

Drug Class Review

Newer Antiemetics

Final Report Update 1

January 2009



Original report date: January 2006

A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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EVIDENCE TABLES

Published in a separate document.

Shading indicates new information.

Note:

A scan of the medical literature relating to the topic is done periodically (see the Drug Effectiveness Review Project website at <http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm>). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see the timeline on the DERP website for details on the date of its release. Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Nausea and vomiting are major concerns for patients undergoing chemotherapy and radiation therapy.^{1,2} Risk factors associated with chemotherapy-induced nausea and vomiting include emetogenicity of the chemotherapy regimen, dose, speed of intravenous infusion, female gender, age under 50 years, history of ethanol consumption, and history of prior chemotherapy.³ Factors predictive of radiation therapy-induced nausea and vomiting include site of irradiation (in particular, total body irradiation and radiation fields that include the abdomen), total field size, dose per fraction, age, and predisposition for emesis (history of sickness during pregnancy or motion sickness).² Secondary risks associated with nausea and vomiting induced by chemotherapy and radiation therapy include electrolyte imbalance, aspiration pneumonia, interruption of potentially curative therapy, and reduction in quality of life.

Nausea and vomiting are also frequently associated with surgical procedures. The incidence of postoperative nausea and vomiting is estimated to be 25%-30%.⁴ The risk of postoperative nausea and vomiting is multifactorial and can be influenced by patient characteristics, type of surgical procedure, and anesthesia.⁵ Female gender, a history of motion sickness or postoperative nausea and vomiting, nonsmoking status, and use of postoperative opioids have been cited as the patient factors most predictive of postoperative nausea and vomiting.⁵ Surgical procedures that are associated with increased risk of postoperative nausea and vomiting include craniotomy, ear, nose, and throat procedures, open abdominal surgeries, major breast procedures, strabismus operations, laparoscopy, and laparotomy.⁵ Anesthesia-related factors that can affect risk of postoperative nausea and vomiting include use of opioids, nitrous oxide, and volatile inhalational agents.⁵ Postoperative nausea and vomiting can result in electrolyte imbalance, surgical wound bleeding, and increase in hospital stay, among other consequences.⁶ Numerous pharmacological and nonpharmacological interventions have been studied in an effort to prevent and manage postoperative nausea and vomiting.^{7,8}

Finally, nausea and vomiting are commonly associated with pregnancy. The most severe and persistent form of pregnancy-related nausea and vomiting, hyperemesis gravidarum, can lead to serious complications, including dehydration, metabolic disturbances, nutritional deficits requiring hospitalization, and even death.⁹

Nausea and vomiting associated with surgical procedures, chemotherapeutic agents, radiation therapy, and pregnancy are thought to be induced by stimulation of the dopamine, acetylcholine, histamine, serotonin and substance P/neurokinin 1 (NK1) neuroreceptors involved in activating areas of the brain that coordinate the act of vomiting. Earlier pharmacologic agents commonly used as antiemetics included histamine-1 blockers such as diphenhydramine, anticholinergics, and dopamine antagonists including phenothiazines (chlorpromazine, perphenazine, prochlorperazine), metoclopramide, and droperidol.¹⁰ The discovery that type 3 serotonin (5-HT₃) receptor-blocking properties were contributing to the effect of one of the dopamine antagonists, metoclopramide, eventually led to the development of newer antiserotonergic drugs.¹¹ There are currently four 5-HT₃ receptor antagonists approved for use in the United States and Canada (Table 1). The newest antiemetic drugs, aprepitant and fosaprepitant, are antagonists of the substance P/neurokinin 1 (NK1) receptors.

The objective of this review was to evaluate the comparative effectiveness and harms of newer antiemetic drugs including the 5-HT₃ and NK-1 antagonists. Table 1 provides an accounting of the indications approved by the US Food and Drug Administration for each of the 5-HT₃ and NK-1 antagonists and Appendixes A and B provide dosage recommendations for adults and children, respectively.

Table 1. Antiemetic drug indications approved by the US Food and Drug Administration

Drug (Brand name)	Dosage form ^d	FDA-approvals				
		Chemotherapy	Postoperative		Radiation	Pregnancy
			Prevention	Treatment		
Aprepitant/	Oral capsule	X ^{a,b}	X			
fosaprepitant (Emend)	Injection	X ^{a,b}				
Dolasetron (Anzamet)	Oral tablet	X ^a	X			
	Injection	X ^{a,b}	X	X		
Granisetron (Kytrel)	Oral tablet	X ^{a,b}			X	
	Injection	X ^{a,b}	X	X		
(Sancuso) ^c	Film, Extended release, Transdermal	X ^{a,b}	X			
Ondansetron (Zofran)	Injection	X ^{a,b}	X			
	oral tablet	X ^{a,b}	X		X	
	oral solution	X ^{a,b}	X		X	
Palonosetron (Aloxi)	Oral capsule	X ^a	X			
	Injection	X ^{a,b}	X			

^a Moderately emetic.

^b Highly emetic.

^c We are aware that a new transdermal patch form of granisetron (Sancuso[®]) was approved by the Food and Drug Administration in September of 2008. As this occurred very late in the time line of the current update, the Drug Effectiveness Review Project's participating organizations voted to defer the addition of granisetron transdermal patch until the next update.

^d Please see product labels for dosing instructions.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. A systematic review focuses on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with a careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix C and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the importance of the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are emphasized over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is

the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, cohort designs are preferred, when conducted well, for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* performed in controlled or academic settings can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as either an efficacy or an effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient

population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for nausea and vomiting. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?

2. What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?
3. Are there subgroups of patients based on demographics (age, race, gender), pregnancy, other medications, or comorbidities for which 1 newer antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adults or children at risk for or with nausea, vomiting (including retching), or both related to the following therapies and conditions:

- Chemotherapy of various emetogenicity
- Radiation therapy
- Surgical procedure
- Pregnancy

In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999^{12, 13} to clarify the level of emetogenicity of the chemotherapeutic regimen with which the cancer population of the study is being treated. This scale rates the emetic potential of the chemotherapeutic agent (or combination of agents) given to a cancer patient as if the patient would not be receiving any antiemetic drugs; that is, it classifies the chemotherapeutic agents by the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as “1” on this scale have a low emetic potential, while agents rated as “5” are considered to be severely emetic (a >90% chance of emesis in patients).

Interventions

Included interventions are listed in Table 2.

Table 2. Included interventions

Drug	Trade name	Formulations
Aprepitant/fosaprepitant	Emend [®]	injectable, ^a oral
Dolasetron	Anzemet [®]	injectable, oral
Granisetron	Kytril [®]	injectable, oral
Ondansetron	Zofran [®] , generics	injectable, oral, orally disintegrating tablet
Palonosetron ^a	Aloxi ^{®a}	injectable, oral

^a Not available in Canada

Effectiveness outcomes

Treatment of established postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching patient
 - Early: Within or close to 6 hours after surgical procedure
 - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting, retching)
 - Early: Within or close to 6 hours after surgical procedure
 - Late: Within or close to 24 hours after surgical procedure

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of postoperative nausea and/or vomiting

- Success: Absence of vomiting and/or retching in the postoperative period
 - Acute: Within or close to 6 hours after surgical procedure
 - Late: Within or close to 24 hours after surgical procedure
- Success: Absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the postoperative period
 - Acute: Within or close to 6 hours after surgical procedure
 - Late: Within or close to 24 hours after surgical procedure
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of nausea and/or vomiting related to chemotherapy

- Success: Absence of vomiting and/or retching
 - Acute: During the first 24 hours of chemotherapy administration
 - Vomiting and/or retching induced by highly emetic chemotherapy
 - Vomiting and/or retching induced by moderately emetic chemotherapy
 - Late: After the first 24 hours of chemotherapy administration
 - Vomiting and/or retching induced by highly emetic chemotherapy
 - Vomiting and/or retching induced by moderately emetic chemotherapy
- Success: Absence of any emetic event (nausea, vomiting, retching)
 - Acute: During the first 24 hours of chemotherapy administration
 - Emetic event induced by highly emetic chemotherapy
 - Emetic event induced by moderately emetic chemotherapy
 - Late: After the first 24 hours of chemotherapy administration
 - Emetic event induced by highly emetic chemotherapy
 - Emetic event induced by moderately emetic chemotherapy
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention of radiation-induced nausea and/or vomiting

- Success: Absence of vomiting and/or retching
 - Acute: During the first 24 hours of onset of radiation therapy
 - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days
- Success: Absence of any emetic event (nausea, vomiting, retching)
 - Acute: During the first 24 hours of onset of radiation therapy
 - Delayed: After the first 24 hours of onset of radiation therapy or after consecutive radiation therapy doses given during several days

- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes, degree of nausea, or need for rescue medications, serious emetic sequelae, worst day nausea/vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Treatment of nausea and/or vomiting associated with pregnancy (including hyperemesis gravidarum)

- Success: Absence of vomiting and/or retching in a nauseated or vomiting and/or retching pregnant woman
- Success: Absence of any emetic event (nausea, vomiting, retching)
- Change in Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: Patients' satisfaction or quality of life, number of vomiting and/or retching episodes per period of time, need for rescue medications, serious emetic sequelae, number of emesis-free days, number of episodes and duration of hospitalization

Wherever possible, data on effective dose range, dose response, and duration of therapy (time to success) will be evaluated within the context of comparative effectiveness.

Harms

- Overall adverse events
- Specific adverse events (headache, constipation, dizziness, sedation, etc)
- Withdrawals due to adverse events
- Serious adverse events reported

Study designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews.
- For safety, controlled clinical trials and observational studies.

The benefit of the randomized controlled trial design is the ability to obtain a reliably unbiased estimate of treatment effects in a controlled setting. This is accomplished by using randomization to produce groups that are comparable based on both known and unknown prognostic factors.^{14,}¹⁵ However, randomized controlled trials can vary in quality, and their generalizability to a broader patient population often is limited. Observational studies are thought to have greater risk of introducing bias, although they typically reflect effects in a broader section of the overall patient population. While some observational studies and randomized controlled trials of the same treatments have similar findings, there are also multiple examples of situations where this has not been true; the question of what type of evidence is best has not been resolved.^{16, 17} While randomized controlled trials also provide good evidence on short-term adverse events, observational designs are useful in identifying rare, serious adverse events, which often require large numbers of patients exposed to a treatment over longer periods of time to be identified.

METHODS

Literature Search

To identify relevant citations for the original report, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2004), Cochrane Database of Systematic Reviews, MEDLINE (1966 to week 1 of February 2005), EMBASE (2nd Quarter 2005), and CancerLit (1974 to March 2005) using terms for included drugs, indications, and study designs (see Appendix D for complete search strategies). For update 1, we searched Medline (1996 to week 2 of 2008), Cochrane Central Register of Controlled Trials (2nd Quarter 2008), Cochrane Database of Systematic Reviews (1st Quarter 2008), and Database of Abstracts of Reviews of Effects (DARE) (2nd Quarter 2008). These searches were repeated in October 2008 in Medline and 3rd Quarter 2008 in Cochrane and DARE Databases to identify any additional publications published before the draft report was finalized. We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the Food and Drug Administration website, and dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote XI).

Study Selection

Using the criteria listed above, two reviewers independently assessed abstracts of citations identified from literature searches for inclusion, Full-text articles of potentially relevant abstracts were retrieved, and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design; setting; population characteristics (including sex, age, ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. In cases where only per protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. In trials with crossover, outcomes for the first intervention were recorded if available. This approach controlled for the potential for biased results caused by differential withdrawal before crossover and for the possibility of either a “carryover effect” (from the first treatment) in studies without a washout period or a “rebound effect” from withdrawal of the first intervention.

Data abstracted from observational studies included design; eligibility criteria; duration; interventions; concomitant medication; assessment techniques; age, gender, and ethnicity; number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up; number of patients analyzed; and results.

Validity Assessment

We assessed the internal validity (quality) of trials with the predefined criteria listed in Appendix E. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.^{18, 19} We rated the

internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist.

External validity of trials was based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention would be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Overall quality ratings for an individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive 2 different ratings: 1 for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Included systematic reviews were also rated for quality based on predefined criteria (see Appendix E) based on clear statement of the question(s) and inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Trials that evaluated 1 newer antiemetic against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. In theory, trials that compare newer antiemetic to other drug classes or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and must be interpreted with caution for a number of reasons, mainly issues related to heterogeneity between trial populations, interventions, and assessment of outcomes. Data from indirect comparisons are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist.

Quantitative analyses were conducted using StatsDirect (Version 2.7.0, 7/7/2008) for meta-analyses of outcomes reported by a sufficient number of studies and for combining results of studies that were homogeneous enough that combining their results could be justified. When quantitative analyses were not possible, the data were summarized qualitatively.

Peer Review and Public Comment

Original Drug Effectiveness Review Project reports are independently reviewed and commented upon by 3 to 5 peer reviewers. Peer reviewers are identified through a number of sources, including but not limited to professional society membership, acknowledged expertise in a particular field, prominent authorship in the published literature, or recommendation by Drug

Effectiveness Review Project participating organizations. A list of individuals who have acted as peer reviewers of Drug Effectiveness Review Project reports is available on the Drug Effectiveness Review Project website.

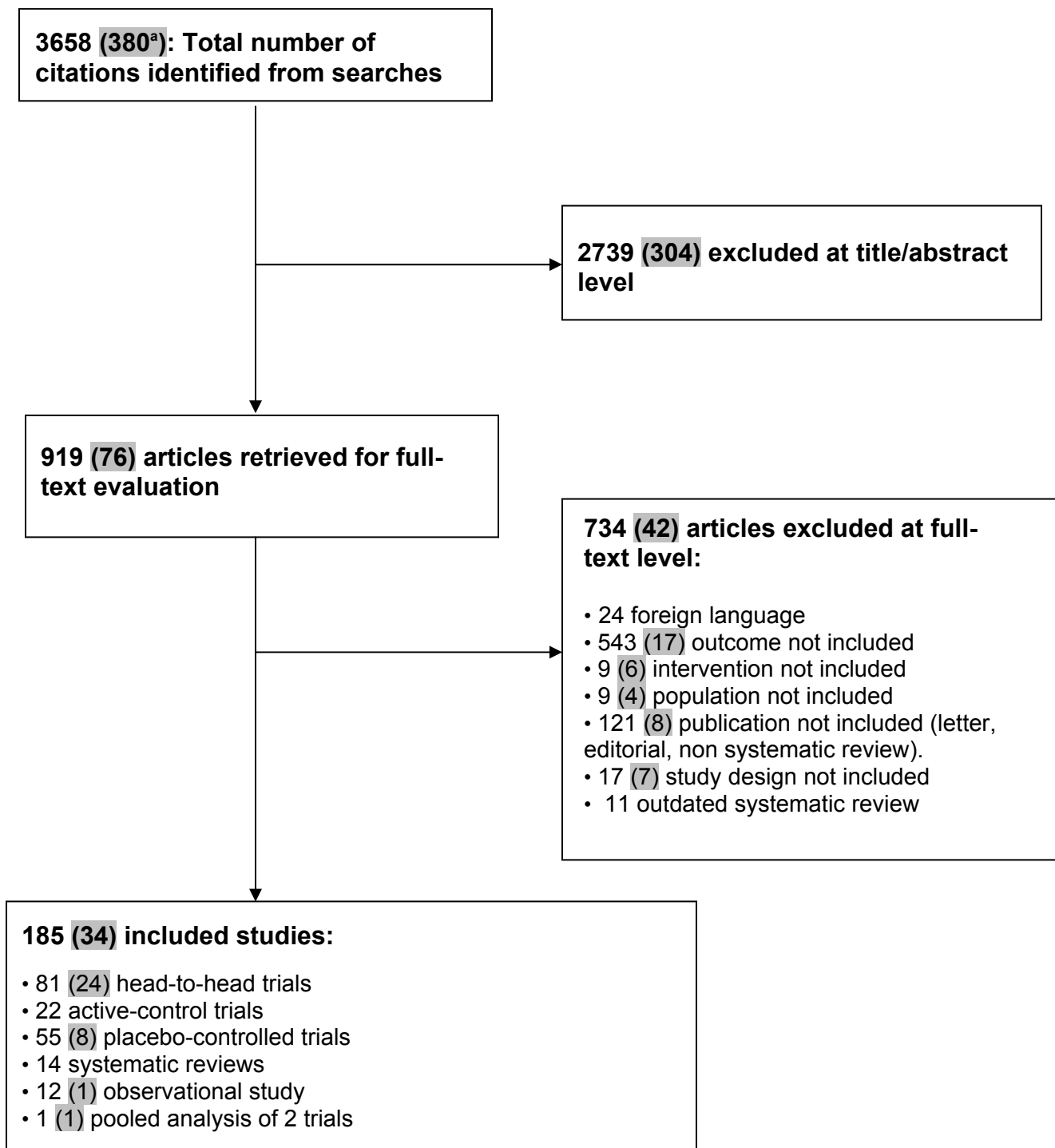
Peer reviewers have a maximum of 3 weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the Drug Effectiveness Review Project team to address all comments adequately. The original antiemetics report was reviewed by 4 content and methodological experts prior to finalization. The Drug Effectiveness Review Project process allows for a 2-week public comment period prior to finalization of the report. Draft reports are posted on the Drug Effectiveness Review Project website and interested individuals or organizations can review the complete draft report and submit comments. Comments from peer reviewers and the public are entered into a spreadsheet and the disposition of each comment is tracked individually.

RESULTS

Overview

For the Original Report, searches identified a total of 3278 citations: 296 came from Medline, 41 from premedline, 2505 from Cochrane, 304 from Embase, 112 from CancerLit, 2 from peer review, 2 from public comment, and 16 from hand searching of reference lists. Dossiers were received from the manufacturers of aprepitant, dolasetron and ondansetron HCl, Zofran. 380 new citations were identified for Update 1: 40 from the Cochrane Central Register of Controlled Trials, 17 from the Cochrane Database of Systematic Reviews, 308 from Medline, 5 from DARE, 9 from dossiers submitted by manufacturers of dolasetron and palonosetron, and 1 from hand searching. Dossiers were received for Update 1 from the manufacturers of aprepitant, dolasetron and palonosetron. Figure 1 shows results of our study selection process. Appendix F lists the excluded studies.

Figure 1. Results of literature search



^a Numbers in parentheses are results of the literature search new to Update 1.

Summary of Findings

Ondansetron, dolasetron, and granisetron: Intravenous and oral formulations

Direct comparisons

- Efficacy
 - Prevention of chemotherapy-induced nausea and vomiting
 - The numbers of patients with complete response (no emesis and no use of rescue medication) in the acute and delayed phase following moderately to severely emetic chemotherapy were similar with ondansetron, dolasetron, and granisetron, with no consistent statistically significant differences.
 - Rates of complete response in the first 24 hours ranged from 46% to 79% with ondansetron, 48% to 53% with granisetron, and 40% to 76% with dolasetron; during the delayed phase (days 2 to 7) the rates of complete response were 27% to 36% with ondansetron, 30% with granisetron, and 39% with dolasetron. The evidence does not indicate differences between oral and intravenous or between various oral formulations.
 - Comparisons of other measures of effect did not identify statistically significant differences.
 - Prevention of postoperative nausea and vomiting in adults
 - No consistent statistically significant differences in antiemetic efficacy outcomes were seen in trials comparing dolasetron (7), granisetron (10), or the orally disintegrating tablet formulation of ondansetron (2) with conventional ondansetron or in trials comparing dolasetron with granisetron (2).
 - Complete response rates generally ranged from 39% to 76% with dolasetron and 46% to 75% with granisetron compared with 48% to 79% with ondansetron.
 - Prevention of postoperative nausea and vomiting in children
 - No consistent statistically significant differences were seen between dolasetron and ondansetron (3 trials) in antiemetic efficacy outcomes.
 - Complete response rates ranged from 68% to 86% with dolasetron and from 52% to 92% with ondansetron.
 - *Treatment of established nausea and vomiting in adults*
 - Dolasetron compared with ondansetron (1 trial): Dolasetron was superior in reducing the need for rescue therapy (40% compared with 70%, $P=0.004$) but showed no significant difference in the number of postoperative nausea and vomiting-related hospital admissions (2% compared with 2%).
 - Granisetron compared with ondansetron (1 trial): No statistically significant differences were seen in complete response rates of 60% for granisetron 0.1 mg, 68% for granisetron 1 mg, and 47% for ondansetron.
- Tolerability and safety
 - Chemotherapy
 - Ondansetron was associated with higher rates of dizziness and abnormal vision than dolasetron and granisetron in 3 trials.
 - Dolasetron was associated with significantly higher rates of constipation and diarrhea than ondansetron in 1 trial.

dexamethasone on days 1 to 4 than regimens containing a 5-HT3 antagonist on day 1 and dexamethasone on days 1 to 4 or a regimen extending 5HT3 antagonist treatment, along with dexamethasone, to days 1 to 4

- Meta-analysis of 3 studies of patients receiving highly emetic chemotherapy indicates that addition of aprepitant to a standard antiemetic treatment results in a relative risk for complete response over the overall period (days 1 to 5) of 1.45 (95% CI 1.32 to 1.60), corresponding to a number needed to treat of 5.
- o The improvement in complete response over standard antiemetic therapy persisted with aprepitant over 4 to 6 cycles of moderately and highly emetic chemotherapy, although the number of patients with complete response decreased with each course in both groups.
- o We found no trials of the fosprepitant formulation and dose (115 mg) available in the US. Two studies of a 100 mg dose were found; their results were mixed.
- Postoperative nausea and vomiting
 - o When aprepitant was compared with ondansetron (2 trials in adults; N=1727), aprepitant was noninferior for complete response 0-24 hours after surgery (45% to 65% for aprepitant 40 mg or 43% to 63% for aprepitant 120 mg compared with 42% to 55% for ondansetron) and superior for no vomiting 0-24 hours after surgery (84% to 92% for aprepitant 40 mg or 86% to 97% for aprepitant 120 mg compared with 71% to 75% for ondansetron).
- Tolerability and safety
 - Chemotherapy and postoperative nausea and vomiting in adults
 - o No difference compared with ondansetron in the rate of overall adverse events, withdrawals due to adverse events, or any particular adverse event
- Gaps in direct comparative evidence
 - Quality of life, patient satisfaction, and hospital stay outcomes were rarely reported in trials of adults undergoing chemotherapy or recovering from surgical procedures.
 - No studies in children
 - No studies of effects on nausea and vomiting associated with radiation therapy or pregnancy or for *treatment* of established postoperative nausea and vomiting.

Palonosetron

Direct comparisons

- Efficacy
 - Chemotherapy-induced nausea and vomiting
 - o Palonosetron's rates of acute and delayed complete responses were noninferior to those of dolasetron (1 trial) and ondansetron (2 trials) in adults undergoing moderately and highly emetic chemotherapy.
 - o Palonosetron 0.25 mg may be superior to dolasetron and ondansetron in patients receiving moderately emetic chemotherapy for mostly breast cancer, with pooled analysis of 2 studies indicating the following:

- Relative risk of complete response = 1.18 (95% CI 1.1 to 1.3); number needed to treat = 9 over the first 24 hours (acute)
- Relative risk of complete response = 1.36 (95% CI 1.20 to 1.54); number needed to treat = 6 over 2-3 days (delayed)
- Results for the 0.75 mg dose were similar, although the differences were smaller.
- Quality-of-life assessments did not differentiate the 3 drugs during the first 24 hours, but palonosetron resulted in higher scores than ondansetron and dolasetron during the delayed phase (days 2 to 3) in patients receiving moderately emetic chemotherapy; differences were not seen at any time in patients receiving highly emetic chemotherapy.
 - o Intravenous palonosetron 0.25 mg may be superior to intravenous ondansetron 8 mg/m² for improving early complete response rates (days 1 to 3) in children undergoing highly emetic chemotherapy.
- Tolerability and safety
 - The most commonly reported adverse events were headache (4% to 15%), constipation (2% to 9%), and diarrhea (<2%); no differences were found between palonosetron and either ondansetron or dolasetron.

Detailed Assessment

Key Question 1.

What is the comparative effectiveness of newer antiemetics in treating or preventing nausea and/or vomiting?

Prevention of chemotherapy-induced nausea and vomiting

Adults

Direct comparisons

Of 46 head-to-head trials (Table 3) of newer antiemetics conducted in adults undergoing chemotherapy regimens, the majority directly compared granisetron with ondansetron. The primary efficacy endpoint in most of the trials was the proportion of patients who achieved a complete response. Definitions of complete response varied across trials but were generally composite outcomes involving any 2 or more of the following improvement indicators: no emesis, no nausea, and no use of rescue medication.

A number of head-to-head trials were rated poor-quality due to combinations of probable biases, including lack of blinding; inadequate randomization and allocation concealment, often reflected in uneven distribution of baseline prognostic factors; and analyses that excluded unacceptably high proportions of patient populations (>15%).²⁰⁻³²

Sources of heterogeneity across trials included the following: (1) chemotherapy regimen—number of courses and level of emetogenicity; (2) antiemetic regimen—dose, route, and schedule; (3) concomitant use of corticosteroids; (4) patients—distribution of gender, age, and primary malignancy; and (5) outcomes reported

Table 3. Quantity of head-to-head trials in adults undergoing chemotherapy^a

	Aprepitant/ fosaprepitant	Dolasetron	Granisetron	Ondansetron	Palonosetron
Aprepitant/ fosaprepitant	*****				
Dolasetron		*****			
Granisetron		2 (1)	1 ^b		
Ondansetron	3 (3)	4	32 (1)	1 (1) ^c	
Palonosetron		1		2 (1)	*****

^a Numbers refer to overall quantity of studies found and discussed in report. The numbers in parentheses refer to new studies added for Update 1.

^b Oral compared with intravenous.

^c Standard oral tablet compared with oral dissolving tablet.

Granisetron compared with ondansetron

Among fair- and good-quality studies, there were very few differences between granisetron and ondansetron, regardless of chemotherapy regimen, antiemetic regimen, concomitant corticosteroid therapy, patient population, and method of reporting outcome.³³⁻⁵⁴ Dose levels ranged widely for both granisetron (oral 1 and 2 mg; intravenous 10 µg/kg and 3 mg) and ondansetron (intravenous 2-32 mg). Inequity of dose level between treatment groups also did not seem to have an impact on comparative efficacy. There were no consistent significant differences between granisetron and ondansetron on the most important outcomes of acute or delayed complete response.^{35, 36, 38, 40, 41, 43, 44, 47, 51, 53} We rated 12 studies poor-quality and did not include them in this analysis.²¹⁻³¹

Complete response – acute. Approximately half of the trials reported complete response at 24 hours.^{35, 36, 38, 40, 41, 43, 44, 47, 51, 53} Table 4 quantifies 24-hour complete response rates, stratified by definition from most to least strict. Complete 24-hour response rates vary widely and magnitude of effect is not clearly related to any single or a combination of demographic, prognostic, or outcome factors.

Complete response – delayed. One quarter of trials reported the rate of delayed complete response, and there were no significant differences between granisetron and ondansetron (Table 4).^{35, 36, 41, 44, 51} In general, rate of complete response declined after the first 24 hours. There was 1 exception: In 1 trial, complete response rates (no emesis or nausea) for granisetron and ondansetron were numerically higher by day 6 (74.5% compared with 71.4%, not significant) than they were at 24 hours (67.3% and 66.5%, not significant).³⁵ A possible explanation is that this was the only study in which oral metoclopramide 20 mg every 6 hours plus intramuscular dexamethasone 8 mg twice daily were added on days 2-6. This is in contrast to the other studies that reported delayed complete response rate, in which antiemetics were either discontinued after day 1 or continued without a change in regimen.

Table 4. Complete response rates for antiemetics in adults undergoing chemotherapy

Trial	Hesketh score	Percent female	Concomitant prophylaxis	Treatment	Percent with complete response ^a	
					Acute (≤ 24 hrs)	Delayed (> 24 hrs)
<i>No emesis, nausea, or use of rescue medication</i>						
Gralla 1998	5	34%	DEX or MPR optional	G 2 mg po qd	55%	NR
N=1054	Respiratory+ Intrathoracic	61.7 years		O 32 mg IV qd	58%	
Perez 1998	3 or 4	80%	Both + DEX/MPR/PR	G 2 mg po qd	59%	47%
N=1085	Breast	55.6 years		O 32 mg IV qd	58%	44%
Navari 1995	5	36%		G 10 or 40 µg/kg IV qd	38%, 41%	NR
N=987	Lung	62.3 years		O 0.15 mg/kg IV tid	39%	
<i>No emesis or nausea</i>						
Del Favero 1995	5	32%	Both + DEX	G 3 mg IV qd	67%	75%
N=966	Lung	61 years		O 8 mg IV qd	67%	71%
<i>No emesis and none-mild nausea</i>						
Walsh 2004	3-5	16%	Concurrent drugs NR	G 10 µg/kg IV qd	83%	56%
N=96	Non-Hodgkin/ Hodgkin lymphoma	52 years		O 0.15 mg/kg IV q8 hrs	90%	46%
Noble 1994	3-4	23%	Concurrent drugs NR	G 3 mg IV qd	92%	39%
N=309	Head/neck	51.8 years		O 8 mg IV tid	89%	37%
de Wit 2001 ^b	5	90%	Both + DEX	G 3 mg IV qd	47%	NR
N=40	Breast	46 years		O 8 mg IV qd	5%	NR
<i>No emesis or rescue medication</i>						
Park 1997	5	47%		G 3 mg IV qd	53%	30%
N=97	Stomach	51 years		O 8 mg IV, q8 hrs, then 8 mg po q12 hrs	46%	27%

Spector 1998	5	44%		G 10 µg/kg IV qd	51%	NR
N=371	Lung	64 years		O 24 mg po (tablet) qd	58%	
No nausea or rescue medication						
Fox- Geiman 2001	4	72%	All + DEX	G 1 mg po q12 hrs	92%, 95%	47%, 48%
N=102	Bone Marrow Transplant	47 years		O 8 mg po q8 hrs O 32 mg IV qd	92%	49%

^a No statistically significant difference between treatment arms unless indicated.

^b Following O failure, patients randomized to G or continued treatment with O; $P=0.005$

Abbreviations: DEX, dexamethasone; G, granisetron; IV, intravenously; MPR, methylprednisolone; NR, not reported; NS, not significant; O, ondansetron; po, orally; PR, prednisolone; q, every; qd, every day; tid, 3 times a day.

Other nausea and vomiting outcomes. There was generally no difference between granisetron and ondansetron in complete protection from acute or delayed nausea or vomiting.^{33-35, 37, 42, 45, 46, 48-50, 52} The exceptions were as follows: More adults with breast cancer (N=54; 98% female; mean age 44) undergoing Hesketh level 3 chemotherapy experienced complete control of emesis at 24 hours after a single dose of intravenous granisetron 3 mg (73.7% compared with 38.8%, $P=0.035$) and during days 2 to 5 (73.7% compared with 33.3%, $P=0.014$) than following a single dose of intravenous ondansetron 8 mg.⁴⁹ Nausea outcomes were not reported.

Fewer participants taking intravenous granisetron 3 mg once per day experienced “nausea+emesis control failure” (47% compared with 80%, $P=0.03$) and “emesis control failure” (27% compared with 47%, $P=0.04$) than those taking intravenous ondansetron 8 mg twice daily after 10 days in 1 study of 45 participants with lymphoma (33% female; mean age, 38 years).⁴⁶ Use of blinding in this study was unclear. In a trial of women with breast cancer (N=48; mean age, 50.3 years), more patients on ondansetron 8 mg (intravenous on day 1, then oral) than intravenous granisetron 3 mg experienced complete protection from nausea (55% compared with 40%, $P<0.009$) on the worst day of days 1-5.⁴⁸

Participant satisfaction and preference outcomes. There was no difference between granisetron and ondansetron in patient satisfaction in 2 trials^{47, 48} and there were mixed results for patient preference in an additional 2 trials.^{33, 41} More patients preferred intravenous granisetron 3 mg over intravenous ondansetron 24 mg in 1 crossover trial of mostly males (77%) with head/neck cancer (combined treatment sequences, 34% compared with 25.6%; $P=0.048$). When treatment sequences were considered separately, however, patient preference correlated with which treatment was received first.⁴¹ In another trial more patients with breast cancer (68% female) preferred intravenous ondansetron 32 mg over intravenous granisetron 3 mg (45% compared with 30%, $P<0.01$).³³

Dolasetron compared with ondansetron

Results from 2 good-quality trials showed no difference between dolasetron and ondansetron in 24-hour complete response rate (no emesis or rescue medication use) when the recommended intravenous⁵⁵ or oral⁵⁶ doses were used.⁵⁴ In contrast, intravenous ondansetron 32 mg (recommended dosage) was superior to intravenous dolasetron 2.4 mg/kg (higher than

recommended dosage) in providing 24-hour complete protection from emesis plus rescue medication use in a fair-quality trial.⁵⁷ This difference was not observed after 7 days (complete response rates 36% and 39%, respectively) and no other differences in effects on nausea (acute and delayed), satisfaction, or quality-of-life outcomes were noted in any of these trials (Table 5 and Evidence Tables 1 and 2).

Table 5. Outcomes of head-to-head trials of dolasetron compared with ondansetron in adults

Trial Characteristics		Treatment		Other anti-emetic	Acute response (≤ 24 hrs)	
Sample size Quality	1° malignancy Percent female Emetogenicity ^a	Dolasetron	Ondansetron		Complete response	Nausea (VAS)
Fauser 1996 N=398 Good	Breast 61.2% Levels 3, 4	100 or 200 mg po qd	24-32 mg 8 mg po tid or qid	None	60% vs 76% vs 72%, NS	Change from baseline: 3.5 vs 0 vs 3, NS
Hesketh 1996 N=609 Good	Lung 38% Level 5	1.8 or 2.4 mg/kg IV qd	32 mg IV qd	None	44% vs 40% vs 43%, NS	Median: 10 vs 22 vs 16, NS
Lofters 1997 N=696 Fair	Breast 71% Level 3	<i>Acute:</i> 2.4 mg/kg IV qd <i>Delayed:</i> 200 mg po qd	<i>Acute:</i> 32 mg IV qd <i>Delayed:</i> 8 mg po bid	Dex	57% vs 67%; P=0.013	Mean VAS: 13.1 vs 10.1; P=0.051

Abbreviations: bid, twice a day; IV, intravenously; NR, not reported; NS, not significant; po, orally; qd, every day; qid, 4 times a day; tid, 3 times a day; VAS, visual analog score.

^a Hesketh score.

Dolasetron compared with granisetron

There was no significant difference in efficacy outcomes between dolasetron and granisetron in 1 good-quality trial (N=474) of mostly men receiving high-dose cisplatin (≥ 80 mg/m²) for head/neck malignancies (Evidence Tables 1 and 2).^{54, 58} Intravenous dolasetron 1.8 or 2.4 mg/kg and intravenous granisetron 3 mg, both as a single dose, were comparable with regard to percentages of patients with 24-hour complete response (54% compared with 47% compared with 48%, not significant) and no nausea (visual analog score ≤ 5 mm, 41% compared with 41% compared with 41%, not significant).⁵⁸ There was also no significant differences between groups in the percentage of patients that investigators rated as having good or excellent global antiemetic efficacy (61% compared with 62% compared with 62%, not significant). Patient satisfaction was described as measured using a visual analog score, but outcomes were not reported.

Aprepitant and fosaprepitant

Seven trials indicate that a regimen of the standard therapy plus aprepitant given prior to highly or moderately emetic chemotherapy is superior to standard therapy (generally a 5HT3 antagonist on day 1 and dexamethasone on day 1 and days 2-3 or 4) or to an extended regimen of a 5-HT3 antagonist (days 2-4). The best evidence about the *comparative* efficacy of aprepitant comes from a good-quality study comparing a regimen that includes aprepitant given over 3 days (125 mg on day 1, 80 mg on days 2 and 3), ondansetron given once (32 mg intravenous on day 1), and dexamethasone given over 4 days (12 mg on day 1, 8 mg daily on days 2 to 4) with a regimen of ondansetron (32 mg intravenous day 1, 8 mg orally twice a day on days 2 to 4) plus dexamethasone (dexamethasone 20 mg on day 1, 8 mg twice a day on days 2 to 4) in patients

undergoing high-dose cisplatin therapy (≥ 70 mg/m²). While the control regimen is not currently standard in the US, previous studies (below) assessed aprepitant as add-on therapy to regimens that did not include treatment with a 5HT₃ antagonist after day 1. The aprepitant regimen was superior, with 72% compared with 61% having a complete response (no vomiting or use of rescue medications) over the entire 5-day period ($P=0.003$).⁵⁹ Complete response was superior in the aprepitant regimen during the acute phase (88% compared with 79%, $P=0.005$) and the delayed phase (74% and 63%, $P=0.004$). The trial population included more men than women (63% male), almost half had a primary cancer of the respiratory system (45%), and approximately one-third had a history indicating higher risk for chemotherapy-induced nausea and vomiting. Time to first episode of emesis was significantly longer with the aprepitant regimen, $P<0.001$ based on log-rank test analysis of Kaplan-Meier curves. The proportion of patients with no vomiting, no significant nausea, or no use of rescue therapy was similar between groups.

Before this study, in 5 fair-quality placebo-controlled trials aprepitant was studied as an add-on to “standard therapy” (single-dose granisetron or ondansetron plus dexamethasone for typically 4 days) for preventing nausea and vomiting induced by highly⁶⁰⁻⁶³ or moderately⁶⁴ emetic chemotherapy (Evidence Tables 3 and 4). The doses of aprepitant varied, but all included a larger initial dose (125 mg to 400 mg intravenously) followed by a lower dose (80 mg to 250 mg intravenously) for 3 to 5 days after chemotherapy. None of these studies used 5-HT₃ antagonists during the delayed nausea and vomiting phase. The cancers most commonly represented in trials were lung and breast cancer, and most patients were receiving high-dose cisplatin. In the studies using the now standard regimen of aprepitant 125 mg prior to chemotherapy on day 1 followed by 80 mg on days 2-3, significantly more patients receiving the add-on aprepitant had a complete response (no emesis and no use of rescue medication) in the acute, delayed, and overall phases than patients receiving standard therapy.^{60-62, 64} In a meta-analysis of the 3 trials where patients were receiving highly emetic chemotherapy,⁶⁰⁻⁶² we found that aprepitant had a relative risk of complete response in the overall period (days 1-5) of 1.45 (95% CI 1.32 to 1.60; pooled analysis using DerSimonian-Laird random-effects model. Heterogeneity assessment $I^2 = 0\%$, chi square for Q statistic = 0.5). This corresponds to a number needed to treat of 5.

In a pilot study combining palonosetron (day 1) and dexamethasone (days 1 to 4) with either a single dose of aprepitant 125 mg or aprepitant for 3 days (125 mg on day 1, then 80 mg on days 2 to 3), no difference was found between the regimens; however, this was a small study (N=75) in which a third arm that combined placebo and palonosetron was discontinued due to lack of efficacy, and no statistical power calculations were undertaken.⁶⁵

Efficacy of aprepitant over multiple cycles of moderately⁶⁶ and highly⁶⁷ emetic chemotherapy was evaluated in 2 trials. In patients receiving moderately emetic chemotherapy, the extent to which aprepitant improved complete response over the standard regimen increased over 4 cycles of chemotherapy, although the actual percentages with complete response decreased with each course (course 4 complete response rates 34.5% aprepitant, 23.9% control; $P=0.017$ by log-rank test).⁶⁶ In patients receiving highly emetic chemotherapy, there was little change in response rate between cycle 1 (64%) and cycle 6 (59%) for aprepitant. But, for standard therapy the response rate declined from 49% in cycle 1 to 34% by cycle 6.⁶⁷ Additionally, Functional Living Index-Emesis scores indicated that chemotherapy-induced nausea and vomiting impacted daily life to a lesser degree over 6 days in patients taking aprepitant than in those receiving standard therapy.^{60, 62, 64}

Two fair-quality studies evaluated regimens including fosaprepitant in a formulation and dose unavailable in the US.^{68, 69} These studies used intravenous fosaprepitant 100 mg, whereas in the US the intravenous dose is 115 mg, which has been shown to be bioequivalent to 125 mg of oral aprepitant.⁷⁰ We found no comparative trials of fosaprepitant 115 mg. Because it is unclear how the dosage (both dose and formulation are different) used in the 2 trials compares to the dose available in the US, we provide only a cursory summary of these trials. Both trials studied patients receiving high-dose cisplatin therapy. The first study randomized patients to 1 of 3 regimens: fosaprepitant (100 mg intravenously on day 1) plus dexamethasone (20 mg intravenously on day 1) followed by aprepitant (300 mg orally on days 2 to 5); fosaprepitant (100 mg intravenously on day 1) plus dexamethasone (20 mg intravenously on day 1); or ondansetron (32 mg intravenously on day 1) plus dexamethasone (20 mg intravenously on day 1).⁶⁹ The ondansetron regimen resulted in the highest rate of complete response (no emesis and no rescue medication) during the acute phase (83% compared with 44% with fosaprepitant and aprepitant and 36% with fosaprepitant alone; $P < 0.001$ for ondansetron compared with combined fosaprepitant groups). The regimen with aprepitant through day 5 resulted in a significantly higher rate of complete response during the delayed period (days 2 to 5) than the ondansetron regimen ($P < 0.05$). The second trial randomized patients ($N = 53$) to a single dose of fosaprepitant 100 mg or ondansetron 32 mg, both intravenous.⁶⁸ Complete response (no emesis and no rescue medication use) during the first 24 hours was similar for the antiemetics (37% with fosaprepitant and 48% with ondansetron). During the delayed phase (days 2 to 7) fosaprepitant resulted in statistically significantly more patients with complete response (48%) than ondansetron (17%; $P < 0.04$). Pooling data from the acute phase from these trials, it appears that ondansetron 32 mg intravenously on day 1 is superior to fosaprepitant 100 mg intravenously on day 1. Our pooled analysis of the proportion of patients with complete acute response in 2 trials^{68, 71} showed a relative risk of 1.79 (95% CI 1.21 to 2.65; pooled analysis using DerSimonian-Laird random-effects model. Test for heterogeneity, I^2 not calculable; chi square = 0.20).

Palonosetron

In single doses starting immediately before moderately to severely emetic chemotherapy, intravenous palonosetron 0.25 mg was noninferior to intravenous dolasetron 100 mg and intravenous ondansetron 32 mg in acute (within 24 hours) complete response rate across 3 fair-quality trials.⁷²⁻⁷⁴ The forest plot of point estimates and confidence intervals (Figure 2) indicates that in 1 of the 3 trials palonosetron 0.25 mg was also superior to ondansetron 32 mg.⁷⁴ An analysis of trial data showed that the largest trial,⁷² where highly emetic chemotherapy was used and fewer women were enrolled, showed very little difference between the treatments. Pooling the results of the 2 studies of patients receiving moderately emetic chemotherapy for mostly breast cancer indicated a small benefit of palonosetron over ondansetron or dolasetron during the first 24 hours (acute phase relative risk 1.18, 95% CI 1.1 to 1.3; number needed to treat = 9) and over days 2-3 (delayed phase relative risk 1.36, 95% CI 1.20 to 1.54; number needed to treat = 6). This analysis was done using a random-effects model (DerSimonian and Laird) and heterogeneity was nonexistent ($I^2 = 0\%$).

All 3 studies also included a dose of palonosetron 0.75 mg, which was also found to be noninferior to ondansetron and dolasetron in the primary outcome measure of complete response at 24 hours. However, this dose resulted in smaller differences between treatments than the smaller dose, palonosetron 0.25 mg. In the study where the 0.25 mg dose was found to be statistically superior to ondansetron 32 mg, the 0.75 mg dose of palonosetron was not superior

and pooled analysis did not indicate a statistically significant difference (relative risk 1.08, 95% CI 0.99 to 1.18 using fixed or random effects models; $I^2 = 0\%$).

Two of the trials involved mostly women with breast cancer undergoing moderately emetic (Hesketh levels 3 to 4) chemotherapy.^{73, 74} The third enrolled a smaller portion of women, and these were undergoing highly emetic chemotherapy (Hesketh level 5).⁷² Across the studies, 60 to 70 percent of patients had never received chemotherapy previously (Table 6 and Evidence Tables 1 and 2). In all 3 trials, randomization was stratified based on factors known to affect response rate (gender, prior exposure to chemotherapy, and pretreatment with a corticosteroid), and noninferiority was defined as the difference between the lower bounds of the 95% confidence intervals being $\leq 15\%$. The method of or criteria for selection of this delta was not described. A difference of 15 percentage points in complete response rate being considered clinically the same seems generous.

Palonosetron 0.25 mg and 0.75 mg were found to be noninferior to ondansetron 32 mg and to dolasetron 100 mg in achieving complete response during the delayed period (24 to 130 hours) and the overall period (0 to 120 hours). Statistical superiority in complete response for the delayed and overall periods was found with 0.25 mg palonosetron over ondansetron 32 mg in 1 study,⁷⁴ while in another similar study both doses of palonosetron were found statistically significantly superior to dolasetron 100 mg on these outcomes.⁷³ In the study with fewer women and higher Hesketh score, however, statistical superiority of palonosetron compared with ondansetron was not found.⁷² Log-rank tests of Kaplan-Meier plots in 2 studies^{72, 73} found that time to treatment failure was significantly longer with palonosetron at both doses. In a third study the time to treatment failure was longer with palonosetron 0.25 mg than with ondansetron 32 mg and unreported for the palonosetron 0.75 mg dose.⁷⁴

Quality-of-life assessments (using the Functional Living Index-Emesis tool; score range 1 to 1800) showed no statistically significant difference among the drugs within 24 hours. However, during days 2 to 4 in the 2 studies with more women and lower emetic chemotherapy regimens, palonosetron resulted in higher scores (1672 compared with 1599, $P=0.0393$ ⁷³ and 1740 compared with 1680, $P=0.014$ ⁷⁴). The study with fewer women and severely emetic chemotherapy found no such difference.⁷²

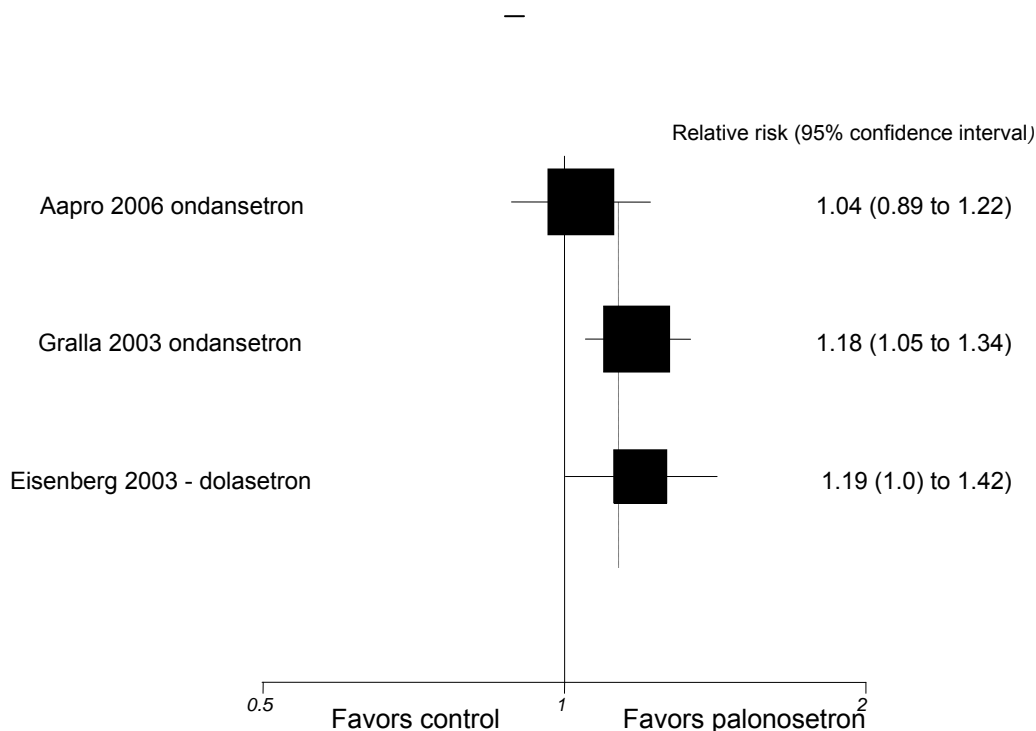
Table 6. Complete response rates with single-dose intravenous palonosetron 0.25 mg and 0.75 mg in adults

Trial (sample size)	Comparator	Acute (24 hour) ^a			Delayed (days 2-5) ^a		
		P 0.25 mg	P 0.75 mg	D or O	P 0.25 mg	P 0.75 mg	D or O
Eisenberg 2003 ⁷³ (N=569)	D 100 mg	63%	57%	53%	54%, $P=0.004$	57%, $P<0.001$	39%
Gralla 2003 ⁷⁴ (N=563)	O 32 mg	81%, $P=0.0085$	73%	69%	74%, $P<0.001$	65%,	55%
Aapro 2006 ⁷² (N=667)	O 32 mg	59%	65%	57%	45%	48%	39%

^a No statistical significant differences unless otherwise noted.

Abbreviations: D, dolasetron; O, ondansetron; P, palonosetron.

Figure 2. Relative risk of complete response at 24 hours: Palonosetron compared with ondansetron or dolasetron



Granisetron: intravenous compared with oral

There was no significant difference in efficacy outcomes between intravenous and oral granisetron in 1 fair-quality trial (N=60) of participants (65% female) who were to undergo emetic chemotherapy (Hesketh levels 3 or 5) as a conditioning regimen for peripheral blood progenitor cell transplantation or bone marrow transplantation.⁷⁵ Similar proportions of patients were completely free from emesis at 24 hours when taking either intravenous or oral doses of granisetron 1 mg every 12 hours (6.9% compared with 9.1%, not significant). Concomitant dexamethasone was allowed for the last 17 patients due to a protocol amendment designed to enhance the efficacy of granisetron.

Ondansetron orally disintegrating tablets

A single, fair-quality trial of patients receiving high-dose epirubicin for breast cancer compared the antiemetic effect of ondansetron standard tablets with ondansetron orally disintegrating tablets. Both formulations controlled major emesis at a similar rate (< 2 episodes over the first 3 days after chemotherapy, the primary outcome measure).⁷⁶ However, the group randomized to standard tablets had statistically significantly higher rates of complete emesis control (0 episodes and no rescue medications over 3 days, 72% compared with 52%, respectively, $P=0.020$). This study was small (N=134), however, and may suffer from recall bias. The main method of recording the number of episodes of emesis or nausea was patient interview after 3 days. Patients were also given diaries to record these episodes, but only 44% completed the diaries. Using only data from completed diaries, the proportion of patients who had complete response was similar

between groups, and the difference was no longer statistically significant (65% with standard tablets and 54.5% with oral dissolving tablets; $P=0.44$).

Placebo-controlled and active-control trials

Head-to-head trials lacked good evidence for quality-of-life and functional capacity outcomes. Numerous placebo-controlled and active-control trials were reviewed to address these gaps, but none were found that reported functional capacity outcomes in patients undergoing chemotherapy.

Quality of life

Five fair-quality active-control trials of ondansetron reported the effects of antiemetic treatment on quality of life in women undergoing moderately to severely emetic chemotherapy (Table 7 and Evidence Tables 5 and 6).⁷⁷⁻⁸¹ However, these trials do not provide any information regarding the indirect comparative efficacy of 5-HT₃ antagonists. Ondansetron was found to be associated with higher quality of life than alizapride (not available in the United States) but not prochlorperazine, and the quality of life associated with ondansetron compared with metoclopramide is less clear.^{77, 78, 80}

Table 7. Quality-of-life outcomes in active-control trials of ondansetron

Trial	Ondansetron dose	Comparator	Hesketh Cancer type	QOL Scale	Results
Bhatia 2004 (N=80)	8 mg IV	Metoclopramide 20 mg IV	4-5 Head/neck	Rotterdam	No differences
Lachaine 1999 (N=52)	21 mg (route unclear)	Metoclopramide 306 mg	4 Breast	EORTC QLQ-C30	No differences
Soukop 1992 (N=187)	8 mg IV	Metoclopramide 60 mg IV	3 or higher Breast	Rotterdam	O superior on psychological subscale across 6 courses
Crucitt 1996 (N=57)	16 mg po (8 mg bid)	Prochlorperazine 20 mg po (10 mg bid)	4 Breast	FLIE	No differences
Clavel 1995 (N=254)	All days: 8 mg po (tablet) bid	Day 1: Alizapride 150 mg IV (50 mg po bid after day 1)	4 Breast	FLIE	O superior

Abbreviations: bid, twice daily; EORTC, European Organization for Research and Treatment of Cancer; FLIE, Functional Living Index-Emesis; IV, intravenous; O, ondansetron; po, by mouth, orally; QLQ-C30, Quality of Life Questionnaire (EORTC); QOL, quality of life.

Children

Direct comparisons

Six head-to-head trials included children (Evidence Tables 1 and 2).^{52, 82-86} One was poor quality due to a combination of flaws that indicate probable bias, including lack of blinding, unclear randomization and allocation concealment methods, uncertainty regarding between-groups balance of baseline characteristics, and analyses that excluded a proportion of the original patient

population.⁸³ A small study comparing intravenous ondansetron with oral disintegrating tablets in children receiving any chemotherapeutic regimen was poor quality for multiple reasons.⁸⁵ Randomization resulted in uneven groups, with 56 assigned to intravenous formulation and 39 assigned to oral disintegrating tablet. A smaller proportion of children received chemotherapy with a Hesketh score of 3 to 4 in the intravenous group than the oral disintegrating tablet group (58% compared with 76%).

Granisetron compared with ondansetron

Two trials comparing granisetron and ondansetron in children found no significant differences in efficacy outcomes.^{52, 82} In Forni et. al. (2000),⁸² the antiemetic efficacy of intravenous ondansetron 5.3 mg/m² and intravenous granisetron 2 mg/m² was compared in 90 teens treated with highly emetogenic chemotherapy for osteosarcoma. Evaluation of efficacy outcomes was based on patient days as the unit of measurement, rather than number of patients, and it is unknown whether the distribution of baseline patient characteristics remained balanced between groups in this type of analysis. Complete control was recorded on 58.3% of 240 patient days for ondansetron and 62.9% of 237 patient days for granisetron.⁸²

Orchard et. al. (1999) compared intravenous granisetron and ondansetron in pediatric and adult patients undergoing bone marrow transplantation.⁵² Results were stratified by age and the subgroup analysis of 51 (26%) participants under age 18 (mean age not reported) is reported here. Patients under 18 years of age received a 0.15 mg/kg loading dose of ondansetron, along with a 0.03 mg/kg/h drip rounded to the nearest 0.1 mg, or granisetron 10 µg/kg every 12 hours. Granisetron and ondansetron, respectively, were associated with 0.54 and 0.87 ($P=0.08$) mean episodes of emesis per day and mean nausea scores (5-point visual analog score scale) of 0.82 and 1.14 per day ($P=0.09$). Between-groups balance of baseline and prognostic factors is unknown because patient-related information was only provided for the group as a whole.

Oral ondansetron syrup compared with intravenous ondansetron

There were no significant differences in complete response between oral ondansetron syrup compared with intravenous ondansetron (78% compared with 81%) in younger children (mean age 8 years) undergoing moderately to highly emetogenic chemotherapy for various malignancies.⁸⁴ Children received loading doses of either oral ondansetron syrup 8 mg or intravenous ondansetron 5 mg/m². Then, all patients then 4 mg of oral ondansetron syrup plus 2-4 mg of oral dexamethasone every 6 to 8 hours for up to 8 days and 4 mg of oral ondansetron oral solution twice daily for the 2 days that followed cessation of the chemotherapy.

Palonosetron compared with ondansetron

Intravenous palonosetron 0.25 mg was superior to intravenous ondansetron 9 mg/m² in reducing emesis during the first 3 days following highly emetic chemotherapy in a trial of 100 children diagnosed with solid tumors conducted in a single center in Mexico City.⁸⁶ Mean age of the children was 11 years and 69% were male. Rates of complete control were 92% for palonosetron and 72% for ondansetron ($P=0.010$) on day 1, 72% and 46% ($P=0.023$), respectively, on day 2, and 78% and 54% ($P=0.028$) on day 3. There was no significant difference between palonosetron and ondansetron in rate of complete control on days 4 to 7. At baseline there was a significantly greater proportion of undernourished children in the palonosetron group (20% compared with 8%, $P=0.040$). Consequently, risk of emetic events in the palonosetron group may have been greater at baseline. Yet despite this imbalance, the palonosetron group had better control of emetic events. If the groups initially were more balanced, the advantage of

palonosetron might have been even greater. However, randomization resulting in uneven groups is indicative of a flawed randomization process, which could bias result in unknown ways. Therefore, we suggest that these results be interpreted with caution.

Prevention of nausea and vomiting associated with radiation therapy

Adults

Direct comparisons

No study evaluated the direct comparative efficacy of newer antiemetics in adults undergoing radiation therapy. One small study evaluated both oral granisetron 2 mg (N=18) and oral ondansetron 8 mg (N=15), but only as each compared with a historical control group who did not receive any 5-HT₃ antagonists (N=90).⁸⁷ Significantly more patients in the granisetron and ondansetron groups had complete control compared to the historical control group (27.8% and 26.7% compared with 0). Based on our analyses using the Fisher's exact test (StatsDirect software), direct comparison of complete control rates for granisetron and ondansetron did not find a significant difference between the 5-HT₃ antagonists.

Placebo-controlled and active-control trials

We identified a number of placebo-controlled and active-control trials of dolasetron, granisetron, and ondansetron (Evidence Tables 7 and 8).^{2, 88-97} Four of the trials of granisetron⁹⁵ and ondansetron,⁸⁹⁻⁹¹ plus 1 incompletely published trial comparing ondansetron with metoclopramide,⁹⁸ were previously analyzed in a good-quality systematic review.⁹⁹ This review by Tramer et al (1998) made no indirect comparisons and noted that the evidence was limited by variability in underlying risk (wide ranges in placebo response rates), clinical setting, drugs compared, radiation therapy regimen, and endpoints. Conclusions were that (1) ondansetron is consistently efficacious in preventing acute vomiting after total body or upper abdominal irradiation (number needed to treat = 3);^{90, 98} (2) limited evidence suggests that ondansetron is efficacious in preventing acute nausea;^{90, 98} and (3) there was no difference between granisetron or ondansetron and any placebo or active control in delayed protection from vomiting or nausea.^{90, 95, 98}

Although our review adds identification of trials that have been published since the final search date for the Tramer review (January 1997),^{2, 88, 97} earlier trials that were not in the Tramer review for unknown reasons,^{2, 88, 93, 94, 96, 97} and a placebo-controlled trial of the oral disintegrating tablet form of ondansetron, we also were unable to make any indirect comparisons due to the variability described above.

Children

Head-to-head trials of newer antiemetics for prevention of radiation-associated nausea and vomiting in children were not found.

Prevention of postoperative nausea and vomiting

Adults

Head-to-head trials

We included 22 head-to-head trials of 5-HT₃ antagonists used to prevent postoperative nausea and vomiting in adults. Trials compared granisetron (10), dolasetron (6), oral aprepitant (2), or

the orally disintegrating tablet formulation of ondansetron (2) with the conventional oral and intravenous forms of ondansetron. There were also 3 trials that involved comparisons of dolasetron and granisetron. We found no head-to-head trials involving palonosetron for prevention of postoperative nausea and vomiting. Complete information on these studies and their quality are in Evidence Tables 9 and 10. Surgical procedures included in these trials varied from “superficial surgical procedures” to gynecologic oncology surgery.

Granisetron compared with ondansetron

We included 10 trials that compared intravenous and oral forms of granisetron and ondansetron at various doses for prevention of postoperative nausea and vomiting in primarily female patients undergoing abdominal or gynecological surgery.¹⁰⁰⁻¹⁰⁹ One exception was a trial in patients undergoing middle ear surgery in which 50% were male. The majority of trials were conducted in single centers in India, Saudi Arabia, and Turkey.^{100, 102, 103, 105-107, 109} Outcome measurement methods varied across trials. Regardless of dose, formulation, and outcome measure, however, there was no consistent difference in the antiemetic efficacy of granisetron compared with ondansetron within the first 24 hours following operation. Complete response for the first 24 hours was reported in only 2 trials, both conducted in the United States. In these trials, only half of all patients treated with granisetron or ondansetron had complete responses within the first 24 hours.^{104, 108} The most common outcome reported in the remaining trials was incidence of postoperative nausea and vomiting, with rates ranging from 4% to 48% in the granisetron groups and 15% to 35% in the ondansetron groups. As expected, despite antiemetic treatment, incidence rate of postoperative nausea and vomiting were highest following cholecystectomy: 30% to 48% for granisetron and 34% to 35% for ondansetron.^{103, 106} The incidence of postoperative nausea and vomiting was lower after nonabdominal operations, such as in trials of patients who had mastectomy and a middle ear operation: 12% to 20% for granisetron and 20% for ondansetron.^{102, 105}

Outcomes related to quality of life were reported in 1 trial comparing of oral granisetron 1 mg with intravenous ondansetron 4 mg in 220 patients (88% females) who underwent abdominal operations.¹⁰⁸ At 48 hours after surgical procedure, there were no significant differences between granisetron and ondansetron groups in percentage of patients who reported a return to normal sleep (68% compared with 76%). There also was no significant difference between granisetron (16 points) and ondansetron (16 points) groups in score on an 18-point quality-of-life recovery scale.

Dolasetron compared with ondansetron

Seven trials in adults compared intravenous dolasetron with intravenous ondansetron.^{101, 110-115} One study focused on adult outpatients at high risk for postoperative nausea and vomiting, as determined by a score of 3 or more on the Surgical Prophylactic Antiemetic Intervention Assessment Scale.¹¹⁵ Complete response rates were reported in all but 1 trial, which instead found no significant difference in incidence of total treatment failure (39% in both groups).¹⁰¹ Overall, complete response rates were not significantly different between drugs but varied widely across the trials, from a low of 17% with dolasetron in a study of women undergoing gynecologic surgery to a high of 98% in a study of “superficial surgical procedures” with 37% men. In addition to differences in surgical procedures and proportions of women, these studies also varied in dose of antiemetic. While ondansetron 4 mg was used in every trial, the dolasetron dose varied more. Five studies of dolasetron used 12.5 mg, 2 studies included 25 mg, and 1 study included 50 mg. The 50 mg dose was superior to the 25 mg dose on total response rate at 24

hours (no emesis plus no rescue medication plus no nausea), and both dolasetron 50 mg and ondansetron 4 mg were superior to dolasetron 25 mg on complete response (no emesis plus no rescue medication use) at 24 hours.¹¹¹ Differences were not found between dolasetron 12.5 mg or 50 mg and ondansetron 4 mg or 8 mg in another study.¹¹⁴

Aprepitant compared with ondansetron

Two fair-quality trials (N=1727) compared oral aprepitant 40 mg and 125 mg with intravenous ondansetron 4 mg in primarily females undergoing open abdominal surgeries.^{116, 117} Both trials were originally designed to test the superiority of aprepitant over ondansetron on the primary efficacy endpoint of complete response, defined as no emesis and no use of rescue medication for the first 24 hours after surgery. In the first trial, no significant difference was seen between aprepitant 40 mg or 125 mg and ondansetron (45% compared with 43% compared with 42%), but both doses of aprepitant were significantly better than ondansetron on the secondary endpoint of no vomiting.¹¹⁷ The odds ratio of no vomiting for aprepitant compared with ondansetron was 3.2 for the 40 mg dose and 6.8 for the 125 mg dose, with $P < 0.001$ for both ratios (confidence intervals not reported). Before the second trial was completed, its plan for statistical analysis was adjusted to accommodate dual primary endpoints: (1) *noninferiority* of aprepitant for complete response and (2) *superiority* of aprepitant for no vomiting during the first 24 hours after surgery. For the complete response endpoint, noninferiority was defined as a lower bound of a 1-sided 95% CI of 0.65 for the odds ratio of aprepitant compared with ondansetron. In this trial, complete response rates were 64%, 63%, and 55%, respectively, for aprepitant 40 mg, aprepitant 125 mg, and ondansetron 4 mg. Noninferiority was confirmed based on the following odds ratios and lower bounds of the associated 1-sided 95% CI (in parentheses): aprepitant 40 mg to ondansetron 1.4 (1.8) and aprepitant 125 mg to ondansetron 1.4 (1.04). Additionally, as in the first trial, significantly more patients had no vomiting during the first 24 hours in the aprepitant 40 mg group (84%; odds ratio 2.1, $P < 0.001$) and 125 mg group (86%; odds ratio 2.5, $P < 0.001$) compared with ondansetron (71%).

Ondansetron: orally disintegrating tablet compared with intravenous

We included 2 trials that compared the oral disintegrating tablet and intravenous forms of ondansetron. Both trials were conducted in Turkey and both found no significant differences in postoperative nausea and vomiting outcomes.^{118, 119} In the first trial, oral disintegrating tablet ondansetron 8 mg, intravenous ondansetron 4 mg, and placebo were compared in 150 young men undergoing minor elective surgeries.¹¹⁹ In this trial, neither oral disintegrating tablet nor intravenous ondansetron was found to be significantly better than placebo in reducing incidence of postoperative nausea and vomiting, vomiting, or use of rescue medication during the first 24 hours after surgery. In the second trial, oral disintegrating tablet ondansetron 8 mg, intravenous ondansetron 8 mg, and placebo were compared in 90 women undergoing major gynecologic surgery (mean age = 47 years).¹¹⁸ In this trial, both oral disintegrating tablet and intravenous forms of ondansetron were found to be better than placebo in reducing incidence of nausea and vomiting during the first 6 hours after surgery. There were no significant differences between the 2 forms of ondansetron.

Dolasetron compared with granisetron

Two trials compared dolasetron 12.5 mg intravenous with various doses of granisetron intravenous and had inconsistent findings.^{101, 120} In the trial of mostly women (84%) undergoing a variety of surgical procedures, a complete response was significantly more frequent with

granisetron 1 mg intravenous (54.7%, $P=0.049$) than with dolasetron (38.7%).¹²⁰ However, in a trial of women undergoing gynecological and breast surgeries, rate of total treatment failure did not differ significantly between low-dose granisetron intravenous (0.1 mg) and dolasetron (39% and 48%, respectively; $P=0.45$).¹⁰¹ In both trials, patient satisfaction was not significantly different between the granisetron and dolasetron groups.

One trial reported time to first intake of fluids or solids and quality of first postoperative night sleep.¹²⁰ There was no significant difference between granisetron and dolasetron in these outcomes.

Placebo-controlled trials

Head-to-head trials rarely reported patient satisfaction, quality of life, functional capacity, or hospital stays. Therefore, we included placebo-controlled trials to address these gaps (Evidence Tables 11 and 12).¹²¹⁻¹⁵⁹

Dolasetron was the only 5-HT₃ antagonist that consistently showed significantly improved patient satisfaction compared with placebo across 4 trials.^{121, 128, 148, 152} Ondansetron was superior to placebo in improving patient satisfaction in only 2^{131, 140} of 12 placebo-controlled trials and was not significantly different than other antiemetics in trials with active controls.^{130, 132, 133, 139} In 1 trial of the orally disintegrating tablet form of ondansetron¹⁵⁹ and 1 trial of intravenous palonosetron,¹⁵⁸ neither antiemetic significantly improved patient satisfaction over placebo.

There is limited evidence to suggest that any 5-HT₃ antagonist has an impact on hospital stay, quality of life, or functional capacity. Compared with placebo, patients who were given dolasetron 12.5 mg before elective extracorporeal shock wave lithotripsy were discharged 6 minutes earlier, a statistically significant difference ($P<0.05$).¹⁵² Discharge time was decreased by 45 minutes ($P<0.05$) in women who received intravenous ondansetron 4 mg compared with placebo following laparoscopic procedures.¹⁴⁶ However, ondansetron did not significantly reduce hospital stay times compared with placebo or other antiemetics in any of the other 10 trials that looked at this outcome.^{129, 130, 133, 137, 139, 140, 143, 145, 147, 151}

One trial assessed whether intravenous ondansetron followed by orally disintegrating tablet ondansetron was more effective than intravenous ondansetron alone in improving the impact of postoperative nausea and vomiting on quality of life.¹⁵⁹ A modified Functional Living Index-Emesis was administered to 60 women undergoing outpatient laparoscopic gynecological surgeries. Compared with intravenous ondansetron alone, orally disintegrating tablet ondansetron following intravenous ondansetron led to a smaller proportion of women reporting their quality of life being affected by nausea (33% compared with 60%; $P<0.04$) or vomiting (3% compared with 20%; $P<0.04$). Another trial assessed whether various dosages of intravenous palonosetron were more effective than placebo in reducing the interference of postoperative nausea and vomiting in daily life activities.¹⁶⁰ The modified Osoba questionnaire was administered to 547 mostly female patients undergoing laparoscopic gynecological or abdominal surgeries. Only the highest dose of palonosetron (0.075 mg) was found to be significantly superior to placebo in reducing the impact of postoperative nausea and vomiting on patient function based on the Osoba total score ($P=0.004$) and for the subdomains appetite ($P=0.018$), social life ($P=0.013$), and enjoyment of life ($P=0.030$).

Children

Head-to-head trials

Dolasetron compared with ondansetron

Two trials compared intravenous dolasetron and intravenous ondansetron^{161, 162} and 1 trial compared oral dolasetron and oral ondansetron in children undergoing surgical procedures.¹⁶³ Dosing was based on weight in all 3 trials and was similar, but not identical, in the 2 trials of intravenous formulations. Two of the studies included tonsillectomy,^{162, 163} while the third excluded these because they routinely involve steroid prophylaxis.¹⁶¹ Of the 2 studies including tonsillectomy, 1 pretreated children with dexamethasone¹⁶² and the other did not.¹⁶³ No significant difference in complete response was found between the drugs at 24 hours. Rate of complete response varied from 52% to 86%, with higher rates seen in the trial using dexamethasone pretreatment. Individual studies assessed shorter-term efficacy (0 to 6 hours), longer-term efficacy (48 hours), and effect on vomiting only, but again no differences were found.

Placebo-controlled and active-control trials in children

As with the head-to-head trials of adults undergoing surgical procedures, no head-to-head trials of children undergoing surgical procedures reported outcomes reflective of quality of life, patient satisfaction, or resource utilization. Again, we included fair-quality placebo and active-control trials to address these gaps (Evidence Tables 11 and 12).^{122, 123, 125-127, 134-136, 138, 141, 142, 144}

Compared with placebo, ondansetron significantly improved patient satisfaction in one¹⁴¹ of two trials^{122, 141} and significantly reduced hospital stay times in four^{127, 136, 141, 142} of seven trials.^{122, 127, 136, 138, 141, 142, 144} Compared with placebo, granisetron significantly reduced hospital stay times in two^{123, 135} of three trials^{123, 125, 135}, but did not significantly improve patient satisfaction.¹²⁵ In the only placebo-controlled trial of dolasetron in children undergoing surgical procedures, there were no differences between placebo and dolasetron in patient satisfaction outcomes.¹³³

Treatment of established postoperative nausea and vomiting

Adults

Direct comparisons

Very little head-to-head trial evidence compares different 5-HT₃ antagonists in treatment of postoperative nausea and vomiting: In 1 head-to-head trial each, only dolasetron¹⁶⁴ and granisetron¹⁵⁴ have been directly compared with ondansetron.

In the trial that compared dolasetron with ondansetron, 76% of patients were women. Randomized patients were 92 (64%) out of 143 eligible adults who experienced postoperative nausea and vomiting after a variety of surgical procedures.¹⁶⁴ Similar proportions of patients randomized to dolasetron and ondansetron received unspecified prophylactic antiemetics (30% compared with 20%). Among the other 51 eligible patients, 47 were excluded because they “did not receive blinded study drug” and 4 patients chose not to participate. As the exclusion rate (36%) was considerable and reasons for not receiving blinded study drug were unclear, some doubt was raised about the results of this study. Compared with ondansetron, dolasetron significantly reduced the need for rescue medication, the primary outcome measure (40% compared with 70%, $P=0.004$). However, there was no significant difference between dolasetron and ondansetron in the number of patients who actually vomited (16% compared with 23%),

who were subsequently admitted to the hospital for the postoperative nausea and vomiting itself (2% compared with 2%), or who were satisfied with their antiemetic treatment (71% compared with 59%).

The second trial assessed whether there was greater benefit with administration of intravenous granisetron 0.1 mg or 1 mg compared with *repeat* intravenous ondansetron 4 mg for rescue treatment of postoperative nausea and vomiting following failure of prophylactic open intravenous ondansetron 4 mg.¹⁵⁴ A total of 250 female patients who underwent unspecified nonemergency operations were enrolled and given prophylactic ondansetron. Among these, 7 (2.8%) patients were excluded due to protocol violations. Among the remaining 243 patients, all 88 who required rescue medication for postoperative nausea and vomiting were randomized to blinded study drug. The trial assessed complete response, defined as resolution of postoperative nausea and vomiting with no further request for rescue medication. Substantial numbers of patients met criteria for a complete response after receiving granisetron 0.1 mg (68%) or 1 mg (60%), but these proportions were not significantly greater than following repeat treatment with intravenous ondansetron (47%). Likewise, no statistical differences among the 3 treatment arms were found on any other nausea or vomiting outcomes in the 24-hour follow-up period.

Placebo-controlled and active-control trials

Four active-control¹⁶⁵⁻¹⁶⁸ and 1 placebo-controlled trial provided additional data on patient satisfaction outcomes.¹⁶⁹

In 3 studies, patients were more satisfied with ondansetron^{166, 167} or granisetron¹⁶⁸ than with metoclopramide or droperidol. It is not possible to indirectly compare ondansetron with granisetron from these studies, however, because they used different methods to measure patient satisfaction.

In a study comparing ondansetron with acustimulation, there was no difference in rate of patient satisfaction between treatment groups.¹⁶⁵ The evidence for dolasetron is from 1 placebo-controlled trial.¹⁶⁹ Patients were more satisfied with dolasetron than placebo as measured by a visual analog scale.

Children

Direct comparisons

No head-to-head studies for treatment of established postoperative nausea and vomiting were found.

Placebo-controlled and active-control trials

The evidence for treatment of established postoperative nausea and vomiting in children is limited to 2 trials of ondansetron: 1 placebo-controlled trial in 375 children ages 2 to 12 years¹⁷⁰ and 1 active-control trial (compared with droperidol) in 29 children ages 2 to 10 years.¹⁷¹ This evidence does not provide indirect comparisons of newer antiemetics.

The placebo-controlled trial reported complete control of vomiting at early and late time points.¹⁷⁰ Ondansetron was superior to placebo both early (within 2 hours; 78.1% for ondansetron and 34.4% for placebo, $P < 0.001$) and late (within 24 hours; 52.7% for ondansetron and 16.8% for placebo, $P < 0.001$). Fewer ondansetron patients needed rescue medication (9% ondansetron compared with 27% placebo within 2 hours; 17% ondansetron compared with 51% placebo within 24 hours).

In a small active-control trial¹⁷¹ the difference between ondansetron 0.1 mg/kg and droperidol 2.0 mg/kg for early efficacy (complete control of postoperative nausea and vomiting

within 4 hours) was not significant (75% for ondansetron compared with 84.6% for droperidol; odds ratio 0.60, 95% CI 0.10 to 3.4). Late control of nausea and vomiting and use of rescue medication were not assessed in this study.

Prevention of nausea and vomiting associated with pregnancy

Evidence on the use of newer antiemetics in pregnant women is extremely limited and is noncomparative for our purposes.¹⁷²⁻¹⁷⁴ The only identified trial compared ondansetron with promethazine in 30 women hospitalized with hyperemesis gravidarum and found no differences on any outcome measure.

Key Question 2.

What are the comparative tolerability and safety of newer antiemetics when used to treat or prevent nausea and/or vomiting?

Overview

The head-to-head trials are heterogeneous for types of adverse events reported. Adverse events were not prespecified and were inadequately defined. Ascertainment techniques were generally inadequately defined, and it was not possible to determine whether they were nonbiased and accurate. Specifically, it was often unclear whether the reported adverse events included those that investigators considered “unrelated” and how this was determined. It was also unclear whether adverse event reporting included all levels of severity and how these were defined. All of these factors likely contribute to the wide range of event rates seen in these trials; these outcomes should be interpreted with caution.

Prevention of chemotherapy-induced nausea and vomiting

Adults

Tolerability

The majority (82%) of trials reported adverse event outcomes and there were generally no statistically significant differences.^{33-35, 37-48, 51, 52, 55-58, 73-75} Proportions of patients with at least 1 adverse event ranged from 34% to 58% for dolasetron, 28% to 87% for granisetron, 24% to 86% for ondansetron, 61% to 79% for palonosetron, and 61% to 85% for aprepitant regimens. Rates of withdrawals were rarely reported and ranged from zero^{51, 55, 73} to less than 3% for palonosetron, granisetron, and ondansetron.^{41, 74} Headache, constipation, and diarrhea were the most common adverse events and rates (ranges) are shown in the Table 8.

Table 8. Rates of common adverse events in head-to-head trials of newer antiemetic drugs

Comparison	Headache	Constipation	Diarrhea
G vs O	1.4% - 53.3% vs 1.3% - 33.3% ^{22, 24, 26-30, 32-35, 37, 38, 40-47, 51}	<1% - 20% vs 0.4-30% ^{22, 26, 27, 30, 34, 35, 37, 38, 40-45, 47, 51}	3% - 12% vs 0% - 9.8% ^{22, 24, 26, 28, 30, 32, 34, 38, 40, 41, 43, 44, 47, 51}
D vs O	19% - 44% vs 14% -36% ⁵⁵⁻⁵⁷	1% - 32% vs 0% - 39% ^{56, 57}	0% - 16% vs 1% - 8% ⁵⁵⁻⁵⁷
D vs G ⁵⁸	22% - 28% vs 23%	NR	11% - 13% vs 6%
P vs O ⁷⁴	4% - 12% vs 5% - 11%	2% - 8% vs 2%	0.4% - 1.3% vs 2.2%
P vs D ⁷³	15% vs 17%	7% - 9% vs 6%	2% vs 2%
A vs O ⁵⁹	NR	16% vs 22%	13% vs 9%
F vs O ^{68, 69}	13% - 47% vs 12-39%	7% - 40% vs 14% - 39%	23% - 60% vs 5-9%
O (ODT) vs O (po) ⁷⁶	4.5% vs 4%	3% vs 6%	NR
G IV vs po ⁷⁵	8% vs 8%	0% vs 2%	NR

Abbreviations: A, aprepitant; D, dolasetron; F, fosaprepitant; G, granisetron; IV, intravenous; NR, not reported; O, ondansetron; ODT, oral disintegrating tablet; P, palonosetron; po, orally.

Ondansetron was associated with significantly higher rates of dizziness and abnormal vision than either granisetron⁴⁴ or dolasetron⁵⁷ in 1 trial of each comparison that used relatively higher than recommended doses of ondansetron (32 mg intravenously). Two other trials reported insignificant differences in dizziness rates for granisetron and ondansetron.^{34, 52} One trial compared ondansetron (intravenous or oral) with dolasetron (intravenous or oral) in 696 patients and reported higher rates of constipation (39.4% compared with 32.1%, $P=0.044$) for ondansetron and higher rates of diarrhea (16.3% compared with 8.2%, $P=0.001$) and abdominal pain (15.7% compared with 9.6%, $P=0.015$) for dolasetron.⁵⁷ Intravenous ondansetron 32 mg had higher rates of dizziness (3.2%) than intravenous palonosetron 0.25 mg (0%) and 0.75 mg (0.5%).⁷⁴

Dyspepsia was reported in 14% of patients who received aprepitant on days 1 through 3 and in 11% of patients who received ondansetron on days 1 through 4, both taken in combination with dexamethasone on days 1 through 4.⁵⁹ Although dyspepsia was seen more often with aprepitant in add-on therapy studies, this difference is not statistically significant. Fosaprepitant resulted in statistically significantly more patients reporting diarrhea than with ondansetron in 1 of 2 studies.^{68, 69}

Serious adverse events

The rate of serious adverse events reported in a trial of patients undergoing chemotherapy was not significantly different for intravenous dolasetron 1.8 mg/kg or 2.4 mg/kg compared with granisetron 3 mg (6% or 7% compared with 5%, not significant).⁵⁸ Only 2 adverse events were considered related to antiemetic treatment; these were angina/myocardial infarction/acute pulmonary edema in 1 patient and fever/abdominal pain in another, both associated with granisetron. Rate of hospital admission for fluid administration was not significantly different for intravenous doses of granisetron 3 mg and ondansetron 32 mg (0.8% compared with 0.8%, not significant) and there were no emergency admissions.³³

Reports of serious adverse events outside the trial setting come only from uncontrolled studies of dolasetron,¹⁷⁵ granisetron,¹⁷⁶ and ondansetron¹⁷⁷⁻¹⁷⁹ in adults (Evidence Tables 16 and 17). These studies were generally poor quality, lacking details of patient selection processes, ascertainment methods, and adverse event descriptions. They do not offer any information about comparative safety, but rather present single cases of serious adverse events. Investigators generally attributed these events to the cytotoxic chemotherapy and/or underlying disease.

Death rate was not different between oral dolasetron and oral ondansetron,⁵⁶ intravenous dolasetron and intravenous ondansetron,⁵⁶ or intravenous and oral granisetron.⁷⁵ The deaths were attributed to the patients' underlying disease.

Children

Tolerability

Evidence about comparative tolerability of newer antiemetics in children is severely limited and indicates no difference in adverse event rates for the oral solution of ondansetron or **intravenous formulation of palonosetron** compared with intravenous ondansetron.^{84, 86} Intravenous and oral solution formulations of ondansetron were associated with similar rates of any adverse event (24% compared with 25%, not significant), abdominal/gastrointestinal discomfort (4% compared with 3%, not significant), fever (3% compared with 3%, not significant), and diarrhea/headache (2% compared with 2%, not significant) in a trial of 428 children undergoing moderate to severely emetic chemotherapy for hematologic malignancy (mean age 8 years).⁸⁴

Serious adverse events

Reports of serious adverse events in observational studies of granisetron¹⁸⁰ and ondansetron^{181, 182} in children (Evidence Tables 16 and 17) suffered from methodological flaws similar to those discussed for adults.

Prevention and treatment of postoperative nausea and vomiting

Adults

Tolerability

Safety outcomes were underreported in head-to-head trials. Only 9 of 22 head-to-head trials of prevention of postoperative nausea and vomiting reported adverse events experienced by participants.^{101, 102, 104, 109-111, 116-118} In these trials, no difference in the rate of overall adverse events, withdrawals due to adverse events, or any particular adverse event was found between intravenous ondansetron and either intravenous granisetron, intravenous dolasetron, **oral aprepitant**, or the orally disintegrating tablet form of ondansetron.

The most frequent adverse event reported in trials of established postoperative nausea and vomiting was headache. Three placebo-controlled trials of ondansetron,¹⁸³⁻¹⁸⁵ 2 of dolasetron,^{169, 186} and 1 of granisetron¹⁸⁷ reported the incidence of headache in treatment and placebo groups. The incidence of headache was similar to placebo for all drugs. Two more recent studies of granisetron^{188, 189} did not report the number of patients with headache in each group but noted that the incidence of headache did not differ from placebo.

The Kazemi systematic review¹⁹⁰ did not report comparative information for adverse events separately by individual antiemetic, but an analysis of headache compared with placebo by dosage is presented for the drugs combined. Only high-dose antiemetics had headache rates higher than placebo, but the difference was not statistically significant at any dose level.

Safety

Rare occurrences of QTc prolongation are reported in the product labels of with dolasetron, ondansetron, and palonosetron. However, we found only 1 single-blind study that prospectively measured QTc changes associated with treatment of postoperative nausea and vomiting by intravenous droperidol 0.75 mg or intravenous ondansetron 4 mg.¹⁹¹ Patients in this study were 85 consecutive adults who experienced postoperative nausea and vomiting in the recovery room and who were assigned to treatment with droperidol or ondansetron based on the judgment of the attending anesthesiologist. Electrocardiograms were obtained immediately before administration of antiemetic drug and multiple times between 1 and 15 minutes after administration. Electrocardiograms were evaluated by a clinician who was blinded to antiemetic drug assignment. There were no significant between-group baseline differences in age, gender, QTc interval before drug administration (mean=439 ± 29 ms), or characteristics of operative procedures and anesthesia techniques. Compared with baseline, mean maximal QTc lengthening was significant ($P<0.0001$) for droperidol (17 ± 9 ms) and ondansetron (20 ± 13 mg) and was similar when using the Fridericia correction formula. Although the study was not designed to compare droperidol with ondansetron for duration of QTc lengthening, post hoc analysis found significant differences between the antiemetics. No ventricular arrhythmias occurred during the study period. We found no trials or observational studies that specifically assessed risk of arrhythmias associated with prophylaxis or treatment of postoperative nausea and vomiting with 5-HT3 antagonists.

Children

No comparative information on adverse events in children is available. Indirect evidence is extremely limited. In a placebo-controlled trial in children,¹⁷⁰ the overall incidence of adverse events was 36% in the ondansetron group and 47% in the placebo group ($P<0.05$). Potentially drug-related headaches were reported in 3% of ondansetron-treated children and 2% of placebo-treated children (difference not significant).

Patients undergoing radiation therapy

Adults

Direct comparisons

Our post hoc analyses suggested no differences between oral granisetron 2 mg and oral ondansetron 8 mg in tolerability in 34 patients undergoing hyperfractionated total body irradiation.⁸⁷ Similar percentages of patients had adverse experiences that were possibly or probably related to study medication (39% compared with 25%, not significant). The most frequently reported adverse experiences were headache (28% compared with 18.8%, not significant) and diarrhea (22.2% compared with 6.3%, not significant). Two patients in each treatment group experienced severe adverse events. These were both headache in the granisetron group and 1 episode each of severe infection and nervousness in the ondansetron group.

Placebo-controlled and active-control trials

Placebo-controlled and active-control trials of dolasetron, granisetron, and ondansetron were sufficiently heterogeneous in populations, compared drugs, radiation therapy regimens, and reporting of adverse events^{2, 88-97} that meaningful indirect comparison was impossible.

Systematic reviews⁹⁹ of earlier trials of granisetron⁹⁵ and ondansetron^{89-91, 98} concluded that these drugs are associated with increased incidence of headache and constipation. Additional placebo-controlled and active-control trials of granisetron⁸⁸ and ondansetron^{93, 94, 96, 97} also reported headache and constipation as being the most common significant adverse events.

Pregnant patients

Short-term tolerability

In a study of ondansetron compared with promethazine in women with hyperemesis gravidarum, significantly more women experienced sedation with promethazine than ondansetron.¹⁷² No other side effects were noted.

Long-term safety

A prospective observational study assessed birth outcomes in women and infants exposed to ondansetron during early pregnancy.¹⁹² The study enrolled 188 pregnant women with exposure to ondansetron during weeks 5 to 9 of gestation. The women had all been treated for nausea and vomiting associated with pregnancy. Loss to follow-up in this group was 6%. The study used 2 comparison groups, women exposed to other antiemetics during pregnancy and women exposed to other nonteratogenic drugs during pregnancy. Although it is stated that enrollment methods for all groups were the same, the total numbers enrolled and lost to follow-up in the control groups are not clear. No differences were found between groups in birth weight, number of live births, proportion of infants with deformities, or other measures.

Key Question 3.

Are there subgroups of patients based on demographics (age, race, gender), pregnancy, other medications, or comorbidities for which one newer antiemetic is more effective or associated with fewer adverse events?

Analyses of the comparative efficacy of newer antiemetics in subpopulations were reported in only a few studies and focused on protection against postoperative and chemotherapy-related nausea, vomiting, or both.^{33, 35, 36, 38, 40, 47, 55, 56, 58, 84} Safety comparisons in subpopulations were rarely reported.

Race and ethnicity was not reported in most trials and nothing about differences in effectiveness or safety can be determined from these limited data.

Comorbidities that were often excluded from these trials included obesity, gastroesophageal reflux disease, cardiovascular diseases, diabetes, and other serious conditions. Studies that did allow patients with these conditions to enroll did not analyze the effects in these subgroups.

Demographics

There were no differences between dolasetron, granisetron, and ondansetron in rate of complete emetic control in subpopulations based on age or gender in adult patients aged 18 to 94 years undergoing emetic chemotherapy for a variety of cancer types.^{35, 38, 40, 44, 47, 55, 56, 58} These drugs

appear to work well in preventing postoperative nausea and vomiting. No differences were found in trials that included primarily women (4 of 10 studies) or in those that included more men.

There were also no differences between intravenous and oral solution formulations of ondansetron in rate of complete or major control of emesis in subpopulations based on age in children 1 to 17 years undergoing moderately to highly emetic chemotherapy for treatment of various cancers.⁸⁴

In the adult populations studied for postoperative nausea and vomiting, the mean ages of patients in studies of dolasetron compared with ondansetron was 45 years and of granisetron compared with ondansetron, 42 years. In the pediatric populations, the mean ages ranged from 6 to 9. However, we found no studies that specifically evaluated the influence of age on the comparative effectiveness and harms among antiemetics for prevention of postoperative nausea and vomiting.

In a pooled analysis of 2 of 6 trials in which aprepitant was added to a regimen of intravenous ondansetron 32 mg plus oral dexamethasone 12 mg on day 1 and oral dexamethasone 8 mg on days 2 through 4, aprepitant improved response rates in women (66% compared with 41%) to a greater extent than in men (69% compared with 53%).¹⁹³ Comparisons of acute and delayed periods were very similar between men and women. Because these are post hoc subgroup analyses and statistical power may be inadequate, the results should be interpreted with caution and used for design of future research.

In additional subgroup analyses from trials of aprepitant submitted by the manufacturer, difference in response based on age or race is not apparent. Because these are small subgroups, statistical analysis was not undertaken.

Other medications

There was no difference in rate of complete emetic control between ondansetron and either dolasetron or granisetron in subpopulations based on concomitant medications including corticosteroids,^{38, 44} H₂-receptor antagonists,³⁵ opioids,³⁵ benzodiazepines,^{35, 55} or NSAIDs³⁵ in patients undergoing emetic chemotherapy for a variety of cancers.

Concomitant medications that were disallowed or used as part of anesthesia, preanesthesia, or postoperative pain control also varied in trials of postoperative nausea and vomiting prevention, with some excluding drugs often used as preanesthetics or anesthetics known or thought to have antiemetic properties. Overall, higher rates of complete response were seen in trials that included use of dexamethasone preoperatively, and lower rates were associated with gynecologic surgeries and lower doses of 5-HT₃ antagonist. Differences between dolasetron, granisetron, and ondansetron in subpopulations based on concomitant medications were not seen in these data.

Prognostic factors

A post hoc subgroup analysis of a trial of patients receiving emetic chemotherapy suggested that ondansetron may be significantly better at preventing vomiting than granisetron in patients with a predisposition to nausea/vomiting (history of motion sickness, previous treatment with emetic chemotherapy).³⁵ Intravenous granisetron 3 mg was associated with a lower rate of complete protection from emesis in patients with a history of motion sickness than in those without motion sickness (17% compared with 43%; $P < 0.0001$). Intravenous ondansetron 24 mg was associated with a similar rate of complete protection regardless of the history of motion sickness (20% compared with 30%, not significant).³⁵ Intravenous granisetron was also associated with

significantly lower rates of protection from emesis than intravenous ondansetron in a subgroup of patients treated with emetic chemotherapy.³⁵ Authors note that these outcomes may be due to chance, given that the numbers of patients in these subgroups were small.

SUMMARY

Table 9 summarizes the results of this review.

Table 9. Summary of the evidence by key question

Key Question 1. What is the comparative effectiveness/efficacy of newer antiemetics in treating or preventing nausea and/or vomiting?			
Comparison	Population (No. trials)	Strength of the evidence	Conclusion
Dolasetron, granisetron, and ondansetron			
Granisetron vs ondansetron	Chemotherapy, adults (32)	Good	No consistent significant differences on any antiemetic efficacy outcomes, regardless of population or formulation
	Chemotherapy, children (3)	Fair	
	Postoperative prevention, adults (10)	Good	
	Postoperative treatment, adults (1)	Fair-Poor	
	Radiation therapy, adults (1)	Fair-Poor	
Dolasetron vs ondansetron	Postoperative prevention, adults (7)	Good	
	Chemotherapy, adults (3)	Good	
	Postoperative prevention, children (2)	Fair	
	Postoperative treatment, adults (1)	Fair-Poor	
Dolasetron vs granisetron	Chemotherapy, adults (1)	Good	
	Postoperative prevention, adults (2)	Fair	
Ondansetron: orally disintegrating tablet vs standard oral or intravenous	Chemotherapy, adults (1)	Fair-Poor	
	Postoperative prevention - Adults (2)	Fair	
Aprepitant/fosaprepitant			
Aprepitant vs ondansetron	Postoperative prevention, adults (2)	Good	Noninferior on 24-hour complete response rates; superior for 24-hour no vomiting outcomes
	Chemotherapy - Adults (1)	Fair	Superior on complete response over 5 days (NNT=9) and for improving quality of life
Fosaprepitant vs ondansetron	Chemotherapy - Adults (2)	Good	For complete response rates, inferior from 0 to 24 hours but superior from days 2 to 5
Palonosetron			
Palonosetron vs ondansetron	Chemotherapy - Adults (2)	Good	Noninferior to dolasetron and ondansetron on acute and delayed complete response following moderately to highly emetic chemotherapy
Palonosetron vs dolasetron	Chemotherapy - Adults (1)	Fair	

			Superior to dolasetron and ondansetron following moderately emetic chemotherapy in pooled analysis of 24-hour (NNT=9) and delayed (NNT=6) complete response rates and in improving delayed quality of life
Palonosetron vs ondansetron	Chemotherapy - Children (1)	Poor	Possibly superior for early complete response rates following highly emetic chemotherapy

Key Question 2. What are the comparative safety and tolerability of newer antiemetics in treating or preventing nausea and/or vomiting?

Comparison	Population	Quality	Conclusion
Aprepitant, dolasetron, granisetron, palonosetron, ondansetron	Mainly postoperative (prevention and treatment) and chemotherapy, adults	Good for dolasetron, granisetron, and ondansetron. Fair for aprepitant and palonosetron.	No consistent significant differences in overall adverse events, withdrawals due to adverse events, or specific adverse events

Key Question 3. Are there subgroups of patients based on demographics (age, race, gender), pregnancy, other medications, or comorbidities for which one newer antiemetic is more effective or associated with fewer adverse events

Comparison	Population	Quality	Conclusion
Dolasetron, granisetron, ondansetron	Demographics and other medications	Fair	No consistent differences in comparisons of 5-HT3 antagonists in different patient subgroups
	Prognostic risk factors: Patients with a predisposition to nausea/vomiting	Poor	Ondansetron superior to granisetron in preventing vomiting in a subgroup analysis of a single trial
Aprepitant	Gender, race	Poor	Inconclusive based on mixed findings across pooled subgroup analysis from 2 of 6 placebo-controlled trials and small subgroup analyses from trials of aprepitant compared with ondansetron submitted by manufacturer

Abbreviations: 5-HT3, type 3 serotonin; NNT, number needed to treat.

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Appendix A. US Food and Drug Administration recommendations for adult dosages

I. Dosages for prevention of emesis associated with chemotherapy^{a,b}

Drug (brand name)	Form	Emetic risk	
		Moderate	High
Aprepitant (Emend [®])	Capsule	125 mg once on day 1 then 80 mg once daily on days 2 to 3	125 mg once on day 1 then 80 mg once daily on days 2 to 3
Fosaprepitant (Emend [®])	Injection	115 mg IV once on day 1 then 80 mg orally once daily on days 2 to 3	115 mg IV once on day 1 then 80 mg orally once daily on days 2 to 3
5-HT3 antagonists			
Dolasetron (Anzemet [®])	Injection	1.8 mg/kg or 100 mg once	1.8 mg/kg or 100 mg once
	Tablet	100 mg once	Not established
Granisetron (Kytril [®])	Injection	10 mcg/kg once	10 mcg/kg once
	Tablet, oral solution	2 mg once or 1 mg BID	2 mg once or 1 mg BID
Ondansetron (Zofran [®])	Injection	32 mg once or 0.15 mg/kg TID	32 mg once
	Tablet, orally disintegrating tablet, oral solution	8 mg BID on Days 1 to 3	24 mg once
Palonosetron (Aloxi [®])	Injection	0.25 mg once	0.25 mg once
	Tablet	0.5 mg once	Not established

Abbreviations: BID, twice daily; IV, intravenous; TID, three times daily.

^a This table does not attempt to address any recommendations regarding the use of NK-1 and 5-HT3 antagonists in combination with other agents, such as steroids.

^b Dosages are for day 1 administered once, prior to chemotherapy, unless otherwise noted.

II. Dosages for prevention of postoperative emesis

Drug (brand name)	Form	Dosage ^a
Aprepitant (Emend [®])	Capsule	40 mg once
Fosaprepitant (Emend [®])	Injection	Not established
5-HT3 antagonists		
Dolasetron (Anzemet [®])	Injection	12.5 mg once
	Tablet	100 mg once
Granisetron (Kytril [®])	Injection	1 mg once
	Tablet, oral solution	Not established
Ondansetron (Zofran [®])	Injection	4 mg once
	Tablet, orally disintegrating tablet, oral solution	16 mg once
Palonosetron (Aloxi [®])	Injection	0.075 mg once
	Tablet	Not established

^a Administered before postoperative procedure or prior to the cessation of anesthesia, unless otherwise specified.

III. Dosages for prevention of emesis following radiotherapy

Drug (brand name)	Form	Dosage^a
Granisetron (Kytril [®])	Injection	Not established
	Tablet, oral solution	2 mg once
Ondansetron (Zofran [®])	Injection	Not established
	Tablet, orally	8 mg three times daily
	disintegrating tablet, oral solution	

^a Administered prior to radiotherapy, unless otherwise specified.

Appendix B. US Food and Drug Administration recommendations for pediatric dosages

I. Prevention of emesis following chemotherapy with moderate to high emetic risk

Drug (brand name)	Form	Age range	Dosage ^b
Aprepitant/fosaprepitant (Emend [®])	Injection/Capsule	N/A	Not established
Dolasetron (Anzemet [®])	Injection, Tablet ^a	2 to 16 years	1.8 mg/kg once (maximum of 100 mg)
Granisetron (Kytril [®])	Injection	2 to 16 years	10 mcg/kg once
	Tablet, oral solution	2 to 16 years	2 mg once or 1 mg BID
Ondansetron (Zofran [®])	Injection	6 months to 18 years	0.15 mg/kg TID
	Tablet ^a , orally disintegrating tablet ^a , oral solution ^a	4 to 11 years	4 mg TID (days 1 to 3)
		≥ 12 years	8 mg BID (days 1 to 3)
Palonosetron (Aloxi [®])	Injection, tablet	N/A	Not established

Abbreviations: BID, twice daily; IV, intravenous; N/A, not applicable; TID, three times daily.

^a Moderate emetic risk only.

^b Administered prior to chemotherapy, unless otherwise specified.

II. Prevention of postoperative emesis

Drug (Brand Name)	Form	Age range	Dosage ^a
Aprepitant/fosaprepitant (Emend [®])	Injection/Capsule	N/A	Not established
Dolasetron (Anzemet [®])	Injection (prevention or treatment)	2 to 16 years	0.35 mg/kg once (maximum of 12.5 mg)
	Tablet	2 to 16 years	1.2 mg/kg once (maximum of 100 mg)
Granisetron (Kytril [®])	Injection, tablet, oral solution	N/A	Not established
Ondansetron (Zofran [®])	Injection	1 month to 12 years	0.1 mg/kg once (for weight of 40 kg or less); 4 mg once (for weight above 40 kg)
	Tablet, orally disintegrating tablet, oral solution	N/A	Not established
Palonosetron (Aloxi [®])	Injection, tablet	N/A	Not established

Abbreviations: BID, twice daily; IV, intravenous; N/A, not applicable; TID, three times daily.

^a Administered before postoperative procedure or before cessation of anesthesia.

Appendix C. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An **adverse event** for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The U.S. Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers — do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study’s point estimate. A horizontal line runs through each square to show each study’s confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity*.

Half-life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2 : A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as $(Q-(n-1))/Q$, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (heart attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combining data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of *Q* suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is < 1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomisation when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term “safe”) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete:* taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal:* taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix D. Search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2004>

Search Strategy:

-
- 1 Dolasetron.mp. (110)
 - 2 Anzemet.mp. (5)
 - 3 Granisetron.mp. (409)
 - 4 Kytril.mp. (14)
 - 5 Zofran.mp. (21)
 - 6 Ondansetron.mp. (1049)
 - 7 Palonosetron.mp. (3)
 - 8 Aloxi.mp. (0)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (1441)
 - 10 random\$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (191618)
 - 11 9 and 10 (1040)
 - 12 limit 9 to randomized controlled trial (841)
 - 13 11 or 12 (1157)
 - 14 from 13 keep 1-1157 (1157)
-

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2004>

Search Strategy:

-
- 1 Dolasetron.mp. (1)
 - 2 Anzemet.mp. (0)
 - 3 Granisetron.mp. (4)
 - 4 Kytril.mp. (0)
 - 5 Zofran.mp. (1)
 - 6 Ondansetron.mp. (13)
 - 7 Palonosetron.mp. (0)
 - 8 Aloxi.mp. (0)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (14)
 - 10 from 9 keep 1-14 (14)
-

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2004>

Search Strategy:

-
- 1 Dolasetron.mp. (3)
 - 2 Anzemet.mp. (0)
 - 3 Granisetron.mp. (9)
 - 4 Kytril.mp. (0)
 - 5 Zofran.mp. (0)
 - 6 Ondansetron.mp. (25)
 - 7 Palonosetron.mp. (0)
 - 8 Aloxi.mp. (0)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (27)
 - 10 from 9 keep 1-27 (27)
-

Database: Ovid MEDLINE(R) <1966 to February Week 1 2005>

Search Strategy:

-
- 1 Dolasetron.mp. (162)
 - 2 Anzemet.mp. (7)
 - 3 Granisetron.mp. (942)
 - 4 Kytril.mp. (33)
 - 5 Zofran.mp. (55)
 - 6 Ondansetron.mp. (2337)
 - 7 Palonosetron.mp. (25)
 - 8 Aloxi.mp. (4)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (3073)
 - 10 exp COHORT STUDIES/ (511895)
 - 11 Retrospective Studies/ (211976)
 - 12 ((cohort or prospective or longitudinal or retrospective) adj (stud\$ or analy\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (487353)
 - 13 10 or 11 or 12 (712751)
 - 14 9 and 13 (322)
 - 15 from 14 keep 1-322 (322)
 - 16 from 15 keep 1-322 (322)
-

Database: Ovid MEDLINE(R) <1966 to February Week 1 2005>

Search Strategy:

-
- 1 Dolasetron.mp. (162)
 - 2 Anzemet.mp. (7)
 - 3 Granisetron.mp. (942)
 - 4 Kytril.mp. (33)
 - 5 Zofran.mp. (55)
 - 6 Ondansetron.mp. (2337)
 - 7 Palonosetron.mp. (25)
 - 8 Aloxi.mp. (4)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (3073)
 - 10 limit 9 to randomized controlled trial (858)
 - 11 limit 10 to humans (856)
 - 12 limit 11 to english language (781)
 - 13 limit 11 to abstracts (838)
 - 14 12 or 13 (855)
 - 15 from 14 keep 1-855 (855)
-

Search strategy Update # 1

Database: Ovid MEDLINE(R) <1996 to May Week 2 2008>

Search Strategy:

-
- 1 Dolasetron.mp. (199)
 - 2 Anzemet.mp. (7)
 - 3 Granisetron.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (718)
 - 4 Kytril.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (21)
 - 5 Zofran.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (34)
 - 6 Ondansetron.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1715)
 - 7 Palonosetron.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (80)
 - 8 Aloxi.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (2335)
 - 10 limit 9 to randomized controlled trial (769)
 - 11 limit 10 to humans (767)
 - 12 limit 11 to english language (704)
 - 13 limit 11 to abstracts (759)
 - 14 12 or 13 (767)
 - 15 (2005\$ or 2006\$ or 2007\$ or 2008\$.ed. (2169387)
 - 16 14 and 15 (155)
 - 17 from 16 keep 1-155 (155)
-

Database: Ovid MEDLINE(R) <1996 to May Week 2 2008>

Search Strategy:

-
- 1 Dolasetron.mp. (199)
 - 2 Anzemet.mp. (7)
 - 3 Granisetron.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (718)
 - 4 Kytril.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (21)
 - 5 Zofran.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (34)
 - 6 Ondansetron.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1715)
 - 7 Palonosetron.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (80)
 - 8 Aloxi.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7)
 - 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (2335)
 - 10 exp COHORT STUDIES/ (400855)
 - 11 Retrospective Studies/ (203369)
 - 12 ((cohort or prospective or longitudinal or retrospective) adj (stud\$ or analy\$)).mp. (461731)
 - 13 10 or 11 or 12 (583482)
 - 14 9 and 13 (328)
 - 15 (2005\$ or 2006\$ or 2007\$ or 2008\$.ed. (2169387)
 - 16 14 and 15 (77)
 - 17 from 16 keep 1-77 (77)
-

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2008>
Search Strategy:

- 1 aprepitant.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (37)
- 2 granisetron.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (476)
- 3 dolasetron.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (126)
- 4 palonosetron.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (15)
- 5 ondansetron.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1221)
- 6 1 or 2 or 3 or 4 or 5 (1699)
- 7 limit 6 to yr="2005 - 2008" (186)
- 8 from 7 keep 1-186 (186)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2008>
Search Strategy:

- 1 Dolasetron.mp. (5)
- 2 Anzemet.mp. (0)
- 3 Granisetron.mp. [mp=title, full text, keywords] (13)
- 4 Kytril.mp. [mp=title, full text, keywords] (0)
- 5 Zofran.mp. [mp=title, full text, keywords] (0)
- 6 Ondansetron.mp. [mp=title, full text, keywords] (33)
- 7 Palonosetron.mp. [mp=title, full text, keywords] (0)
- 8 Aloxi.mp. [mp=title, full text, keywords] (0)
- 9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (35)
- 10 from 9 keep 1-35 (35)

Aprepitant Searches

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2005>
Search Strategy:

- 1 aprepitant.mp. (14)
- 2 emend.mp. (4)
- 3 1 or 2 (14)
- 4 limit 3 to (humans and english language) [Limit not valid; records were retained] (14)
- 5 [from 4 keep 1-61] (0)
- 6 [from 4 keep 1-61] (0)
- 7 [from 4 keep 1-61] (0)
- 8 from 4 keep 1-14 (14)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2nd Quarter 2005>
Search Strategy:

- 1 aprepitant.mp. (1)
- 2 emend.mp. (0)
- 3 1 or 2 (1)
- 4 limit 3 to (humans and english language) [Limit not valid; records were retained] (1)

- 5 [from 4 keep 1-61] (0)
- 6 [from 4 keep 1-61] (0)
- 7 [from 4 keep 1-61] (0)
- 8 [from 4 keep 1-14] (0)
- 9 from 4 keep 1 (1)

Database: Ovid MEDLINE(R) <1996 to April Week 4 2005>

Search Strategy:

-
- 1 aprepitant.mp. (74)
 - 2 emend.mp. (41)
 - 3 1 or 2 (103)
 - 4 limit 3 to (humans and english language) (61)
 - 5 from 4 keep 1-61 (61)
 - 6 from 4 keep 1-61 (61)
 - 7 from 4 keep 1-61 (61)

Aprepitant Searches Update #1

Database: Ovid MEDLINE(R) <1996 to May Week 2 2008>

Search Strategy:

-
- 1 aprepitant.mp. (177)
 - 2 emend.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (70)
 - 3 1 or 2 (222)
 - 4 ((2005\$ or 2006\$ or 2007\$ or 2008\$) not (200501\$ or 200502\$ or 200503\$)).ed. (2018019)
 - 5 3 and 4 (122)
 - 6 from 5 keep 1-122 (122)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <2nd Quarter 2008>

Search Strategy:

-
- 1 aprepitant.mp. (37)
 - 2 emend.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (4)
 - 3 1 or 2 (37)
 - 4 from 3 keep 1-37 (37)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2008>

Search Strategy:

-
- 1 aprepitant.mp. (2)
 - 2 emend.mp. [mp=title, abstract, full text, keywords, caption text] (1)
 - 3 1 or 2 (2)

4 from 3 keep 1-2 (2)

Searches repeated In October 2008 for Update 1

Database: Ovid MEDLINE(R) <1996 to October Week 1 2008>

Search Strategy:

-
- 1 aprepitant.mp. (187)
 - 2 emend.mp. (70)
 - 3 Dolasetron.mp. (205)
 - 4 Anzemet.mp. (7)
 - 5 Granisetron.mp. (736)
 - 6 Kytril.mp. (21)
 - 7 Zofran.mp. (34)
 - 8 Ondansetron.mp. (1760)
 - 9 Palonosetron.mp. (91)
 - 10 Aloxi.mp. (7)
 - 11 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5 (2563)
 - 12 limit 11 to (english language and humans) (1660)
 - 13 limit 12 to randomized controlled trial (741)
 - 14 (200805\$ or 200806\$ or 200807\$ or 200808\$ or 200809\$ or 200810\$.ed. (287150)
 - 15 13 and 14 (21)
 - 16 from 15 keep 1-21 (21)

Database: Ovid MEDLINE(R) <1996 to October Week 1 2008>

Search Strategy:

-
- 1 aprepitant.mp. (187)
 - 2 emend.mp. (70)
 - 3 Dolasetron.mp. (205)
 - 4 Anzemet.mp. (7)
 - 5 Granisetron.mp. (736)
 - 6 Kytril.mp. (21)
 - 7 Zofran.mp. (34)
 - 8 Ondansetron.mp. (1760)
 - 9 Palonosetron.mp. (91)
 - 10 Aloxi.mp. (7)
 - 11 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5 (2563)
 - 12 limit 11 to (english language and humans) (1660)
 - 13 exp Cohort Studies/ (417358)
 - 14 Retrospective studies/ (212548)
 - 15 ((cohort or prospective or longitudinal or retrospective) adj (stud\$ or analy\$)).mp. (482325)
 - 16 13 or 15 or 14 (608038)
 - 17 16 and 12 (317)
 - 18 (200805\$ or 200806\$ or 200807\$ or 200808\$ or 200809\$ or 200810\$.ed. (287150)
 - 19 18 and 17 (15)

20 from 19 keep 1-15 (15)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2008>
Search Strategy:

-
- 1 aprepitant.mp. (40)
 - 2 emend.mp. (4)
 - 3 Dolasetron.mp. (126)
 - 4 Anzemet.mp. (5)
 - 5 Granisetron.mp. (479)
 - 6 Kytril.mp. (14)
 - 7 Zofran.mp. (24)
 - 8 Ondansetron.mp. (1228)
 - 9 Palonosetron.mp. (16)
 - 10 Aloxi.mp. (1)
 - 11 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5 (1711)
 - 12 limit 11 to yr="2007 - 2008" (73)
 - 13 from 12 keep 1-73 (73)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2008>
Search Strategy:

-
- 1 aprepitant.mp. (2)
 - 2 emend.mp. (1)
 - 3 Dolasetron.mp. (4)
 - 4 Anzemet.mp. (0)
 - 5 Granisetron.mp. (7)
 - 6 Kytril.mp. (0)
 - 7 Zofran.mp. (0)
 - 8 Ondansetron.mp. (17)
 - 9 Palonosetron.mp. (3)
 - 10 Aloxi.mp. (0)
 - 11 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5 (18)
 - 12 limit 11 to yr="2007 - 2008" (4)
 - 13 from 12 keep 1-4 (4)
 - 14 from 13 keep 1-4 (4)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2008>
Search Strategy:

-
- 1 aprepitant.mp. (0)
 - 2 emend.mp. (0)
 - 3 Dolasetron.mp. (5)
 - 4 Anzemet.mp. (0)
 - 5 Granisetron.mp. (13)
 - 6 Kytril.mp. (0)

- 7 Zofran.mp. (0)
- 8 Ondansetron.mp. (33)
- 9 Palonosetron.mp. (0)
- 10 Aloxi.mp. (0)
- 11 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5 (35)
- 12 from 11 keep 1-35 (35)

Appendix E. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination^{1,2} criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of “good,” “fair,” or “poor”. Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. It is usually considered sufficient if a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

- Computer-generated random numbers
- Random numbers tables

Inferior approaches to sequence generation:

- Use of alternation, case record number, birth date, or day of week

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

- Centralized or pharmacy-controlled randomization
- Serially-numbered identical containers
- On-site computer based system with a randomization sequence that is not readable until allocation

Inferior approaches to concealment of randomization:

- Use of alternation, case record number, birth date, or day of week
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)
2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Was the duration of follow-up reasonable for investigated events?

References

1. Center for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD Report*. 2001(4).
2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. . *American Journal of Preventive Medicine*. 2001;20(3 Suppl):21-35.

Appendix F. Excluded studies

Original report

Exclusion codes 1: Foreign language, 2: Wrong outcome, 3: Wrong intervention, 4: Wrong population, 5: Wrong publication type, 6: Wrong study design, 8: Outdated systematic review

Excluded Studies	Exclusion code #
Head-to-head trials	
Adamo V, Aiello R, Altavilla G, et al. Ondansetron (OND) vs granisetron (GRA) in the control of chemotherapy-induced acute emesis. <i>European Journal of Cancer</i> . 1995;31(178);(Suppl 5):S256 Abs. 1225.	5
Audhuy B, Cappelaere P, Claverie N. Double-blind, comparative trial of the anti-emetic efficacy of two IV doses of dolasetron mesilate (DM) and granisetron (G) after infusion of high-dose cisplatin chemotherapy (CT). <i>Eur-J-Cancer</i> . 1995;31(192);(Suppl 5):S253 Abs.1213.	5
Audhuy B, Cappelaere P, Claverie N. Double-blind comparison of the antiemetic efficacy of two single IV doses of dolasetron and one IV dose of granisetron after cisplatin (80 mg/m ²) chemotherapy. <i>Supportive Care in Cancer</i> . 1995;3(338):21.	5
Beck T, Bryson J, Crawford K, McQuade B. Oral ondansetron (OND) for the prevention of nausea and vomiting (n&v) associated with cisplatin (CDDP) chemotherapy (CT). <i>Ann-Oncol</i> . 1998;9(Suppl 4):142.	5
Bianchi A, Maccio A, Curreli L, Ghiani M, Santona MC, Astaro G. Comparison of granisetron vs ondansetron vs tropisetron in the prophylaxis of acute nausea and vomiting induced by high-dose cisplatin for treatment of primary head and neck cancer: an open randomized controlled trial. <i>Ann-Oncol</i> . 1996;7(Suppl 5):135.	5
Bonnetterre J, Hecquet B, Fenaux I, et al. Granisetron (IV) compared with ondansetron (IV plus oral) in the prevention of nausea and vomiting induced by moderately-emetogenic chemotherapy. A cross-over study. <i>Bulletin du Cancer</i> . 1995;82(12):1038-1043.	1
Brohee D, Mesina F. Comparison of dexamethasone (DXM) + granisetron (G) or + ondansetron (O) in cancer patients treated with moderately emetic cytotoxics. <i>European Journal of Cancer</i> . 1995;31(178);(Suppl 5):S257 Abs.1231.	5
Bubalo J, Seelig F, Karbowicz S, Maziarz RT. Randomized open-label trial of dolasetron for the control of nausea and vomiting associated with high-dose chemotherapy with hematopoietic stem cell transplantation. <i>Biology of Blood and Marrow Transplantation</i> . 2001;7(8):439-445.	3
Cho JY, Park JO, Rha SY, Yoo NC, Kim JH, Roh JK. A comparative study of granisetron i.v. versus ondansetron i.v./oral in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy. <i>Ann-Oncol</i> . 1996;7(Suppl 5):142.	5

Excluded Studies	Exclusion code #
Del Favero A, Bergerat J, Chemaissani A, Dressler H. Single oral doses of dolasetron versus multiple doses of ondansetron in preventing emesis after moderately emetogenic chemotherapy. Supportive Care in Cancer. 1995A;3(337):19.	5
Fauser AA, Bergerat Cocquyt V, Chemaissani A, Del Favero A, Dressler HT. Double-blind, comparison trial of four single oral doses of dolasetron mesilate (DM) and multiple doses of ondansetron (OND) for emesis prevention after moderately emetogenic chemotherapy (CT). Eur-J-Cancer. 1995;31ƒ(Suppl 5):S254 Abs. 1217.	5
Fumoleau P, Giovannini M, Rolland F, Votan B, Paillarse JM. Ondansetron suppository: An effective treatment for the prevention of emetic disorders induced by cisplatin-based chemotherapy. Oral Oncology. 1997;33(5):354-358.	6
Goode K, Laeder C. A comparison of the efficacy of intravenous granisetron and ondansetron in preventing postoperative vomiting in pediatric tonsillectomy and adenoidectomy procedures. Journal of the American Association of Nurse Anesthetists. 1997;65(4):385-386.	5
Gralla RJ, Popovic W, et al. Can an oral antiemetic regimen be as effective as intravenous treatment against cisplatin: results of a 1054 patient randomized study of oral granisetron versus IV ondansetron. Proc Annu Meet Am Soc Clin Oncol. 1997.	5
Huang XB, Hou M, Li H, et al. Randomized comparison of granisetron and ondansetron in the prevention of nausea and vomiting induced by cisplatin. West China Journal of Pharmaceutical Sciences. 2002;17(6):419-421.	1
Huston CL, Sheridan CA, Ungard SD, et al. Comparison of oral granisetron, intravenous granisetron, and droperidol in the prevention of nausea and vomiting after outpatient laparoscopic procedures. Journal of the American Association of Nurse Anesthetists. 1996;64(5):437-438.	5
Lacerda JF, Martins C, Carmo JA, et al. Randomized trial of ondansetron, granisetron, and tropisetron in the prevention of acute nausea and vomiting. Transplantation Proceedings. 2000;32(8):2680-2681.	5
Lacerda JMF, Matrins C, Carmo JA, et al. Randomized trial of ondanestron (OND), granisetron (GRA) and tropisetron (TRO) in the prevention of acute nausea and vomiting in stem cell transplantation (SCT) [abstract]. Blood. 1999;94(10 Suppl 1):150a.	5
Lofters WS, Zee B. Dolasetron (DOL) vs ondansetron (OND) with and without dexamethasone (DEX) in the prevention of nausea (N) and vomiting (V) in patients (PTS) receiving moderately emetogenic chemotherapy (MEC). The Symptom Control Committee of the National Cancer Institute of Canada Clinical Trials Group and Nordic Merrel Dow Research Canada. Supportive Care in Cancer. 1995;3(338).	5

Excluded Studies	Exclusion code #
Lofters WS, Zee B. Dolasetron (DOL) vs ondansetron (OND) with and without dexamethasone (DEX) in the prevention of nausea (N) and vomiting (V) in patients (pts) receiving moderately emetogenic chemotherapy (MEC). Eur-J-Cancer. 1995A;31?(Suppl 5):S252 Abs. 1205.	5
Mabro M, Kerbrat P. Comparative trial of oral granisetron and intravenous ondansetron in patients receiving chemotherapy for breast cancer. Bulletin du Cancer. 1999;86(3):295-301.	1
Mantovani G, Maccio A, Bianchi A, et al. Comparison of granisetron vs ondansetron vs tropisetron in the prophylaxis of acute nausea and vomiting induced by highly emetogenic chemotherapy (high-dose cisplatin) for treatment of primary head and neck cancer: an open cross-over randomized controlled trial. Eur-J-Cancer. 1995;31?(Suppl 5):S252 Abs. 1206.	5
Massidda B, Ionta MT. Tropisetron vs granisetron vs ondansetron, all three in single i.v. bolus, in non-cisplatin acute and delayed emesis. A randomized study. Ann-Oncol. 1996;7(Suppl 1):141.	5
Metaxari M, Petrou A, Zeaki M, Psaromichalaki M, Askitopoulou H. Prophylactic perioperative antiemesis in thyroid surgery: a randomised, double-blind comparison of granisetron, ondansetron and tropisetron [abstract]. Br J Anaesth. 1999;82(1):123.	5
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Smith E, Wasiak J, Boyle M. Prophylactic antiemetic therapy in the emergency and ambulance setting for preventing opioid induced nausea and vomiting. <i>Cochrane Database of Systematic Reviews</i> . 2004;4.	4
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Excluded Studies: Update 1

Excluded studies	Exclusion code #
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Rosow CE, Haspel KL, Smith SE, Grecu L, Bittner EA. Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. <i>Anesthesia & Analgesia</i> . of contents, 2008 May 2008;106(5):1407-1409.	2
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Teran L, Hawkins JK. The effectiveness of inhalation isopropyl alcohol vs granisetron for the prevention of postoperative nausea and vomiting. <i>AANA Journal</i> . Dec 2007;75(6):417-422.	2
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Excluded studies	Exclusion code #
Bano F, Zafar S, Aftab S, Haider S. Dexamethasone plus ondansetron for prevention of postoperative nausea and vomiting in patients undergoing laparoscopic cholecystectomy: a comparison with dexamethasone alone. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan. May 2008;18(5):265-269.	3
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D'Angelo R, Philip B, Gan TJ, et al. A randomized, double-blind, close-ranging, pilot study of intravenous granisetron in the prevention of postoperative nausea and vomiting in patients abdominal hysterectomy. European Journal of Anaesthesiology. Oct 2005;22(10):774-779.	2
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Subramaniam K, Pandia MP, Dash M, et al. Scheduled prophylactic ondansetron administration did not improve its antiemetic efficacy after intracranial tumour resection surgery in children. European Journal of Anaesthesiology. 2007;24(7):615-619.	2
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Excluded studies	Exclusion code #
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Hasler SB, Hirt A, Ridolfi Luethy A, Leibundgut KK, Ammann RA. Safety of ondansetron loading doses in children with cancer. <i>Supportive Care in Cancer</i> . May 2008;16(5):469-475.	2
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Piwko C, Lasry A, Alanezi K, Coyte PC, Ungar WJ. Economic evaluation of ondansetron vs dimenhydrinate for prevention of postoperative vomiting in children undergoing strabismus surgery. <i>Paediatric Anaesthesia</i> . Sep 2005;15(9):755-761.	2
Siu SS, Chan MT, Lau TK. Placental transfer of ondansetron during early human pregnancy. <i>Clinical Pharmacokinetics</i> . 2006;45(4):419-423.	3
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Alhashimi, Alhashimi, Fedorowicz. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents [Systematic Review]. <i>Cochrane Database of Systematic Reviews</i> . 2008;1:1.	4
Carlisle, Jb, Stevenson, Ca. Drugs for preventing postoperative nausea and vomiting [Systematic Review]. <i>Cochrane Database of Systematic Reviews</i> . 2008;1:1.	3
Figueredo E, Canosa L. Prophylactic ondansetron for postoperative emesis. Meta-analysis of its effectiveness in patients with previous history of postoperative nausea and vomiting. <i>Acta Anaesthesiologica Scandinavica</i> . 1999;43(6):637-644.	6
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