of Evidence: I, II, III, and Expert Consensus.

Grade of Recommendation: A-B.

Documentation of risk for some of the chemotherapy agents in this category (Table 4A), such as cyclophosphamide,[93] is well established. Overall, the risk of emesis in this category is greater than 30% and less than that seen with cisplatin. If the classification were based on the incidence of emesis, rather than on treatment recommendations, a case could be made to place some of these drugs in a separate, higher-risk group (dacarbazine, nitrogen mustard, extremely high doses of cyclophosphamide) in which the risk of acute emesis is greater than 90%.[188]

Other commonly used agents in this category are the anthracyclines, the nitrosoureas, and cytarabine. For these agents, especially when given in higher doses, it is expected that the majority of patients would have emesis if not given effective antiemetics. The Panel was unanimous in its treatment recommendation for the agents in this category.

The type and level of evidence varied according to the agent. As mentioned above, there are level I data for cyclophosphamide, the anthracyclines, and combinations of these agents. In these instances, several large, randomized, multicenter trials have documented 85% to 90% complete control of acute emesis, using the recommended regimen.[191] A lower level of evidence has been demonstrated for agents such as dacarbazine.

ii. *Intermediate risk*:

Guideline: A corticosteroid is suggested for patients treated with agents of intermediate emetic risk.

Level of Evidence: III, IV, and Expert Consensus.

Grade of Recommendation: B, D.

Table 4B lists several commonly used chemotherapy agents in this category. Without treatment, many patients, but not the majority, would have emesis. The risk of emesis is in the 10% to 30% range for agents in this group. The emesis induced by these agents is also easier to control than that found in the greater-risk categories. The first few agents in this list were considered by some Panel members to be on the border of the upper category; the lower few were listed in the low-risk group by some panelists. Evidence for emetic risk is often found as part of phase I and II chemotherapeutic trials for the newer agents in this category, rather than as part of comparative antiemetic studies.

The Panel agreed that the complete control rate should exceed 90% with the use of a single dose of a corticosteroid. There is no formal documentation of efficacy with antiemetic treatments for these lower-risk chemotherapy agents.

iii. *Low risk*:

Guideline: It is suggested that for patients treated with agents of low emetic risk, no antiemetic be routinely administered before chemotherapy.

Level of Evidence: V and Expert Consensus.

Grade of Recommendation: D.

Few antiemetic studies were found that used these chemotherapeutic agents, which are listed in Table 4C. With a low perception of risk (much less than 10% for most agents), it is understandable that trials were not conducted. Because the agents in this category are older agents (all of the agents have been in use for at least 20 years), enumeration of the emetic incidence was not often given as part of the drug-testing process. Although most hormonal agents are not included in Table 4C, an exception is made for tamoxifen, which is so commonly given and is of low risk for inducing emesis. Some of the agents listed at the top of this category would be placed in the intermediate-risk category by some panelists. The Panel reached the following consensus for treatment of this group.

As in all the categories, individual patients, especially those with poor emetic control and prior drug administration, may require alteration of their antiemetic regimen. Panelists agreed that antiemetic control should exceed 95% in this group. Occasional use of a single dose of a corticosteroid, or as-needed prescribing of oral metoclopramide or a phenothiazine, is common.

iv. *Combination chemotherapy*:

Guideline: The Panel suggests that when combination chemotherapy is given, the patient should be given antiemetics appropriate for the chemotherapeutic agent of greatest emetic risk.

Level of Evidence: IV.

Grade of Recommendation: D.

When combination chemotherapy is given, the patient should be treated for the agent in the combination with the highest emetic risk.[188] For example, if low-risk agents are added to cisplatin therapy, the patient should be given antiemetics appropriate for cisplatin. If low-risk chemotherapy is added to an anthracycline regimen, the patient should be given antiemetics recommended for noncisplatin high-risk agents (the anthracycline category). The Panel was unanimous in this recommendation.

The Panel could not reach consensus concerning added emetic risk if patients are given combinations of chemotherapeutic agents in which all the drugs are in the low emetic risk categories. It has been suggested that these combinations may raise the emetic risk one category higher, but there is no definitive evidence at this time. In the absence of firm evidence, the panelists nonetheless believed that oncologists should be aware of this issue and should carefully evaluate the emetic experience of patients given these chemotherapy combinations. Most experts would continue to treat patients given these chemotherapy combinations with the antiemetics appropriate for the chemotherapeutic agent of the greatest emetic risk.

v. *Multiple consecutive days of chemotherapy*:

Guideline: It is suggested that antiemetics appropriate for the risk class of the chemotherapy, as outlined above, be administered for each day of the chemotherapy.

Level of Evidence: II and III.

Grade of Recommendation: B.

Few studies have assessed vomiting control for specific chemotherapy combinations. There is, however, some evidence that dexamethasone combined with metoclopramide is useful for patients receiving oral cyclophosphamide, methotrexate, and fluorouracil.[30] If the chemotherapy can be given as effectively and safely on day 1 of a multiple-day cycle, the likelihood of controlling emesis will be improved. When chemotherapy likely to induce emesis is given on several consecutive days with antiemetics (best demonstrated with cisplatin and with dacarbazine), control of emesis decreases. The explanation for this has not been elucidated; however, it may be that problems of both delayed and anticipatory emesis are added to the difficulty of controlling acute chemotherapy-induced emesis. 5-HT_3 antagonists plus dexamethasone are especially indicated in high-risk settings,[192-197] because the risk of dystonic reactions with dopamine antagonists increases with consecutive-day therapy (particularly in younger patients). If appropriate for the chemotherapy administered, antiemetics for delayed emesis should be given after the completion of the chemotherapy.

B. Delayed Emesis (Vomiting Occurring > 24 Hours After Chemotherapy)

The neuropharmacologic mechanism of delayed emesis is not well understood.[9,18,198-203] Prevention of this problem has been based on empiric results.[24,29,30,47,82,89,92,128,160,168,176,186,204-215] Fewer agents have been tested or are commonly used for this indication than for acute emesis.

1. Antiemetic Agents

a. Single Agents. i. *Corticosteroids*:

These agents are the most consistently useful drugs for the prevention of delayed emesis.[47,205-207,211] As shown repeatedly in clinical trials, their widespread availability in oral form, low cost, and benefit make corticosteroids the single most appropriate agents for this indication. Side effects are of some concern because corticosteroids are typically used for 2 to 4 days. Adrenal insufficiency after corticosteroid usage is not a problem for this relatively brief period; however, hyperglycemia in susceptible patients requires attention. As with corticosteroids in many other settings, including for acute chemotherapy-induced emesis, the doses and schedules have not been determined by formal testing. Most trials have given the agents twice daily. Dexamethasone has been the agent tested most frequently, often at the dose of 8 mg for 2 to 3 days, occasionally tapering to 4 mg for 1 or 2 additional days. Most panelists recommended oral use of the agent. There are reports of dexamethasone given intramuscularly, but there is no clear advantage to this route. Panelists agreed unanimously that corticosteroids should be part of any regimen for delayed emesis, unless there is a strong contraindication to their usage.

There are some reports of the use of adrenocorticotropic hormone in delayed emesis,[216] but formal trials are few and panelists did not see any advantage for this agent over more readily available and easily administered corticosteroids.

ii. *Metoclopramide and serotonin receptor antagonists*:

Several trials have reported efficacy for oral metoclopramide given in combination with corticosteroids.[168,205,206,209,210,217] Doses typically vary between 20 mg and 40 mg (or 0.5 mg/kg) given two to four times per day for 3 to 4 days. This agent is generally well-tolerated, with few acute dystonic reactions in the adult population (the group for which dystonic reactions are significantly less frequent). Akathisia (restlessness) may occur in some patients. This side effect may be related to dopamine receptor antagonism. Initial reports indicated some efficacy for oral prochlorperazine[209,210] with corticosteroids. There are no formal reports, however.

Studies have yielded conflicting results concerning the use of serotonin antagonists for delayed emesis. Ondansetron and granisetron have been given either singly[17,18,65,82,176,198,199,212] or in combination with corticosteroids,[30,47,168,211,213,214,217] but trial results have varied in regard to whether or not these agents are effective against delayed emesis. One randomized study indicates efficacy of a serotonin antagonist for delayed emesis in patients receiving chemotherapy of intermediate emetogenicity.[82] The doses and schedules of these drugs have not been formally determined. Usually, these agents have been given orally twice a day, with ondansetron administered at 8 mg per dose and granisetron at 1 mg or 2 mg per dose. Side effects have been few and are similar to those reported for the use of these agents in acute chemotherapy-induced emesis.

There is little evidence for the use of other classes of agents for the prevention of delayed chemotherapy-induced emesis.

b. Combinations of Agents. In delayed emesis, as with acute vomiting, combination regimens seem to be the most effective. In a random-assignment trial with patients receiving cisplatin, the oral combination of metoclopramide plus dexamethasone was significantly more effective than dexamethasone alone.[205] There are conflicting results with regard

to serotonin receptor antagonist use with corticosteroids. In one comparison study, granisetron did not add to the efficacy of the corticosteroid[211]; however, in another large comparison trial, the combination of ondansetron plus dexamethasone was equivalent to the combination of metoclopramide plus dexamethasone.[217] The majority of the panelists favored the use of combination antiemetics in high-risk settings for delayed emesis.

Few reports address the incidence and treatment of delayed emesis in children receiving cancer chemotherapy.[133] Dopamine antagonists, especially when given over several consecutive days, cause a high incidence of dystonic reactions and are not a good choice for general multiple-day use in the pediatric population.[133,134]

2. Risk Factors for Delayed Emesis

Risk factors for delayed emesis include patient characteristics and the chemotherapy being administered, as is the case for acute chemotherapy-induced emesis. Oncologists must be aware of these factors to identify patients who need preventive treatment on a routine basis and individuals who may be at greater risk.

a. Patient Characteristics. The most important patient characteristic predicting for greater risk for delayed emesis is poor control of acute chemotherapy-induced emesis.[9,206,214] Patients who experience acute emesis with chemotherapy are significantly more likely to have delayed emesis. Thus, any patient characteristic that predicts a greater risk for acute emesis (such as female sex, emesis with prior cycles of chemotherapy, and low prior alcohol intake history) should be considered as a predictive factor for delayed emesis as well.

b. Chemotherapeutic Agents. Delayed emesis was initially described in patients receiving cisplatin.[204,206,214] Only recently has the problem been formally outlined in patients given other chemotherapy.[82,186,207] The risk of delayed emesis in patients receiving many chemotherapy drugs has not been studied. The recommendations listed in Table 5 are tempered by a lack of formal data in many settings.

c. Guidelines. i(a). *High risk: cisplatin*:

Guideline: In all patients receiving cisplatin, a corticosteroid plus metoclopramide or a 5-HT_3 antagonist is recommended for the prevention of delayed emesis.

Level of Evidence: I.

Grade of Recommendation: A.

Trials have indicated that the majority of patients receiving cisplatin will experience delayed emesis if not given preventative antiemetics, with reports indicating an incidence of 60% to nearly 90%.[17,18,128,168,176,198,199,204-206,211,212,217] The rate seems to increase with higher total doses of cisplatin, and delayed emesis occurs with both single doses and multiple daily doses of cisplatin. The Panel recommended that antiemetics be given to prevent delayed emesis in patients receiving cisplatin. Most panelists recommended a combination of antiemetics that includes a corticosteroid, as outlined in Table 4A.

Trials indicate that the above regimen can give rates of complete control of delayed emesis in the range of 50% to more than 70%, compared with only 11% to 30% control without antiemetics.[204,205] A large, multicenter, randomized trial[217] obtained equivalent rates of control with corticosteroids plus either metoclopramide or ondansetron, showing that either regimen could be given. The low side-effect rates in the adult population with both regimens do not indicate a clear choice for either combination. The markedly lower cost of the metoclopramide regimen and similar efficacy are strong points in favor of this combination.

i(b). *High risk: non-cisplatin*:

Guideline: A prophylactic corticosteroid as a single agent, a prophylactic corticosteroid plus metoclopramide, and a prophylactic corticosteroid plus a 5-HT_3 antagonist are regimens suggested for the prevention of delayed emesis.

Level of Evidence: III-V.

Grade of Recommendation: B-D.

Only recently has prospectively gathered information become available concerning the incidence of delayed emesis in patients receiving chemotherapy in this category.[47,82,207,213] In particular, among patients receiving cyclophosphamide, anthracyclines, carboplatin, or combinations of these agents, the incidence of delayed emesis varied from 20% to 30% in patients not given prophylactic antiemetics for delayed emesis. Use of a corticosteroid as part of the acute emesis regimen was associated with a lower incidence of delayed emesis. The majority of panelists recommended that a delayed emesis regimen be given with this degree of risk, but data are lacking concerning efficacy and specific regimen choices.

Formal trials are needed to determine the length of treatment for delayed emesis regimens in this category. Most panelists recommended using the same dosages as given for cisplatin-induced emesis, although it is possible that fewer days of antiemetic treatment (ie, 2 days) may be needed for these chemotherapy agents.

ii. *Intermediate-low risk*:

Guideline: No regular preventive use of antiemetics for delayed emesis is suggested for patients receiving these chemotherapeutic agents.

Level of Evidence: V and Expert Consensus.

Grade of Recommendation: D.

Few studies have addressed the issues of either the incidence or prevention of delayed emesis in patients

Table 4A. High Emetic Risk: Chemotherapeutic Agents and Guidelines for Acute and Delayed Emesis

Acute Emetic Category	Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis	Evidence (type and grade)	
				Acute Emesis	Delayed Emesis
High: cisplatin	Cisplatin (*Platinol,* Bristol-Myers Oncology, Princeton, NJ)	Pretreatment: 5-HT_3 Antagonist plus a corticosteroid*	Oral corticosteroid plus oral metoclopramide (or plus an oral 5-HT_3 antagonist) *Dexamethasone* 8 mg twice daily for 3 to 4 days, plus either *Metoclopramide* 30-40 mg, two to four times per day for 2-4 days, or *5-HT3 antagonists* at doses in Table 3, for 2-3 days	I, A	I, A
High: noncisplatin	Dacarbazine (*DTIC-Dome,* Bayer, West Haven, CT) actinomycin-D (*Cosmegen,* Merck, Whitehouse Station, NJ) mechlorethamine (*Mustargen,* Merck) streptozotocin (*Zanosar,* Pharmacia & Upjohn, Kalamazoo, MI) hexamethylmelamine (*Hexalen,* US Bioscience, Westconshohocken, PA) carboplatin (*Paraplatin,* Bristol-Myers Oncology) cyclophosphamide (*Cytoxan,* Bristol-Myers Oncology) lomustine (*CeeNU,* Bristol-Myers Oncology) carmustine (*BiCNU,* Bristol-Myers Oncology) daunorubicin (*DaunoXome,* NeXstar Pharmaceuticals, San Dimas, CA) doxorubicin (*Adriamycin,* Pharmacia & Upjohn) epirubicin (*Pharmorubicin,* Pharmacia & Upjohn) idarubicin (*Idamycin,* Pharmacia & Upjohn) cytarabine (*Cytosar,* Pharmacia & Upjohn) ifosfamide (*Ifex,* Bristol-Myers Oncology)		(guideline for all agents in this class, except cisplatin) *Dexamethasone* 8 mg twice daily for 2-3 days, plus either *Metoclopramide* 30-40 mg, two to four times per day for 2-3 days, or *5-HT_3 antagonists* at doses in Table 3, for 2-3 days	II-III, A-B (range for agents below in this class)	III-V, B-D (range for agents below in this class)

*See Table 3 for dosing.

Table 4B. Intermediate Emetic Risk: Chemotherapeutic Agents and Guidelines for Acute and Delayed Emesis

Acute Emetic Category	Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis	Evidence (type and grade)	
				Acute Emesis	Delayed Emesis
Intermediate	Irinotecan (*Camptosar,* Pharmacia & Upjohn) mitoxantrone (*Novantrone,* Immunex, Seattle, WA) paclitaxel (*Taxol,* Bristol-Myers Oncology) docetaxel (*Taxotere,* Rhone-Poulenc Rorer, Collegeville, PA) mitomycin (*Mutamycin,* Bristol-Myers Oncology) topotecan (*Hycamtin,* SmithKline Beecham, Philadelphia, PA) gemcitabine (*Gemzar,* Lilly, Indianapolis, IN) etoposide (*Vepesid,* Bristol-Myers Oncology) teniposide (*Vumon,* Bristol-Myers Oncology)	Pretreatment: a corticosteroid (such as dexamethasone 4-8 mg by mouth, given once before chemotherapy)	No regular preventive use of antiemetics for delayed emesis	III-IV, B-D (range for agents in this class)	V, D (applies to all agents in this class)

NOTE: Individual patients may require treatment similar to that recommended for high emetic risk agents. Combinations of agents in this class are not well studied, but they may occasionally cause more emesis for some patients, requiring treatment similar to that recommended for high-emetic-risk agents.

Table 4C. Low Emetic Risk: Chemotherapeutic Agents and Guidelines for Acute and Delayed Emesis

Chemotherapy Agent (trade name)	Guideline for Acute Emesis	Guideline for Delayed Emesis	Evidence (type and grade)	
			Acute Emesis	Delayed Emesis
Vinorelbine (*Navelbine,* Glaxo Wellcome, Research Triangle Park, NC) fluorouracil (*Efudex,* Hoffman-LaRoche, Nutley, NJ) methotrexate (*Rheumatrex,* Lederle) thioguanine (*Lanvis,* Glaxo Wellcome) mercaptopurine (*Purinethol,* Glaxo Wellcome) bleomycin (*Blenoxane,* Bristol-Myers Oncology) 1-asparaginase (*Elspar,* Merck) vindesine (*Eldisine,* Lilly) vinblastine (*Velban,* Lilly) vincristine (*Oncovin,* Lilly) busulphan (*Myleran,* Glaxo Wellcome) chlorambucil (*Leukeran,* Glaxo Wellcome) melphalan (*Alkeran,* Glaxo Wellcome) hydroxyurea (*Hydrea,* Bristol-Myers Oncology) fludarabine (*Fludara,* Berlex, Wayne, NJ) 2-chlorodeoxyadenosine (*Leustatin,* Ortho Biotech, Raritan, NJ) tamoxifen (*Nolvadex,* Zeneca, Wilmington, DE)	No routine pretreatment antiemetics	No regular preventive use of antiemetics for delayed emesis	V, D (applies to all agents in this class)	V, D (applies to all agents in this class)

NOTE: Individual patients may require treatment similar to that recommended for intermediate-emetic-risk agents. Combinations of agents in this class are not well studied, but they may occasionally cause more emesis for some patients, requiring treatment similar to that recommended for intermediate-emetic-risk agents.

receiving these chemotherapy agents. The opinion of the panelists is that the risk is quite low for most patients; groups of patients receiving these drugs who are at greater risk have not been identified.

Although no prophylactic use of antiemetics is recommended, it may be reasonable for patients to have a small supply of oral dexamethasone, dopamine receptor antagonists, or metoclopramide for use if needed.

Table 5. Radiation-Induced Emesis: Radiation Emetic Risk Categories and Guidelines

Risk Categories	Area Receiving Radiation	Antiemetic Guideline	Evidence (type and grade)
High risk	TBI	Before each fraction: 5-HT_3 antagonist	II, III/B, C
Intermediate risk	Hemibody irradiation Upper Abdomen Abdominal-Pelvic Mantle Cranium (radiosurgery) Craniospinal	Before each fraction: 5-HT_3 antagonist or dopamine receptor antagonist	II, III/B
Low risk	Cranium only	As-needed basis: dopamine receptor or 5-HT_3 antagonist	IV, V/D
	Breast Head and neck Extremities Pelvis Thorax		II, III, IV/B, D (range for class)

C. Anticipatory Emesis

Anticipatory or conditioned emesis may occur in patients who have had poor control of either acute or delayed emesis with prior chemotherapy.[218-228] Some factors that predispose patients to anticipatory emesis have been identified,[229-234] including a history of motion sickness.[174,235]

1. Prevention

Prevention of chemotherapy-induced emesis is seen as the best strategy for preventing anticipatory emesis. Consensus was reached concerning prevention and treatment of anticipatory emesis, as outlined below.

Guideline: Use of the most active antiemetic regimens appropriate for the chemotherapy being given to prevent acute or delayed emesis is suggested. Such regimens must be used with the initial chemotherapy, rather than after assessing the patient's emetic response with less effective treatment.

Level of Evidence: III.

Grade of Recommendation: D.

2. Treatment

Guideline: If anticipatory emesis occurs, behavioral therapy with systematic desensitization is effective and is suggested.[236-244]

Level of Evidence: III.
Grade of Recommendation: B.

d. Special Emetic Problems

1. Emesis in Pediatric Oncology

Guideline: The combination of a 5-HT_3 antagonist plus a corticosteroid is suggested before chemotherapy in children receiving chemotherapy of high emetic risk.

Level of Evidence: III.

Grade of Recommendation: B.

Studies in children receiving chemotherapeutic agents have documented the efficacy of several antiemetics. The most commonly used and best demonstrated antiemetics in children are the serotonin receptor antagonists, which are often given with corticosteroids.[245-248] Although the activity of such agents is well-documented, dosing studies have not clearly established the best doses or special dosing considerations by age, weight, or square meter of body surface area. Typically used doses follow the adult regimens (eg, ondansetron 0.15 mg/kg and granisetron 0.01 mg/kg). The absence of dystonic reactions and the low side-effect profile in general have made these agents excellent choices for use in pediatrics. Predisposition to acute dystonic reactions with dopamine antagonists and metoclopramide have been well documented, especially with consecutive daily use of these antiemetics.

Although studies have not systematically outlined emetic risk factors in children, it seems that the chemotherapy selected (with similar classifications as for adults) and prior emetic experience with chemotherapy are important predictors of risk.[249]

As is the case with dose-finding trials, few comparative antiemetic studies have been conducted in children. Until such studies are conducted, the Panel, led by the pediatric consultant, agreed that the antiemetic recommendations for adults (with doses adjusted for the pediatric population) are reasonable at this time. The major exception is that dopamine receptor antagonists (as outlined in Delayed Emesis) are not considered good choices for children receiving chemotherapy. Behavioral intervention for reduction of nausea and vomiting may also have some value.[250-252]

2. High-Dose Chemotherapy

Guideline: A 5-HT_3 antagonist combined with a corticosteroid is suggested.

Level of Evidence: II and III.

Grade of Recommendation: C.

High-dose chemotherapy, often given as part of a bone marrow transplant or autologous stem-cell transplantation program, presents many concurrent problems in the control of emesis.[253,254] First, the chemotherapy is generally categorized as high or intermediate risk as part of a combination. Second, it is often given on consecutive days. Third, the patient may also be receiving radiation therapy, including total-body irradiation. Fourth, the patient may also have other medical problems or may be receiving other supportive care medicines likely to cause emesis. Fifth, the majority of patients have experienced emesis with prior chemotherapy or irradiation. These are not only problems in emetic control, but they are confounding factors that make clinical research in this area and comparison between different studies difficult.

Some investigators have suggested that higher doses of serotonin receptor antagonists are more effective in this setting.[255] If so, this is the only situation in which such dose escalation would be beneficial. It is difficult to understand this argument based on the concept of the threshold dose saturating all relevant receptors.

Few randomized trials have been done in the setting of high-dose chemotherapy.[253,256-259] Recommendations are based on phase II studies performed in patients with a variety of different risk factors.[260,261]

3. Vomiting and Nausea Despite Optimal Prophylaxis in Current or Prior Cycles

Guideline: The Panel suggests that clinicians (1) conduct a careful evaluation of risk, antiemetic, chemotherapy, tumor, and concurrent disease and medication factors, (2) ascertain that the best regimen is being given for the emetic setting, (3) consider adding an antianxiety agent to the regimen, and (4) consider substituting a dopamine receptor antagonist such as high-dose metoclopramide for the 5-HT_3 antagonist (or add the dopamine antagonist to the regimen).

Level of Evidence: V and Panel Consensus.

Grade of Recommendation: D and Panel Consensus.

Approaching the patient who has not had good control with the initial use of antiemetics for chemotherapy-induced emesis presents several problems. The patient is predisposed to anticipatory emesis, and if the most effective antiemetics were given with the prior cycle of chemotherapy, good control is not likely with the next treatment. When presented with such a patient, the physician should review several factors. These factors include antiemetic agent, chemotherapy, and tumor status.

It is important to evaluate whether appropriate antiemetics for the patient's chemotherapy and risk factors were given previously, and if they were given at the proper dose and schedule. If not, corrections in the antiemetic regimen could be helpful. If the patient were receiving chemotherapy with lower emetic risk, then adjustment of the regimen to that typically used for a higher-risk group should be tried. Because all serotonin antagonists share the same mechanism of action, it is unlikely that substitution of one for another

would be superior to using the original agent, but well-designed studies investigating this have not been performed. If the patient received an oral regimen, the physician could consider giving agents intravenously, although there is no demonstration that this will improve efficacy. If the patient is likely to have increased anxiety before the subsequent chemotherapy, the possibility of anticipatory emesis warrants attention. How poor was the control? One or two episodes of emesis with cisplatin is not an ideal outcome, but it still reflects substantial efficacy of the antiemetics, with not much likelihood that another regimen would be superior.

Can the chemotherapy be altered to lessen emesis while still maintaining antitumor efficacy? Alteration could include avoiding multiple-day chemotherapy, lengthening infusion time, stopping an agent, or substituting with a chemotherapeutic drug less likely to induce emesis, if possible and prudent. Clearly, maintaining a good antitumor response, or maximizing the chance of avoiding recurrence in the adjuvant setting, is of primary importance; however, in a palliative setting, consideration of improvement in the chemotherapy regimen, if unacceptable emesis is occurring, should be given.

Finally, if the patient is having poor control with appropriate antiemetics, early evaluation of the tumor response is reasonable. Is the chemotherapy achieving its goal? Is response occurring, or is the patient receiving palliation worth the side effects? If the pattern of the occurrence of the emesis is not typical for the chemotherapy, are there other disease-related factors (such as intestinal obstruction or brain metastases) that may be causing the emesis? Can one rule out other medications (pain medicines, bronchodilators) or other disease factors (infection, gastritis) that could be complicating the treatment and evaluation of emesis?

II. RADIATION-INDUCED EMESIS

A. Risk Factors for Radiation-Induced Emesis

The risk of emesis with radiotherapy varies with the treatment administered.[262-271] Only a minority of patients receive radiation therapy of high emetic potential, and in that group of patients, the problem can be difficult to prevent or manage. Controversy, due to a lack of systematic evaluation, exists concerning definitions of emetic risk groups. As with chemotherapy-induced emesis, it is the identification of these risk groups that indicates whether antiemetic therapy should be given routinely on a preventative basis or whether antiemetics should be reserved for treatment as needed by individual patients. The radiation oncology literature indicates that treatment field is one of the major determinants of emetic risk. More difficult to define, but also important considerations for risk, are the dose of radiotherapy administered per fraction and the pattern of fractionation. Using available data and clinical experience, the Panel reached consensus on definitions of radiotherapy-induced emesis risk groups (Table 5).

1. Guidelines

a. High Risk: Total-body irradiation (TBI). Guideline: The Panel suggested giving a serotonin receptor antagonist with or without a corticosteroid before each fraction and for at least 24 hours after.

Level of Evidence: II and III

Grade of Recommendation: B and C.

Review of the results of trials that used radiation allows for a series of recommendations. The highest-risk group includes patients treated with TBI. The Panel was unanimous in its recommendation.

Complete control rates with 5-HT_3 antagonists for TBI vary between 50% and 90%.[254,263,272] The role of corticosteroids in combination with 5-HT_3 antagonists has not been studied. If this approach adds efficacy, as occurs with chemotherapy, such regimens would be appropriate for this group. Some panelists advised giving corticosteroids to patients receiving TBI because of the marked risk in this situation and findings in preliminary reports.[273] There are reports that serotonin receptor antagonists are more effective than metoclopramide or phenothiazines.[264,274]

b. Intermediate Risk: Hemibody irradiation, upper abdomen, abdominal-pelvic, mantle, craniospinal irradiation, and cranial radiosurgery. Guideline: The Panel suggested giving a serotonin receptor antagonist or a dopamine receptor antagonist before each fraction.

Level of Evidence: II and III.

Grade of Recommendation: B.

Existing evidence suggests that preventative treatment is better than intervention on an as-needed basis in this group (see Table 5 for group definition) and that serotonin receptor antagonists are more effective than metoclopramide or phenothiazines.[264,274] There may be smaller differences between these agents in intermediate-risk settings than in higher-risk settings, and therefore dopamine receptor antagonists may be more appropriate, particularly in patients receiving craniospinal or lower-half-body radiotherapy, where there is somewhat less risk of emesis.[275] There is also some evidence to suggest that in fractionated radiotherapy, the efficacy of 5-HT_3 antagonists may decrease after the first week of treatment,[276] making it difficult to suggest what the optimal duration of prophylactic treatment should be.

Trials indicate that both serotonin and dopamine receptor antagonist agents are effective for patients who require treatment in this group, with most studies indicating better control with serotonin receptor antagonists.[274,275] In trials, cannabinoids (such as nabilone and levonantradol) have not provided adequate control of emesis and have had a higher rate of side effects than seen with dopamine or serotonin receptor antagonists.[277] A recent study indicates that dexamethasone has efficacy similar to 5-HT_3 antagonists when given to patients receiving radiotherapy to the upper abdomen.[275]

c. Low Risk: Radiation of the Cranium Only, Breast, Head and Neck, Extremities, Pelvis, and Thorax. Guideline: The Panel suggested that treatment be given on an as-needed basis only. Dopamine or serotonin receptor antagonists are advised. Antiemetics should be continued prophylactically for each remaining radiation treatment day.

Level of Evidence: IV and V.

Grade of Recommendation: B-D.

The incidence of emesis in this patient group, as defined in Table 5, is relatively low (0% to 30%). Treatment should be reserved for those patients who experience nausea and vomiting. With a paucity of trials, and because of the previously mentioned evidence that the difference in efficacybetween 5-HT_3 antagonists and dopamine antagonists is smaller in intermediate- and low-risk settings, dopamine antagonists are recommended for routine use with 5-HT_3 antagonists reserved for rescue.

ACKNOWLEDGMENT

The Expert Panel expresses its gratitude to Drs Douglas W. Blayney, George J. Bosl, Allen B. Bredt, David R. Gandara, Patricia A. Ganz, John D. Hainsworth, Robert M. Langdon, Jr, Rudolph M. Navari, T.J. Priestman, and Fausto Roila for their thoughtful reviews of earlier versions of the guidelines.

APPENDIX
Antiemetic Guideline Expert Panel

Investigator	Institution
Richard J. Gralla, MD, Co-Chair	Ochsner Cancer Institute, New Orleans, LA *Medical Oncology*
David Osoba, MD, Co-Chair	QOL Consulting, Vancouver, British Columbia, Canada *Medical Oncology*
Lawrence W. Chinnery	Rockville, MD *Patient Representative*
Rebecca Clark-Snow, RN, BSN, OCN	University of Kansas Cancer Center, Kansas City, KS *Oncology Nurse*
David P. Gill, MD	Webster, TX *Medical Oncology/Hematology*
Susan Groshen, PhD	University of Southern California, Norris Cancer Center, Los Angeles, CA *Biostatistician*
Steven M. Grunberg, MD	University of Vermont Medical Center, Burlington, VT *Medical Oncology*
Paul J. Hesketh, MD	St Elizabeth's Medical Center, Boston, MA *Medical Oncology*
Peter Kirkbride, MD	Princess Margaret Hospital, Toronto, Ontario, Canada *Radiation Oncology*
Mark G. Kris, MD	Memorial Sloan-Kettering Cancer Center, New York, NY *Medical Oncology*
Jim M. Koeller, MS	University of Texas at Austin and the Health Science Center, San Antonio, TX *Pharmacist*
Gary R. Morrow, PhD	University of Rochester Cancer Center, Rochester, NY *Behavioral Medicine*
Edith A. Perez, MD	Mayo Clinic, Jacksonville, FL *Medical Oncology/Hematology*
Jeffrey H. Silber, MD, PhD	Children's Hospital of Philadelphia, Philadelphia, PA *Pediatric Oncology*

REFERENCES

1. Plosker GL, Milne RJ: Ondansetron: A pharmacoeconomic and quality-of-life evaluation of its antiemetic activity in patients receiving cancer chemotherapy. Pharmacoeconomics 2:285-304, 1992

2. Weeks JC: Special issues that arise in applying techniques of economic analysis to evaluation of cancer therapies. Monogr Natl Inst 19:11-12, 1995

3. Aapro MS: Costs and benefits of antiemetic therapy. Support Care Cancer 2:304-306, 1994

4. Canadian Medical Association: The Canadian task force on the periodic health examination. Can Med Assoc J 121:1193-1254, 1979

5. American Society of Clinical Oncology Ad Hoc Colony-Stimulating Factor Guideline Expert Panel: American Society of Clinical Oncology recommendations for the use of hematopoietic colony stimulating factors: Evidence-based, clinical practice guidelines. J Clin Oncol 12:2471-2508, 1994

6. American Society of Clinical Oncology: Disclosure declaration form. Alexandria, VA, American Society of Clinical Oncology, 1999, www.asco.org

7. Aapro MS: Methodological issues in antiemetic studies. Invest New Drugs 11:243-253, 1993

8. Gralla RJ, Clark RA, Kris MG, et al: Methodology in anti-emetic trials. Eur J Cancer 27:S5-S8, 1991

9. Fetting JH, Grochow LB, Folstein MF, et al: The course of nausea and vomiting after high-dose cyclophosphamide. Cancer Treat Rep 66:1487-1493, 1982

10. Andrews PLR, Davis CJ: The physiology of emesis induced by anti-cancer therapy, in Reynolds DJM, Andrews PLR, Davis CJ (eds): Serotonin and the Scientific Basis of Anti-Emetic Therapy. Oxford, United Kingdom, Oxford Clinical Communications, 1995, pp 25-49

11. Morrow GR: A patient report measure for the quantification of chemotherapy induced nausea and emesis: Psychometric properties of the Morrow Assessment of Nausea and Emesis (MANE). Br J Cancer 19:S72-S74, 1992 (suppl)

12. Willan A, Warr D, Pater J, et al: Methodological issues and antiemetic studies, in Osoba D (ed): Effect of Cancer on Quality of Life. Boca Raton, FL, CRC Press, 1991, pp 229-249

13. Clark R, Tyson L, Frisone M: A correlation of objective (OBJ) and subjective (SUBJ) parameters in assessing antiemetic regimens (AER). Oncol Nurs Forum 12:96, 1985 (suppl)

14. Perez EA, Hesketh P, Sandbach J, et al: 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. J Clin Oncol 16:754-760, 1998

15. Gralla R, Navari RM, Hesketh PJ, et al: Single-dose granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. J Clin Oncol 16:1568-1573, 1998

16. Addelman M, Erlichman C, Fine S, et al: Phase I/II trial of granisetron: A novel 5-hydroxytryptamine antagonist for the prevention of chemotherapy-induced nausea and vomiting. J Clin Oncol 8:337-341, 1990

17. Marty M, Pouillart P, Scholl S, et al: Comparison of the 5-hydroxytryptamine 3 (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. N Engl J Med 322:816-821, 1990

18. De Mulder PHM, Seynaeve C, Vermorken JB, et al: Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting. Ann Intern Med 113:834-840, 1990

19. Hainsworth J, Harvey W, Pendergrass K, et al: A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. J Clin Oncol 9:721-728, 1991

20. 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 49:295-304, 1992

21. Tsavaris N, Charalambidis G, Ganas N, et al: Ondansetron versus metoclopramide as antiemetic treatment during cisplatin-based chemotherapy. Acta Oncol 34:243-246, 1995

22. Chevallier B, Cappelaere P, Splinter T, et al: A double-blind, multicentre comparison of intravenous dolasetron mesylate and metoclopramide in the prevention of nausea and vomiting in cancer patients receiving high-dose cisplatin chemotherapy. Support Care Cancer 5:22-30, 1997

23. Bonneterre J, Chevallier B, Metz R, et al: A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. J Clin Oncol 8:1063-1069, 1990

24. Kaasa S, Kvaly S, Dicato MA, et al: A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: A randomized, double-blind study—International Emesis Study Group. Eur J Cancer 26:311-314, 1990

25. Fauser AA, Bleiberg H, Chevallier B, et al: A double-blind, randomized, parallel study of IV dolasetron mesylate versus IV metoclopramide in patients receiving moderately emetogenic chemotherapy. Cancer J 9:196-202, 1996

26. Burris H, Hesketh P, Cohn J, et al: Efficacy and safety of oral granisetron versus oral prochlorperazine in preventing nausea and emesis in patients receiving moderately emetogenic chemotherapy. Cancer J Sci Am 2:85-90, 1996

27. Warr D, Willan A, Fine S, et al: Superiority of granisetron to dexamethasone plus prochlorperazine in the prevention of chemotherapy-induced emesis. J Natl Cancer Inst 83:1169-1173, 1991

28. Marty M: A comparative study of the use of granisetron, a selective 5-HT3 antagonist, versus a standard anti-emetic regimen of chlorpromazine plus dexamethasone in the treatment of cytostatic-induced emesis. Eur J Cancer 26:S28-S32, 1990 (suppl 1)

29. Jones AL, Hill AS, Soukop M, et al: Comparison of dexamethasone and ondansetron in the prophylaxis of emesis induced by moderately emetogenic chemotherapy. Lancet 338:483-487, 1991

30. Levitt M, Warr D, Yelle L, et al: Ondansetron compared with dexamethasone and metoclopramide as antiemetics in the chemotherapy of breast cancer with cyclophosphamide, methotrexate, and fluorouracil. N Engl J Med 328:1081-1084, 1993

31. Warr D, Willan A, Venner P, et al: A randomised, double-blind comparison of granisetron with high-dose metoclopramide, dexamethasone and diphenhydramine for cisplatin-induced emesis. Eur J Cancer 29A:33-36, 1993

32. Chevallier B: Efficacy and safety of granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. Eur J Cancer 26:S33-S36, 1990 (suppl 1)

33. Heron JF, Goedhals L, Jordaan JP, et al: Oral granisetron alone and in combination with dexamethasone: A double-blind randomized comparison against high-dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis. Ann Oncol 5:579-584, 1994

34. Sorbe B, Berglind AM: Tropisetron, a new 5-HT_3-receptor antagonist, in the prevention of radiation-induced nausea, vomiting and diarrhoea. Drugs 43:33-39, 1992 (suppl 3)

35. Sorbe B, Hogberg T, Himmelmann A, et al: Efficacy and tolerability of tropisetron in comparison with a combination of tropisetron and dexamethasone in the control of nausea and vomiting induced by cisplatin-containing chemotherapy. Eur J Cancer 30A:629-634, 1994

36. Rusthoven J, O'Brien BJ, Rocchi A: Ondansetron versus metoclopramide in the prevention of chemotherapy-induced nausea and vomiting: A meta-analysis. Int J Oncol 1:443-450, 1992

37. Bruntsch U, Drechsler S, Hiller E, et al: Prevention of chemotherapy-induced nausea and emesis in patients responding poorly to previous antiemetic therapy comparing tropisetron with optimised standard antiemetic therapy. Drugs 43:23-26, 1992 (suppl 3)

38. Ruff P, Paska W, Goedhals L, et al: Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: A multi-centre double-blind, randomised, parallel-group study. Oncology 51:113-118, 1994

39. Gebbia V, Cannata G, Testa A, et al: Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. Cancer 74:1945-1952, 1994

40. Navari R, Gandara D, Hesketh P, et al: Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. J Clin Oncol 13:1242-1248, 1995

41. Martoni A, Angelelli B, Guaraldi M, et al: An open randomised cross-over study on granisetron versus ondansetron in the prevention of acute emesis induced by moderate dose cisplatin-containing regimens. Eur J Cancer 32A:82-85, 1996

42. Bonneterre J, Hecquet B: Granisetron (IV) compared with ondansetron (IV plus oral) in the prevention of nausea and vomiting induced by moderately-emetogenic chemotherapy: A cross-over study. Bull Cancer 82:1038-1043, 1995

43. Stewart A, McQuade B, Cronje JD, et al: Ondansetron compared with granisetron in the prophylaxis of cyclophosphamide-induced emesis in outpatients: A multicentre, double-blind, double-dummy, randomized, parallel group study. Oncology 52:202-210, 1995

44. Jantunen IT, Muhonen TT, Kataja V, et al: 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy: A randomised study. Eur J Cancer 29A:1669-1672, 1993

45. Hesketh P, Navari R, Grote T, et al: Double-blind, randomized comparison of the antiemetic efficacy of intravenous dolasetron mesylate and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. J Clin Oncol 14:2242-2249, 1996

46. Fauser AA, Duclos B, Chemaissani A, et al: Therapeutic equivalence of single oral doses of dolasetron mesylate and multiple doses of ondansetron for the prevention of emesis after moderately emetogenic chemotherapy. Eur J Cancer 32A:1523-1529, 1996

47. Lofters WS, Pater JL, Zee B, et al: Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy. J Clin Oncol 15:2966-2973, 1997

48. Audhuy B, Cappelaere P, Martin M, et al: A double-blind, randomised comparison of the anti-emetic efficacy of two intravenous doses of dolasetron mesylate and granisetron in patients receiving high-dose cisplatin chemotherapy. Eur J Cancer 32A:807-813, 1996

49. Mantovani G, Maccio A, Bianchi A, et al: Comparison of granisetron, ondansetron, and tropisetron in the prophylaxis of acute nausea and vomiting induced by cisplatin for the treatment of head and neck cancer: A randomized controlled trial. Cancer 77:941-948, 1996

50. Marty M, Kleisbauer JP, Fournal P, et al: Is Navoban (tropisetron) as effective as Zofran (ondansetron) in cisplatin-induced emesis. Anticancer Drugs 6:15-21, 1995 (suppl 1)

51. Andrews PLR, Bhandari P, Davey PT, et al: Are all 5-HT3 receptor antagonists the same? Eur J Cancer 28A:S2-S6, 1992 (suppl 1)

52. Beleslin DB: Neurotransmitter receptor subtypes related to vomiting, in Bianchi AL, Grelot L, Miller AD, et al (eds): Mechanisms and Control of Emesis. London, United Kingdom, John Libbey Eurotext Ltd, 1992, pp 11-18

53. Blackwell CP, Harding SM: The clinical pharmacology of ondansetron. Eur J Cancer Clin Oncol 25:S21-S24, 1989

54. Butler A, Hill JM, Ireland SJ, et al: Pharmacological properties of GR38032F, a novel antagonist at 5-HT_3 receptors. Br J Clin Pharmacol 94:397-412, 1988

55. Hesketh PJ, Gandara DR: Serotonin antagonists: A new class of antiemetic agents. J Natl Cancer Inst 83:613-20, 1991

56. Wilder-Smith O, Borgeat A, Chappius P, et al: Urinary serotonin metabolic excretion during cisplatin chemotherapy. Cancer 72:2239-2241, 1993

57. Andrews PL, Bhandri P: The 5-hydroxytryptamine receptor antagonists as antiemetics: Preclinical evaluation and mechanism of action. Eur J Cancer 29A:S11-S16, 1993

58. Beattie DT, Beresford IJM, Connor HE, et al: The pharmacology of GR203040, a novel, potent and selective non-peptide tachykinin NK1 receptor antagonist. Br J Pharmacol 116:3149-3157, 1995

59. Freeman A, Cunningham K, Tyers M: Selectivity of 5HT3 receptor antagonists and antiemetic mechanisms of action. Anticancer Drugs 3:79-85, 1992

60. Marr H, Dancy P, Bartlett A: Emerging differences between 5-HT3 receptor antagonists. Anticancer Drugs 2:513-518, 1991

61. Grunberg SM: Phase I and other dose-ranging studies of ondansetron. Semin Oncol 19:16-22, 1992

62. The Italian Group for Antiemetic Research: Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. N Engl J Med 332:1-5, 1995

63. Kris MG, Gralla RJ, Clark RA, et al: Phase II trials of the serotonin antagonist GR38032F for the control of vomiting caused by cisplatin. J Natl Cancer Inst 81:42-46, 1989

64. Grunberg SM, Stevenson LL, Russell CA, et al: Dose ranging phase I study of the serotonin antagonist GR38032F for prevention of cisplatin-induced nausea and vomiting. J Clin Oncol 7:1137-1141, 1989

65. Grunberg SM, Lane M, Lester EP: Randomized double-blind comparison of three dose levels of intravenous ondansetron in the prevention of cisplatin-induced emesis. Cancer Chemother Pharmacol 32:268-272, 1993

66. Seynaeve C, Schuller J, Buser K, et al: Comparison of the anti-emetic efficacy of different doses of ondansetron, given as either a continuous infusion or a single intravenous dose, in acute cisplatin-induced emesis: A multicentre, double-blind, randomised, parallel group study. Br J Cancer 66:192-197, 1992

67. Beck TM, Hesketh PJ, Madajewicz S, et al: Stratified, randomized, double-blind comparison of intravenous ondansetron administered as a multiple-dose regimen versus two single-dose regimens in the prevention of cisplatin-induced nausea and vomiting. J Clin Oncol 10:1969-1975, 1992

68. Riviere A: Dose finding study of granisetron in patients receiving high-dose cisplatin chemotherapy. Br J Cancer 69:967-971, 1994

69. Navari RM, Kaplan HG, Gralla RJ, et al: Efficacy and safety of granisetron, a selective 5-hydroxytryptamine-3 receptor antagonist, in the prevention of nausea and vomiting induced by high-dose cisplatin. J Clin Oncol 12:2204-2210, 1994

70. Soukop M: A comparison of two dose levels of granisetron in patients receiving high-dose cisplatin. Eur J Cancer 26:S15-S19, 1990 (suppl 1)

71. Smith IE: A comparison of two dose levels of granisetron in patients receiving moderately emetogenic cytostatic chemotherapy. Eur J Cancer 26:S19-S23, 1990 (suppl 1)

72. Kris MG, Grunberg SM, Gralla RJ, et al: Dose-ranging evaluation of the serotonin antagonist dolasetron mesylate in patients receiving high-dose cisplatin. J Clin Oncol 12:1045-1049, 1994

73. Thant M, Pendergrass K, Harman G, et al: Double-blind, randomized study of the dose response relationship across five single doses of IV dolasetron mesylate for prevention of acute nausea and vomiting after cisplatin chemotherapy. Proc Am Soc Clin Oncol 15:533, 1996 (abstr 1727)

74. Pendergrass K, Audhuy B, Hesketh P, et al: Analysis of optimal dose from eight pooled clinical trials assessing the acute antiemetic efficacy of IV dolasetron mesylate after emetogenic chemotherapy. Proc Am Soc Clin Oncol 15:547, 1996 (abstr 1782)

75. Khojasteh A, Sartiano G, Tapazoglou E, et al: Ondansetron for the prevention of emesis induced by high-dose cisplatin: A multi-center dose-response study. Cancer 66:1101-1105, 1990

76. Kris MG, Gralla RJ, Clark RA, et al: Dose-ranging evaluation of the serotonin antagonist GR-C507/75 (GR38032F) when used as an antiemetic in patients receiving anticancer chemotherapy. J Clin Oncol 6:659-662, 1988

77. Rubenstein E, Fauser A, Grote T, et al: Determination of optimal dolasetron mesylate (DM) dose in prevention of acute nausea and vomiting (ANV) after moderately emetogenic chemotherapy (MECT) using pooled data from three pivotal trials. Proc Am Soc Clin Oncol 15:532, 1996 (abstr 1722)

78. Wymenga ANM, Van Der Graaf WTA, Wils JA, et al: A randomized, double-blind, multicentre study comparing daily 2 and 5 mg of tropisetron for the control of nausea and vomiting induced by low-dose cisplatin- or non-cisplatin-containing chemotherapy. Ann Oncol 7:505-510, 1996

79. Garbe C, Drechsler S, Fiedler H, et al: Dose comparison of tropisetron (Navoban) 5 mg and 10 mg orally in the prophylaxis of dacarbazine-induced nausea and emesis. Semin Oncol 21:12-16, 1994 (suppl 9)

80. Ettinger DS, Eisenberg PD, Fitts D, et al: A double-blind comparison of the efficacy of two dose regimens of oral granisetron in preventing acute emesis in patients receiving moderately emetogenic chemotherapy. Cancer 78:144-151, 1996

81. Harman GS, Omura GA, Ryan K, et al: A randomized, double-blind comparison of single-dose and divided multiple-dose dolasetron for cisplatin-induced emesis. Cancer Chemother Pharmacol 38:323-328, 1996

82. Kaizer L, Warr D, Hoskins P, et al: Effect of schedule and maintenance on the antiemetic efficacy of ondansetron combined with dexamethasone in acute and delayed nausea and emesis in patients receiving moderately emetogenic chemotherapy: A phase III trial by the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 12:1050-1057, 1994

83. de Bruijn KM: Tropisetron: A review of the clinical experience. Drugs 43:11-22, 1992 (suppl 3)

84. Dogliotti L, Antonacci RA, Paze E, et al: Three years' experience with tropisetron in the control of nausea and vomiting in cisplatin-treated patients. Drugs 43:6-10, 1992 (suppl 3)

85. 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 54:273-298, 1997

86. Rache K, Schworer H, Kilbinger H: The Pharmacology of 5-HT3 Release from Enterochromaffin Cells. 1995, p 18

87. Grote TH, Pineda LF, Figlin RA, et al: Oral dolasetron mesylate in patients receiving moderately emetogenic platinum-containing chemotherapy: Oral Dolasetron Dose Response Study Group. Cancer J Sci Am 3:45-51, 1998

88. Rubenstein EB, Gralla RJ, Hainsworth JD, et al: Randomized, double-blind, dose response trial across four oral doses of dolasetron for the prevention of acute emesis after moderately emetogenic chemotherapy. Cancer 79:1216-1224, 1998

89. Kris MG, Radford JE, Pizzo BA, et al: Use of an NK-1 receptor antagonist to prevent delayed emesis following cisplatin. J Natl Cancer Inst 89:817-818, 1997

90. Fraschini G, Ciociola A, Esparza L, et al: Evaluation of three oral dosages of ondansetron in the prevention of nausea chemotherapy. J Clin Oncol 9:1268-1274, 1991

91. Beck TM, Ciociola AA, Jones SE, et al: Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. Ann Intern Med 118:407-413, 1993

92. Beck T, York M, Chang A, et al: Oral ondansetron 8 mg twice daily is as effective as 8 mg three times daily in the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Cancer Invest 15:297-303, 1997

93. Cubeddu LX, Pendergrass K, Ryan T, et al: Efficacy of oral ondansetron, a selective antagonist of 5-HT3 receptors, in the treatment of nausea and vomiting associated with cyclophosphamide-based chemotherapy. Am J Clin Oncol 17:137-146, 1994

94. Dicato MA: Oral treatment with ondansetron in an outpatient setting. Eur J Cancer 27:518-519, 1991 (suppl)

95. Clavel M, Bonneterre J, d'Allens H, et al: Oral ondansetron in the prevention of chemotherapy-induced emesis in breast cancer patients: French Ondansetron Study Group. Eur J Cancer 31A:15-19, 1995

96. The Italian Group for Antiemetic Research: Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. Ann Oncol 6:805-810, 1995

97. Roila F, Tonato M, Cognetti F, et al: Prevention of cisplatin-induced emesis: A double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 9:675-678, 1991

98. Smyth JF, Coleman RE, Nicolson M, et al: Dose dexamethasone enhance control of acute cisplatin induced emesis by ondansetron. BMJ 303:1423-1426, 1991

99. Hesketh PJ, Harvey WH, Harker WG, et al: A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of nausea and vomiting associated with high-dose cisplatin. J Clin Oncol 12:596-600, 1994

100. Joss RA, Bacchi M, Buser K, et al: Ondansetron plus dexamethasone is superior to ondansetron alone in the prevention of emesis in chemotherapy-naive and previously treated patients. Ann Oncol 5:253-258, 1994

101. Latreille J, Pater J, Johnston D, et al: Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy: National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 16:1174-1178, 1998

102. Carmichael J, Bessel EM, Harris AL, et al: Comparison of granisetron alone and granisetron plus dexamethasone in the prophylaxis of cytotoxic-induced emesis. Br J Cancer 70:1161-1164, 1994

103. Garcia-del-muro X, Vadell C, Flores E, et al: Tropisetron alone and in combination with dexamethasone in the prevention of acute and delayed cisplatin-induced emesis. Proc Am Soc Clin Oncol 15:553, 1996 (abstr 1725)

104. The Italian Group for Antiemetic Research: Ondansetron + dexamethasone vs metoclopramide + dexamethasone + diphenhydramine in prevention of cisplatin-induced emesis. Lancet 340:96-99, 1992

105. Cunningham D, Dicato M, Verweij J: Optimum anti-emetic therapy for cisplatin induced emesis over repeat courses: Ondansetron plus dexamethasone compared with metoclopramide, dexamethasone plus lorazepam. Ann Oncol 7:277-282, 1996

106. Aapro MS, Plezia PM, Alberts DS, et al: Double-blind crossover study of the antiemetic efficacy of high-dose dexamethasone versus high-dose metoclopramide. J Clin Oncol 2:466-471, 1984

107. Cassileth PA, Lusk EJ, Torri S, et al: Antiemetic efficacy of dexamethasone therapy in patients receiving cancer chemotherapy. Arch Intern Med 143:1347-1349, 1983

108. Cassileth PA, Lusk EJ, Torri S, et al: Antiemetic efficacy of high-dose dexamethasone in induction therapy in acute nonlymphocytic leukemia. Ann Intern Med 100:701-702, 1984

109. Markman M, Sheidler V, Ettinger DS, et al: Antiemetic efficacy of dexamethasone: Randomized double-blind crossover study with prochlorperazine in patients receiving cancer chemotherapy. N Engl J Med 311:549-552, 1984

110. Aapro MS, Alberto DS: High-dose dexamethasone for prevention of cisplatinum-induced vomiting. Cancer Chemother Pharmacol 7:11-14, 1981

111. D'Olimpio J, Camacho F, Chrandra P, et al: Antiemetic efficacy of high-dose dexamethasone versus placebo in patients receiving cisplatin-based chemotherapy: A randomized double-blind controlled clinical trial. J Clin Oncol 3:1133-1135, 1985

112. Lee B: Methylprednisolone as an antiemetic. N Engl J Med 304:486-498, 1981

113. Osoba D, Erlichman C, Willan A, et al: Superiority of methylprednisolone succinate over low-dose metoclopramide hydrochloride in the prevention of nausea and vomiting produced by cancer chemotherapy. Clin Invest Med 9:225-231, 1986

114. Osoba D, Erlichman C, Willan A, et al: Failure of methylprednisolone acetate to prolong the antinauseant effect of intravenous methylprednisolone sodium succinate in patients receiving chemotherapy. Clin Invest Med 11:377-379, 1988

115. Roila F, Basurto C, Minotto V, et al: Methylprednisolone versus metoclopramide for prevention of nausea and vomiting in breast cancer patients treated with intravenous cyclophosphamide methotrexate 5-flourouracil: A double-blind randomized study. Oncology 45:346-348, 1988

116. Campora E, Chiari S, Bruzzi P, et al: The antiemetic efficacy of methylprednisolone compound with metoclopramide in out-patients receiving adjuvant CMF chemotherapy for breast cancer: A randomized trial. Tumori 71:459-462, 1985

117. Jez E, Sulkes A, Ochayen L, et al: Methylprednisolone versus metoclopramide as antiemetic treatment in patients receiving adjuvant cyclophosphamide, methotrexate, 5 fluorouracil (CMF) chemotherapy: A randomized crossover blind study. J Chemother 1:365-368, 1989

118. Chiara S, Campora E, Lionetto R, et al: Methylprednisolone for the control of CMF-induced emesis. Am J Clin Oncol 10:264-267, 1987

119. Morrow G, Laughner J, Bennett J: Prevalence of nausea and vomiting and other side effects in patients receiving cytoxan, methotrexate, fluorouracil (CMF) therapy with and without prednisone. Proc Am Soc Clin Oncol 3:105, 1984 (abstr C-408)

120. Kris MG, Gralla RJ, Tyson LB, et al: Improved control of cisplatin-induced emesis with high-dose metoclopramide and with combinations of metoclopramide, dexamethasone, and diphenhydramine: Results of consecutive trials in 255 patients. Cancer 55:527-534, 1985

121. Italian Group for Antiemetic Research: Double-blind, dose-finding study of four intravenous doses of dexamethasone in the prevention of cisplatin-induced acute emesis. J Clin Oncol 16:2937-2942, 1998

122. Herrstedt J, Aapro MS, Smyth JF, et al: Corticosteroids, dopamine antagonists and other drugs. Support Care Cancer 6:204-214, 1998

123. Fozard JR, Mobarok Ali ATM: Blockade of neuronal tryptamine receptors by metoclopramide. Eur J Pharmacol 49:109-112, 1978

124. Alavi JB, Torri S, Glick JH: High dose oral metoclopramide: An effective antiemetic agent. Proc Am Soc Clin Oncol 3:109, 1984 (abstr C-424)

125. Gralla RJ, Braun TJ, Squillante A, et al: Metoclopramide: Initial clinical studies of high dose regimens in cisplatin-induced emesis, in Poster D (ed): The Treatment of Nausea and Vomiting Induced by Cancer Chemotherapy. New York, NY, Masson, 1981, pp 167-176

126. Gralla RJ, Itri LM, Pisko SE, et al: Antiemetic efficacy of high-dose metoclopramide: Randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. N Engl J Med 305:905-909, 1981

127. Grunberg SM, Akerley WA, Krailo MD, et al: Comparison of metoclopramide and metoclopramide plus dexamethasone for complete protection from cisplatinum-induced emesis. Can Invest 4:379-385, 1986

128. Grunberg SM, Ehler E, McDermed JE, et al: Oral metoclopramide with or without diphenhydramine: Potential for prevention of late nausea and vomiting induced by cisplatin. J Natl Cancer Inst 80:864-868, 1988

129. Hays H: Antiemetic efficacy of metoclopramide. N Engl J Med 306:485-486, 1982

130. Strum SB, McDermed JE, Opfell RW, et al: Intravenous metoclopramide: An effective antiemetic in cancer chemotherapy. JAMA 247:2683-2686, 1982

131. Allan SG, Cornbleet MA, Warrington PS, et al: Dexamethasone and high dose metoclopramide: Efficacy in controlling cisplatin induced nausea and vomiting. BMJ 289:878-879, 1984

132. Anthony LB, Krozely MG, Woodward NJ, et al: Antiemetic effect of oral versus intravenous metoclopramide in patients receiving cisplatin: A randomized, double-blind trial. J Clin Oncol 4:98-103, 1984

133. Allen JC, Gralla R, Reilly L, et al: Metoclopramide: Dose-related toxicity and preliminary antiemetic studies in children receiving cancer chemotherapy. J Clin Oncol 3:1136-1141, 1985

134. Kris MG, Tyson LB, Gralla RJ, et al: Extrapyramidal reactions with high-dose metoclopramide. N Engl J Med 309:433-434, 1983 (letter)

135. Owens NJ, Schauer AR, Nightingale CH, et al: Antiemetic efficacy of prochlorperazine, haloperidol, and droperidol in cisplatin-induced emesis. Clin Pharm 3:167-170, 1984

136. Grunberg SM, Gala KV, Lampenfeld M, et al: Comparison of the antiemetic effect of high-dose intravenous metoclopramide and high-dose intravenous haloperidol in a randomized double-blind cross-over study. J Clin Oncol 2:782-787, 1984

137. Silvey L, Carpenter JT, Wheeler RH, et al: A randomized comparison of haloperidol plus dexamethasone versus prochlorperazine plus dexamethasone in preventing nausea and vomiting in patients receiving chemotherapy for breast cancer. J Clin Oncol 6:1397-1400, 1988

138. Bregni M, Siena S, DiNicola M, et al: Tropisetron plus haloperidol to ameliorate nausea and vomiting associated with high-dose alkylating agent cancer chemotherapy. Eur J Cancer 27:561-565, 1991

139. Moertel CG, Reitemeier RJ, Gage R: A controlled clinical evaluation of antiemetic drugs. JAMA 186:116-118, 1963

140. Goldstein D, Levi JA, Woods RL, et al: Double-blind randomized cross-over trial of dexamethasone and prochlorperazine as antiemetics for cancer chemotherapy. Oncology 46:105-108, 1989

141. Carr BI, Blayney DW, Goldberg DA, et al: High doses of prochlorperazine for cisplatin-induced emesis: A prospective, random dose-response study. Cancer 60:2165-2169, 1987

142. Saller R, Hellenbrect D: High doses of metoclopramide or droperidol in the prevention of cisplatin-induced emesis. Eur J Cancer Clin Oncol 22:1199-1203, 1986

143. Einhorn L: Nabilone: An effective antiemetic agent in patients receiving cancer chemotherapy. Cancer Treat Rev 9:55-61, 1982

144. Frytak S, Moertel CG, O'Fallon JR, et al: Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. Ann Intern Med 91:825-830, 1979

145. Herman TS, Einhorn LH, Jones SE, et al: Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. N Engl J Med 300:1295-1297, 1979

146. McCabe M, Smith FP, MacDonald JS, et al: Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Invest New Drugs 6:243-246, 1988

147. Chang AE, Shiling DJ, Stillman RC, et al: Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. Ann Intern Med 91:819-24, 1979

148. Sallan SE, Zinberg NE, Frei E III: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med 293:795-797, 1975

149. Sallan SE, Cronin C, Zellen M, et al: Antiemetics in patients receiving chemotherapy for cancer: A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. N Engl J Med 302:135-138, 1980

150. Pomeroy M, Fennelly JJ, Towers M: Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. Cancer Chemother Pharmacol 17:285-288, 1986

151. Niiranen A, Mattson K: Antiemetic efficacy of nabilone and dexamethasone: A randomized study of patients with lung cancer receiving chemotherapy. Am J Clin Oncol 10:325-329, 1987

152. Plasse TF, Gorter RW, Krasnow SH, et al: Recent clinical experience with dronabinol. Pharmacol Biochem Behav 40:695-700, 1991

153. Gralla RJ, Tyson LB, Bordin LA, et al: Antiemetic therapy: A review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. Cancer Treat Rep 68:163-172, 1984

154. Chang AE, Shiling DJ, Stillman RC, et al: A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and Cytoxan chemotherapy. Cancer 47:1746-1751, 1981

155. Levitt M, Faiman C, Hawks R, et al: Randomized double-blind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. Proc Am Soc Clin Oncol 3:91, 1984 (abstr C-354)

156. Tyson LB, Gralla RJ, Clark RA, et al: Phase 1 trial of levonantradol in chemotherapy-induced emesis. Am J Clin Oncol 8:528-532, 1985

157. Cunningham D, Forrest GJ, Soukoup M, et al: Nabilone and prochlorperazine: A useful combination for emesis induced by cytotoxic drugs. BMJ 291:864-865, 1985

158. Greenblatt DJ, Shader RI, Abernathy DL: Current status of benzodiazepines (first of two parts). N Engl J Med 309:354-358, 1983

159. Greenblatt DJ, Shader RI, Abernathy DR: Current status of benzodiazepines (second of two parts). N Engl J Med 309:410-416, 1983

160. Kris MG, Gralla RJ, Clark RA, et al: Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone: A double-blind, randomized trial. Cancer 60:2816-2822, 1987

161. Bishop JF, Olver IN, Wolf MM, et al: Lorazepam: A randomized, double-blind, crossover study of a new antiemetic in patients receiving cytotoxic chemotherapy and prochlorperazine. J Clin Oncol 2:691-695, 1984

162. Bowcock SJ, Stockdale AD, Bolton JAR, et al: Antiemetic prophylaxis with high dose metoclopramide or lorazepam in vomiting induced by chemotherapy. BMJ 288:1879, 1984

163. Friedlander ML, Kearsley JH, Sims K, et al: Lorazepam as an adjunct to antiemetic therapy with haloperidol in patients receiving cytotoxic chemotherapy. Aust N Z J Med 13:53-56, 1983

164. Kris MG, Gralla RJ, Clark RA, et al: Consecutive dose-finding trials adding lorazepam to the combination of metoclopramide plus dexamethasone: Improved subjective effectiveness over the combination of diphenhydramine plus metoclopramide plus dexamethasone. Cancer Treat Rep 69:1257-1262, 1985

165. Laszlo J, Clark RA, Hanson DC, et al: Lorazepam in cancer patients treated with cisplatin: A drug having antiemetic, amnestic, and anxiolytic effects. J Clin Oncol 3:864-869, 1985

166. Maher J: Intravenous lorazepam to prevent nausea and vomiting associated with cancer chemotherapy. Lancet 1:91-92, 1981

167. Baltzer L, Pisters KMW, Kris MG, et al: High-dose ondansetron (OND) plus dexamethasone (DEX) for the prevention of nausea and vomiting with multiple day cisplatin chemotherapy. Proc Am Soc Clin Oncol 12:462, 1993 (abstr 1607)

168. Gebbia V, Testa A, Valenza R, et al: Oral granisetron with or without methylprednisolone versus metoclopramide plus methylprednisolone in the management of delayed nausea and vomiting induced by cisplatin-based chemotherapy. Cancer 76:1821-1828, 1995

169. Smith DB, Newlands ES, Rustin GJ, et al: A phase I/II study of the 5-HT3 antagonist GR38032F in the anti-emetic prophylaxis of patients receiving high-dose cisplatin chemotherapy. Cancer Chemother Pharmacol 25:291-294, 1990

170. Gralla RJ, Tyson LB, Kris MG, et al: The management of chemotherapy-induced nausea and vomiting. Med Clin North Am 71:289-301, 1987

171. Sullivan JR, Leyden MJ, Bell R: Decreased cisplatin-induced nausea and vomiting with chronic alcohol ingestion. N Engl J Med 309:796, 1983 (letter)

172. Roila F, Tonato M, Basurto C, et al: Antiemetic activity of high doses of metoclopramide combined with methylprednisolone versus metoclopramide alone in cisplatin-treated cancer patients: A randomized double-blind trial of the Italian Oncology Group for Clinical Research. J Clin Oncol 5:141-149, 1987

173. Morrow GR: The effect of a susceptibility to motion sickness on the side effects of cancer chemotherapy. Cancer 55:2766-2770, 1985

174. Morrow GR: Chemotherapy-related nausea and vomiting: Etiology and management. CA Cancer J Clin 39:89-104, 1989

175. Roila F, Bracarda S, Tonato M, et al: Ondansetron (GR38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. Clin Oncol 2:268-272, 1990

176. Tonato M, Roila F, Del Favero A: Methodology of antiemetic trials: A review. Ann Oncol 2:107-114, 1991

177. Pollera CF, Giannarelli D: Prognostic factors influencing cisplatin-induced emesis. Cancer 64:1117-1122, 1989

178. Pater J, Slamet L, Zee B, et al: Inconsistency of prognostic factors for post-chemotherapy nausea and vomiting. Support Care Cancer 2:161-166, 1994

179. Morrow G: Behavioral factors influencing the development and expression of chemotherapy-induced side effects. Br J Cancer 19:554-561, 1992 (suppl)

180. Osoba D, Zee B, Warr D, et al: Quality of life studies in chemotherapy-induced emesis. Oncology 53:92-95, 1996 (suppl)

181. Osoba D, Zee B, Pater J, et al: Determinants of post-chemotherapy nausea and vomiting in patients with cancer. J Clin Oncol 15:116-123, 1997

182. Craig JB, Powell BL: Review: The management of nausea and vomiting in clinical oncology. Am J Med Sci 293:34-44, 1987

183. Laszlo J: Treatment of nausea and vomiting caused by cancer chemotherapy. Cancer Treat Rev 9:3-9, 1982

184. Lindley CM, Bernard S, Fields SM: Incidence and duration of chemotherapy-induced nausea and vomiting in the outpatient oncology population. J Clin Oncol 7:1142-1149, 1989

185. Cubeddu LX, Hoffman IS, Fuenmayor NT, et al: Antagonism of serotonin S3 receptors with ondansetron prevents nausea and emesis induced by cyclophosphamide-containing chemotherapy regimens. J Clin Oncol 8:1721-1727, 1990

186. Cubeddu LX, Hoffmann IS, Fuenmayor NT, et al: Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 322:810-816, 1990

187. Hesketh PJ, Kris MG, Grunberg SM, et al: A proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 15:103-109, 1997

188. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer: Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference. Ann Oncol 9:811-819, 1998

189. Cupissol DR, Serrou B, Caubel M: The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high-dose cisplatin-induced emesis. Eur J Cancer 26:S23-S27, 1990

190. Jantunen IT, Kataja VV, Muhonen TT: An overview of randomized studies comparing 5-HT3 receptor antagonists to conventional antiemetics in the prophylaxis of acute chemotherapy-induced vomiting. Eur J Cancer 33:66-74, 1997

191. Hainsworth JD: The use of ondansetron in patients receiving multiple-day cisplatin regimens. Semin Oncol 19:48-52, 1992

192. Hainsworth JD, Omura GA, Khojasteh A, et al: Ondansetron (GR 38032F): A novel antiemetic effective in patients receiving a multiple-day regimen of cisplatin chemotherapy. Am J Clin Oncol 14:336-340, 1991

193. Sledge GW, Einhorn L, Nagy C, et al: Phase III double-blind comparison of intravenous ondansetron and metoclopramide as antiemetic therapy for patients receiving multiple-day cisplatin-based chemotherapy. Cancer 70:2524-2528, 1992

194. Bremer K: A single-blind study of the efficacy and safety of intravenous granisetron compared with alizapride plus dexamethasone in the prophylaxis and control of emesis in patients receiving 5-day cytostatic therapy: The Granisetron Study Group. Eur J Cancer 28A: 1018-1022, 1992

195. Nicolai N, Mangiarotti B, Salvioni R, et al: Dexamethasone plus ondansetron versus dexamethasone plus alizapride in the prevention of emesis induced cisplatin-containing chemotherapies for urological cancers. Eur Urol 23:450-456, 1993

196. Rath U, Upadhyaya BK, Arechavala E, et al: Role of ondansetron plus dexamethasone in fractionated chemotherapy. Oncology 50:168-172, 1993

197. Kris MG, Tyson LB, Clark RA, et al: Oral ondansetron for the control of delayed emesis after cisplatin: Report of a phase II study and a review of completed trials to manage delayed emesis. Cancer 70:1012-1016, 1992

198. Gandara DR, Harvey WH, Monaghan GG, et al: The delayed-emesis syndrome from cisplatin: Phase III evaluation of ondansetron versus placebo. Semin Oncol 19:67-71, 1992

199. Kris MG, Pisters KMW, Hinkley L: Delayed emesis following anticancer chemotherapy. Support Care Cancer 2:297-300, 1994

200. Rudd JA, Jordan CC, Naylor RJ: Profiles of emetic action of cisplatin in the ferret: A potential model of acute and delayed emesis. Eur J Pharmacol 262:R1-R2, 1994

201. Rudd JA, Jordan CC, Naylor RJ: The action of the NK 1 tachykinin receptor antagonist CP 99,994 to antagonise the acute and delayed emesis induced by cisplatin in the ferret. Br J Pharmacol 119:931-936, 1996

202. Milano S, Blower P, Romain D, et al: The piglet as a suitable animal model for studying the delayed phase of cisplatin-induced emesis. J Pharmacol Exp Ther 274:951-961, 1995

203. 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 3:1379-1384, 1985

204. Kris MG, Gralla RJ, Tyson LB, et al: Controlling delayed vomiting: Double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 7:108-114, 1989

205. Roila F, Boschetti E, Tonato M: Predictive factors of delayed emesis in cisplatin treated patients and antiemetic activity and tolerability of metoclopramide or dexamethasone: A randomized single-blind study. Am J Clin Oncol 14:238-242, 1991

206. Koo WH, Ang PT: Role of maintenance oral dexamethasone in prophylaxis of delayed emesis caused by moderately emetogenic chemotherapy. Ann Oncol 7:71-74, 1996

207. Kris MG, Radford J, Pizzo B, et al: Dose ranging antiemetic trial of the NK-1 receptor antagonist CP-122,721: A new approach for acute and delayed emesis following cisplatin. Proc Am Soc Clin Oncol 15:547, 1996 (abstr 1780)

208. Clark R, Kris M, Tyson L, et al: Antiemetic trials to control delayed vomiting following high-dose cisplatin. Proc Am Soc Clin Oncol 5:257, 1986 (abstr 1005)

209. Strum S, McDermed J, Abrahano-Umall R, et al: Management of cisplatin (DDP)-induced delayed-onset nausea (N) and vomiting (V): Preliminary results with 2 drug regimens. Proc Am Soc Clin Oncol 4:263, 1985 (abstr C-1024)

210. Johnston D, Latreille J, Laberge F, et al: Preventing nausea and vomiting during days 2-7 following high-dose cisplatin chemotherapy (HDCP): A study by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG). Proc Am Soc Clin Oncol 14:529, 1995 (abstr 1745)

211. Navari RM, Madajewicz S, Anderson N, et al: Oral ondansetron for the control of cisplatin-induced delayed emesis: A large multicenter, double-blind, randomized comparative trial of ondansetron versus placebo. J Clin Oncol 13:2408-2416, 1995

212. Pater JL, Lofters WS, Zee B, et al: The role of the 5-HT3 antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Ann Oncol 8:181-185, 1997

213. Roila F: Dexamethasone, granisetron, or both for the prevention of nausea and vomiting during chemotherapy for cancer. N Engl J Med 332:1-5, 1995

214. Ossi M, Anderson E, Freeman A: 5-HT3 receptor antagonists in the control of cisplatin-induced delayed emesis. Oncology 53:78-85, 1996 (suppl)

215. Passalacqua R, Cocconi G, Bella M, et al: Double-blind, randomized trial for the control of delayed emesis in patients receiving cisplatin: Comparison of placebo vs. adrenocorticotropic hormone (ACTH). Ann Oncol 3:481-485, 1992

216. Italian Group for Antiemetic Research: Ondansetron versus metoclopramide, both combined with dexamethasone, in the prevention of cisplatin-induced delayed emesis. J Clin Oncol 15:124-130, 1997

217. Andrykowski MA, Redd WH, Hatfield AK: Development of anticipatory nausea: A prospective analysis. J Consult Clin Psychol 53:449-454, 1985

218. Andrykowski MA, Jacobsen PB, Marks E, et al: Prevalence, predictors, and course of anticipatory nausea in women receiving adjuvant chemotherapy for breast cancer. Cancer 62:2607-2613, 1988

219. Andrykowski MA: Development of anticipatory nausea in cancer chemotherapy: A review and synthesis. Psychosom Med 52:458-475, 1990

220. Burish TG, Carey MP: Conditioned aversive responses in cancer chemotherapy patients: Theoretical and developmental analysis. J Consult Clin Psychol 54:593-600, 1986

221. Morrow GR: Prevalence and correlates of anticipatory nausea and vomiting in chemotherapy patients. J Natl Cancer Inst 68:585-588, 1982

222. Morrow GR: Clinical characteristics associated with the development of anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment. J Clin Oncol 2:1170-1176, 1984

223. Morrow GR, Dobkin PL: Anticipatory nausea and vomiting in cancer patients undergoing chemotherapy treatment: Prevalence, etiology, and behavioral interventions. Clin Psychol Rev 8:517-556, 1988

224. Morrow GR, Lindke J, Black PM: Predicting development of anticipatory nausea in cancer patients: Prospective examination of eight clinical characteristics. J Pain Symptom Manage 6:215-223, 1991

225. Morrow GR, Rosenthal SN: Models, mechanisms and management of anticipatory nausea and emesis. Oncol 53:4-7, 1996 (suppl 1)

226. Morrow GR, Lindke J, Black PM: Anticipatory nausea development in cancer patients: Replication and extension of a learning model. Br J Psychol 82:61-72, 1991

227. Aapro MS, Kirchner V, Terrey JP: The incidence of anticipatory nausea and vomiting after repeat cycle chemotherapy: The effect of granisetron. Br J Cancer 69:957-960, 1994

228. Alba E, Bastus R, de Andres L, et al: Anticipatory nausea and vomiting: Prevalence and predictors in chemotherapy patients. Oncology 46:26-30, 1989

229. Challis GB, Stam HJ: A longitudinal study of the development of anticipatory nausea and vomiting in cancer chemotherapy patients: The role of absorption and autonomic perception. Health Psychol 11:181-189, 1992

230. Chin SB, Kucuk O, Peterson R, et al: Variables contributing to anticipatory nausea and vomiting in cancer chemotherapy. Am J Clin Oncol 15:262-267, 1992

231. Jacobsen PB, Bovbjerg DH, Redd WH: Anticipatory anxiety in women receiving chemotherapy for breast cancer. Health Psychol 12:469-475, 1993

232. Jacobsen PB, Bovbjerg DH, Schwartz MD, et al: Conditioned emotional distress in women receiving chemotherapy for breast cancer. J Consult Clin Psychol 63:108-114, 1995

233. Kvale G, Hugdahl K, Asbjornsen A, et al: Anticipatory nausea and vomiting in cancer patients. J Consult Clin Psychol 59:894-898, 1991

234. Morrow GR: Susceptibility to motion sickness and chemotherapy-induced side effects. Lancet 1:390-391, 1984 (letter)

235. Fallowfield LJ: Behavioural interventions and psychological aspects of care during chemotherapy. Eur J Cancer 28A:S39-S41, 1992 (suppl 1)

236. Morrow GR, Morrell C: Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. N Engl J Med 307:1474-1480, 1982

237. Morrow GR, Asbury R, Hammon S, et al: Comparing the effectiveness of behavioral treatment for chemotherapy-induced nausea and vomiting when administered by oncologists, oncology nurses, and clinical psychologists. Health Psychol 11:250-256, 1992

238. Morrow GR: Effect of hierarchy in the systematic desensitization treatment of anticipatory nausea in cancer patients: A component comparison with relaxation only, counseling, and no treatment. Cognit Ther Res 10:421-446, 1986

239. Redd WH, Andrykowski MA: Behavioral intervention in cancer treatment: Controlling aversion reactions to chemotherapy. J Consult Clin Psychol 20:1018-1029, 1982

240. Redd WH, Jacobsen PB, Die-Trill M, et al: Cognitive/attentional distraction in the control of conditioned nausea in pediatric cancer patients receiving chemotherapy. J Consult Clin Psychol 55:391-395, 1987

241. Burish TG, Lyles JN: Effectiveness of relaxation training in reducing the aversiveness of chemotherapy in the treatment of cancer. J Behav Ther Exp Psychiatry 10:357-361, 1979

242. Burish TG, Carey MP, Krozely MG, et al: Conditioned side effects induced by cancer chemotherapy: Prevention through behavioral treatment. J Consult Clin Psychol 55:42-48, 1987

243. Burish TG, Tope DM: Psychological techniques for controlling the adverse side effects of cancer chemotherapy: Findings from a decade of research. J Pain Symptom Manage 7:287-301, 1992

244. Jurgens H, McQuade B: Ondansetron as prophylaxis for chemotherapy and radiotherapy induced emesis in children. Oncology 49:279-285, 1992

245. Carden PA, Mitchell SL, Waters KD, et al: Prevention of cyclophosphamide/cytarabine-induced emesis with ondansetron in children with leukemia. J Clin Oncol 8:1531-1535, 1990

246. Pinkerton CR, Williams D, Wootton C, et al: 5-HT3 antagonist ondansetron: An effective outpatient antiemetic in cancer treatment. Arch Dis Child 65:822-825, 1990

247. Stevens RF: The role of ondansetron in paediatric patients: A review of three studies. Eur J Cancer 27:S20-S22, 1991 (suppl 1)

248. Dolgin MJ, Katz ER, McGinty K, et al: Anticipatory nausea and vomiting in pediatric cancer patients. Pediatrics 75:547-552, 1985

249. Zeltzer L, Kellerman J, Ellenberg L, et al: Hypnosis for reduction of vomiting associated with chemotherapy and disease in adolescents with cancer. J Adolesc Health Care 4:77-84, 1983

250. Zeltzer L, LeBaron S, Zeltzer PM: The effectiveness of behavioral intervention for reduction of nausea and vomiting in children and adolescents receiving chemotherapy. J Clin Oncol 2:683-690, 1984

251. Zeltzer LK, Dolgin MJ, LeBaron S, et al: A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. Pediatrics 88:34-42, 1991

252. Okamoto S, Takahashi S, Tanosaki R, et al: Granisetron in the prevention of vomiting induced by conditioning for stem cell transplantation: A prospective randomized study. Bone Marrow Transplant 17:679-683, 1996

253. Or R, Drakos P, Nagler A, et al: The anti-emetic efficacy and tolerability of tropisetron in patients conditioned with high-dose chemotherapy (with and without total body irradiation) prior to bone marrow transplantation. Support Care Cancer 2:245-248, 1994

254. Spitzer TR, Grunberg SM, Dicato MA: Antiemetic strategies for high-dose chemoradiotherapy-induced nausea and vomiting. Support Care Cancer 6:233-236, 1998

255. Bosi A, Guidi S, Messori A, et al: Ondansetron versus chlorpromazine for preventing emesis in bone marrow transplant recipients: A double-blind randomized study. J Chemother 5:191-196, 1993

256. Crenier L, Lemoine F, Bastin G, et al: A comparative study on the efficacy of the different 5-HT3 antagonists to control acute emesis in blood stem cell transplantation. Support Care Cancer 4:253, 1996 (abstr)

257. Gilbert CJ, Ohly KV, Rosner G, et al: Randomized, double-blind comparison of a prochlorperazine-based versus a metoclopramide-based antiemetic regimen in patients undergoing autologous bone marrow transplantation. Cancer 76:2330-2337, 1995

258. Agura ED, Brown MC, Schaffer R, et al: Antiemetic efficacy and pharmacokinetics of intravenous ondansetron infusion during chemotherapy conditioning for bone marrow transplant. Bone Marrow Transplant 16:213-222, 1995

259. Abbott B, Ippoliti C, Neumann J, et al: Standard practice protocol of granisetron (Kytril) for antiemetic control in bone marrow transplant (BMT) patients receiving highly emetogenic chemotherapy with or without total body irradiation (TBI). Blood 88:252b, 1996 (abstr) (suppl 1)

260. Barbounis V, Koumakis G, Vassilomanolakis M, et al: A phase II study of ondansetron as antiemetic prophylaxis in patients receiving high-dose polychemotherapy and stem cell transplantation. Support Care Cancer 3:301-306, 1995

261. Spitzer TR, Bryson JC, Cirenza E, et al: Randomized double-blind, placebo-controlled evaluation of oral ondansetron in the prevention of nausea and vomiting associated with fractionated total-body irradiation. J Clin Oncol 12:2432-2438, 1994

262. Hunter AE, Prentice HG, Pothecary K, et al: Granisetron, a selective 5-HT3 receptor antagonist, for the prevention of radiation-induced emesis during total body irradiation. Bone Marrow Transplant 7:439-441, 1991

263. Prentice HG, Cunningham S, Gandhi L, et al: Granisetron in the prevention of irradiation-induce emesis. Bone Marrow Transplant 15:445-448, 1995

264. Tiley C, Powles R, Catalano J, et al: Results of a double-blind placebo controlled study of ondansetron as an antiemetic during total body irradiation in patients undergoing bone marrow transplantation. Leuk Lymphoma 7:317-321, 1992

265. Scarantino CW, Ornitz RD, Hoffman LG, et al: Radiation-induced emesis: Effects of ondansetron. Semin Oncol 19:38-43, 1992

266. Scarantino CW, Ornitz RD, Hoffman LG, et al: On the mechanism of radiation-induced emesis: The role of serotonin. Radiat Oncol Biol Phys 30:825-830, 1994

267. Danjoux E, Rider WD, Fitzpatrick PJ, et al: The acute radiation syndrome. Clin Radiol 30:581-584, 1979

268. Lippens RJ, Broeders GC: Ondansetron in radiation therapy of brain tumors in children. Pediatr Hematol Oncol 13:247-252, 1996

269. Miralbell R, Coucke P, Behrouz F, et al: Nausea and vomiting in fractionated radiotherapy: A prospective on demand trial of tropisetron rescue for non-responders to metoclopramide. Eur J Cancer 31A:1461-1464, 1995

270. Westbrook GJ, Barrett A: Vomiting associated with whole body irradiation. Clin Radiol 38:263-266, 1987

271. Schwella N, Konig V, Schwerdtfeger R, et al: Ondansetron for efficient emesis control during total body irradiation. Bone Marrow Transplant 13:169-171, 1994

272. Kirkbride P, Pater J, Zee B, et al: A phase III study of the efficacy of dexamethasone (DEX) in the prophylaxis of radiation induced emesis (RIE). Proc Am Soc Clin Oncol 17:51a, 1998 (abstr 196)

273. Priestman TJ, Roberts JT, Lucraft H, et al: Results of a randomized, double-blind comparative study of ondansetron and metoclopramide in the prevention of nausea and vomiting following high-dose upper abdominal irradiation. Clin Oncol 2:71-75, 1990

274. Priestman TJ, Roberts JT, Upadhyaya BK: A prospective randomized double-blind trial comparing ondansetron versus prochlorperazine for the prevention of nausea and vomiting in patients undergoing fractionated radiotherapy. Clin Oncol 5:358-363, 1993

275. Franzen L, Nyman J, Hagberg H, et al: A randomised placebo controlled study with ondansetron in patients undergoing fractionated radiotherapy. Ann Oncol 7:587-592, 1996

276. Priestman SG, Priestman TJ, Canney PA: A double-blind randomised cross-over comparison of nabilone and metoclopramide in the control of radiation-induced nausea. Clin Radiol 38:543-544, 1987

277. Ungerleider JT, Andrysiak TA, Fairbanks LA, et al: Tetrahydrocannabinol vs. prochlorperazine: The effects of two antiemetics on patients undergoing radiotherapy. Radiology 150:598-599, 1984