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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Published in a separate document.

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 antiserotoninergic 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				
			Postoperative			
		Chemotherapy	Prevention	Treatment	Radiation	Pregnancy
Aprepitant/ fosaprepitant (Emend)	Oral capsule	X[a,b]	X			
	Injection	X[a,b]				
Dolasetron (Anzamet)	Oral tablet	X[a]	X			
	Injection	X[a,b]	X	X		
Granisetron (Kytril) (Sancuso)[c]	Oral tablet	X[a,b]			X	
	Injection	X[a,b]	X	X		
	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 groups, 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 questions(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.

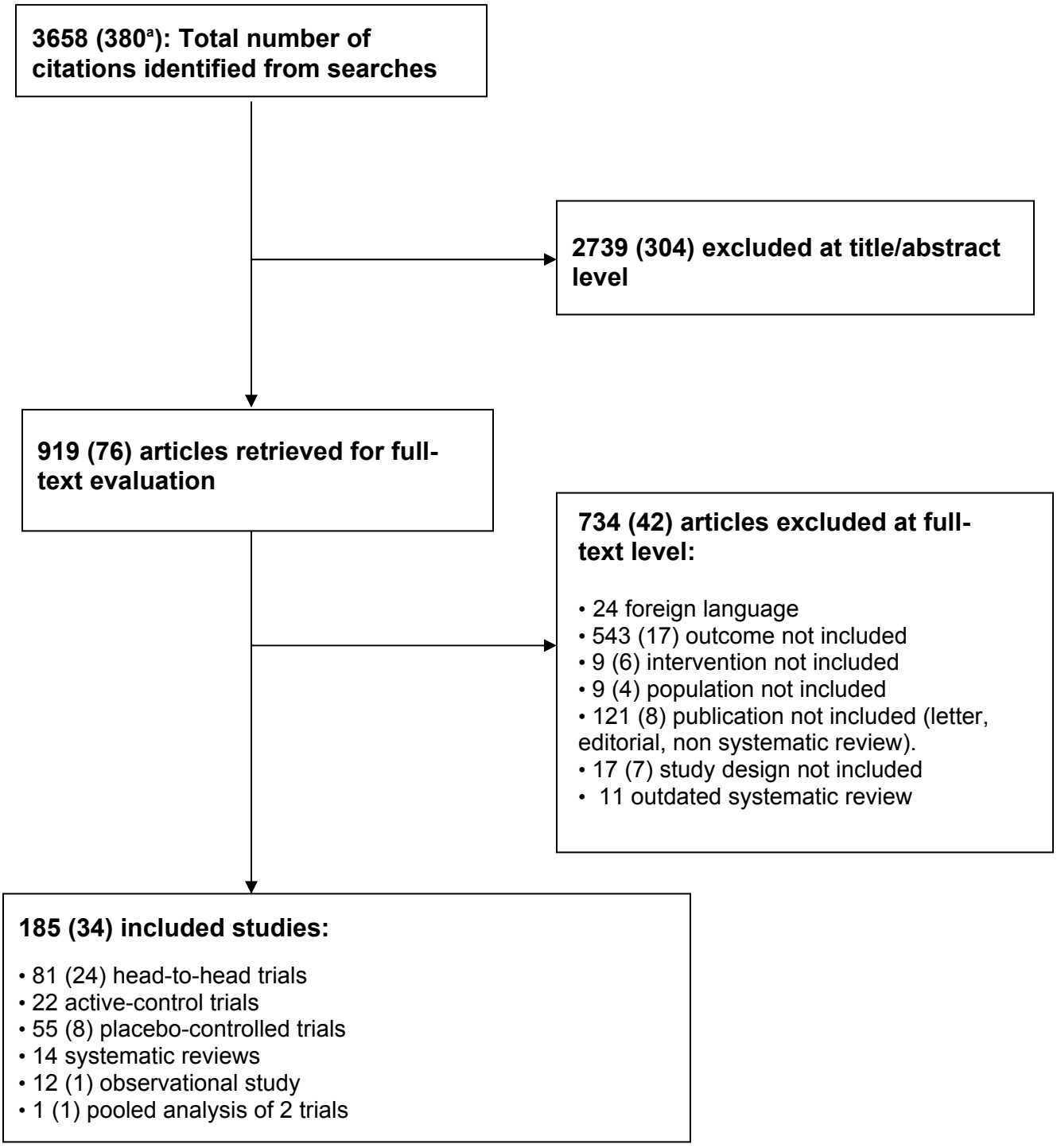
Peer reviewers have a maximum of 3 weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the Drug Effectiveness Review Project team to address all comments adequately. The original 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.

    - Prevention and treatment of postoperative nausea and vomiting
        - Tolerability and safety outcomes were rarely reported in trials of adults and absent in trials of children.
        - No consistent significant differences were seen in adults for overall adverse events, withdrawals due to adverse events, or any particular adverse event.
- Gaps in direct comparative evidence
    - Chemotherapy-induced nausea and vomiting
        - Trials in adults or children undergoing chemotherapy did not report quality of life, patient satisfaction, or hospital stay outcomes; evidence from placebo-controlled trials is inconclusive.
    - Prevention and treatment of postoperative nausea and vomiting
        - Treatment of established postoperative nausea and vomiting in children:
            - Ondansetron was superior to placebo and similar to droperidol in improving total control outcomes (1 trial each).
        - Patient satisfaction, quality of life, and hospital stay outcomes:
            - Dolasetron is the only 5-HT3 antagonist that has consistently and significantly improved patient satisfaction outcomes compared with placebo in adults (3 out of 3 trials).
            - Granisetron (3 trials) and ondansetron (2 trials) were superior to placebo in reducing hospital stay outcomes in children.
    - Radiation therapy-induced nausea and vomiting
        - No conclusions can be made regarding the indirect comparative efficacy and safety of dolasetron, granisetron, and ondansetron (including the oral disintegrating tablet form) based on active-control and placebo-controlled trials due to heterogeneity in patient populations, drug comparisons, radiation therapy regimens, and outcome reporting.
    - Pregnancy-induced nausea and vomiting
        - One trial of ondansetron and promethazine in hospitalized women with hyperemesis gravidarum does not provide evidence of comparative efficacy or safety among newer antiemetics.
    - Serious adverse events
        - There were no differences between ondansetron and other antiemetics or other nonteratogenic drugs in number of live births, number of malformations, birth weight, or gestational age at birth in 176 pregnant women who were exposed to treatment during gestational weeks 5 to 9.
        - Ondansetron and droperidol were associated with similarly significant lengthening of the QTc interval in a prospective, nonrandomized study (20 ms compared with 17 ms).

Aprepitant

Direct comparisons

- Efficacy
    - Chemotherapy-induced nausea and vomiting
        - For acute, delayed, and combined periods, significantly more patients had complete response to a regimen of aprepitant 125 mg on day 1 and 80 mg on days 2 to 3 plus standard therapy of a 5-HT3 antagonist on day 1 and

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.

- 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.
- 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
  - 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
    - 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
    - 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.
    - 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.

  - Intravenous palonosetron 0.25 mg may be superior to intravenous ondansetron 8 mg/m^2 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 Primary malignancy	Percent female Mean age	Concomitant prophylaxis	Treatment	Percent with complete response[a] Acute (≤ 24 hrs)	 Delayed (> 24 hrs)
No emesis, nausea, or use of rescue medication						
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%	
No emesis or nausea						
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%
No emesis and none-mild nausea						
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
No emesis or rescue medication						
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	92%	49%
				O 32 mg IV qd		

[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 intravenous[55] or oral[56] 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			Acute response (≤ 24 hrs)	
Sample size Quality	1° malignancy Percent female Emetogenicity[a]	Dolasetron	Ondansetron	Other anti-emetic	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	*Acute*: 2.4 mg/kg IV qd *Delayed*: 200 mg po qd	*Acute:* 32 mg IV qd *Delayed:* 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/m^2) 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/m^2). 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 highly[60-63] or moderately[64] 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 moderately[66] and highly[67] 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 palonsetron 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, palonsetron 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 ≤ 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 palonsetron 0.75 mg dose.[74]

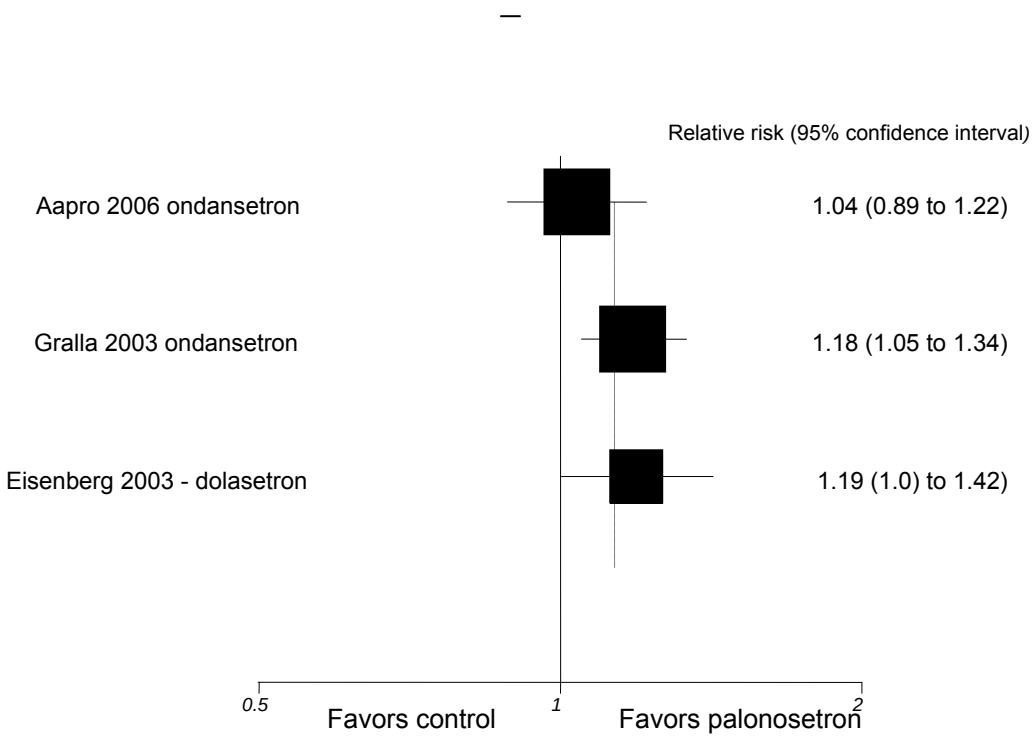
Quality-of-life assessments (using the Functional Living Index-Emesis tool; score range 1 to 1800) showed no statistically significant difference among the drugs within 24 hours. However, during days 2 to 4 in the 2 studies with more women and lower emetic chemotherapy regimens, palonosetron resulted 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/m^2 and intravenous granisetron 2 mg/m^2 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/m^2. 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/m^2 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 granisetron[95] 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 ondansetron[159] 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 dexamethasone[162] 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 one[141] 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.[153]

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 dolasetron[164] and granisetron[154] 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-control[165-168] 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 granisetron[168] 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 years[170] 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 trial[171] 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 granisetron[44] or dolasetron[57] 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 ondansetron[177-179] 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] Intervenous 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 granisetron[180] 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 granisetron[187] 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 review[190] 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. Theses 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 reviews[99] of earlier trials of granisetron[95] 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 granisetron[88] 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 NSAIDs[35] 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 (Anzamet®)	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 disintegrating tablet, oral solution	8 mg three times daily

[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 interval 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 (hear 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 ood 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 combing 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 measureable 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. European Journal of Cancer. 1995;31Ÿ(Suppl 5):S256 Abs. 1225.	5
Audhuy B, Cappelaeare 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). Eur-J-Cancer. 1995;31ƒ(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/m2) chemotherapy. Supportive Care in Cancer. 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). Ann-Oncol. 1998;9(Suppl 4):142.	5
Bianchi A, Maccio A, Curreli L, Ghiani M, Santona MC, Astara 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. Ann-Oncol. 1996;7(Suppl 5):135.	5
Bonneterre 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. Bulletin du Cancer. 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 cyctotoxics. European Journal of Cancer. 1995;31Ÿ(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. Biology of Blood and Marrow Transplantation. 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. Ann-Oncol. 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 chemotheraphy. 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 Commitee 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
Muller D, Armbruster W, Unkel W, Apfel CC, Bornfeld N, Peters J. Blockade nozizeptiver ocularer Afferenzen durch Retrobulbaranasthesie vermindert nicht Ubelkeit und Erbrechen nach Propofol- Remifentanil-Anasthesie. [Blocking nociceptive afferents by retrobulbar bupivacaine does not decrease nausea and vomiting after propofol-remifentanil anaesthesia]. Anasthesiol-Intensivmed-Notfallmed-Schmerzther. 2003;Anasthesiologie,-Intensivmedizin,-Notfallmedizin,-Schmerztherapie-AINS. 38(11):689-694.	1
Roila F, De Angelis V, De Marinis F, et al. Ondansetron vs granisetron, both combined with dexamethasone in the prevention of cisplatin-induced emesis. The Italian Group for Antiemetic research. Supportive Care in Cancer. 1995;3(337).	5
Scoponi CA, Torresi U, Di Giuseppe M, Giustozzi M. Are 5-HT3 antagonists a standard antiemetic treatment also in slightly and moderately emetogenic regimens? Oncologia. 1998;21(9):40-44.	1
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Ulusoy HO, Akturk G, Luleci N, Kalac N, Albayrak D. Prophylactic administration of ondansetron in emergency intraabdominal operations. Middle East Journal of Anesthesiology. 1996;13(5):513-526.	2
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Van Den Berg AA. The prophylactic antiemetic efficacy of prochlorperazine and ondansetron in nasal septal surgery: A randomized double-blind comparison. Anaesthesia and Intensive Care. 1996;24(5):538-545.	2
Van den Berg AA. A comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after tympanoplasty. Canadian Journal of Anaesthesia. 1996;43(9):939-945.	2
Volpe N, Gesini A, Collini S, et al. Single dose ondansetron for prevention of postoperative nausea and vomiting. Results from the Italian Multicentre Ondansetron Study. Drug Investigation. 1994;8(2):67-72.	2
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White LA, Vanarase M, Brockbank K, Barrett RF. Patient-controlled analgesia and postoperative nausea and vomiting: Efficacy of a continuous infusion of ondansetron. Anaesthesia. 2001;56(4):365-369.	2
Yazigi A, Chalhoub V, Madi-Jebara S, Haddad F, Hayek G. Prophylactic ondansetron is effective in the treatment of nausea and vomiting but not on pruritus after cesarean delivery with intrathecal sufentanil-morphine. Journal of Clinical Anesthesia. 2002;14(3):183-186.	2
Yuksek MS, Alici HA, Erdem AF, Cesur M. Comparison of prophylactic anti-emetic effects of ondansetron and dexamethasone in women undergoing day-case gynaecological laparoscopic surgery. Journal of International Medical Research. 2003;31(6):481-488.	2
Zajac K, Zajac M. Ondansetron can be highly effective in treatment of postoperative nausea and vomiting (phnv). Acta-Anaesthesiol-Scand. 1997;41(suppl 111):330.	2
Observational studies	
Aapro M, Bourke JP. Rapid intravenous administration of granisetron prior to chemotherapy is not arythmogenic: Results of a pilot study. European Journal of Cancer. 2003;39(7):927-931.	2
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Excluded Studies	Exclusion code #
Belle SV, Cocquyt V, Smet MD, et al. Comparison of a neurokinin-1 antagonist, L-758,298 {aprepitant}, to ondansetron in the prevention of cisplatin-induced emesis. Proc Annu Meet Am Soc Clin Oncol. Abstract # 198p. 1998.	5
Bernstein BJ, Ong C. Efficacy of a single 8-mg i.v. dose of ondansetron hydrochloride for preventing chemotherapy-induced emesis. American Journal of Health-System Pharmacy. 2002;59(7):650-652.	2
Berry WR, House KW, Lee JT, Plagge PB, Meshad MW, Grapski R. Results of a compassionate-use program using intravenous ondansetron to prevent nausea and vomiting in patients receiving emetogenic cancer chemotherapy. Seminars in Oncology. 1992;19(6 SUPPL. 15):33-37.	2
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Campora E, Oliva C, Mammoliti S, et al. Oral ondansetron (GR 38032F) for the control of CMF-induced emesis in the outpatient. Breast Cancer Research and Treatment. 1991;19(2):129-132.	2
Campora E, Vidili G, Oliva C, Ardizzoni A, Rosso R. Control of refractory, chemotherapy-induced emesis with the serotonin antagonist ondansetron (GR38032F). Oncology. 1991;48(5):403-405.	2
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Carmichael J, Harris AL. High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: Cardiac safety and tolerability. Anti-Cancer Drugs. 2003;14(9):739-744.	2
Carmichael J, Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. Cancer Chemotherapy and Pharmacology. 2004;53(2):123-128.	2
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Casper J, Casper S, Kohne-Wompner CH, Bokemeyer C, Hecker H, Schmoll - HJ. 5-HT3 antagonist ondansetron for the treatment of chemotherapy induced nausea and vomiting in an outpatient population. International Journal of Oncology. 1994;4(6):1283-1289.	2
Coates AS, Childs A, Cox K, et al. Severe vascular adverse effects with thrombocytopenia and renal failure following emetogenic chemotherapy and ondansetron. Annals of Oncology. 1992;3(9):719-722.	2

Excluded Studies	Exclusion code #
Cohen IJ, Zehavi N, Buchwald I, et al. Oral ondansetron: An effective ambulatory complement to intravenous ondansetron in the control of chemotherapy-induced nausea and vomiting in children. Pediatric Hematology and Oncology. 1995;12(1):67-72.	2
Conroy T, Cappelaere P, Fabbro M, et al. Acute antiemetic efficacy and safety of dolasetron mesylate, a 5-HT3 antagonist, in cancer patients treated with cisplatin. American Journal of Clinical Oncology: Cancer Clinical Trials. 1994;17(2):97-102.	2
Currow DC, Coughlan M, Fardell B, Cooney NJ. Use of ondansetron in palliative medicine. Journal of Pain and Symptom Management. 1997;13(5):302-307.	2
De Wet M, Falkson G, Rapoport BL. Repeated use of granisetron in patients receiving cytostatic agents. Cancer. 1993;71(12):4043-4049.	2
Einhorn LH, Nagy C, Werner K, Finn AL. Ondansetron: a new antiemetic for patients receiving cisplatin chemotherapy. J Clin Oncol. Apr 1990;8(4):731-735.	2
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Framarino dei Malatesta M, Veneziano M, Fiorelli C, et al. Ondansetron in chemotherapy-induced emesis - Our experience. European Journal of Gynaecological Oncology. 1995;16(2):97-106.	2
Franchi M, Donadello N, Zanaboni F, Tusei A, Scorbati E. Oral ondansetron and intravenous dexamethasone in the prevention of cisplatin-induced emesis. A phase II trial in women. Oncology. 1995;52(6):509-512.	2
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Gratz I, Allen E, Afshar M, Joslyn AF, Buxbaum J, Prilliman B. The effects of the menstrual cycle on the incidence of emesis and efficacy of ondansetron. Anesthesia and Analgesia. 1996;83(3):565-569.	6
Grote TH, Pineda LF, Figlin RA, et al. Oral dolasetron mesylate in patients receiving moderately emetogenic platinum-containing chemotherapy. Cancer Journal from Scientific American. 1997;3(1):45-51.	6

Excluded Studies	Exclusion code #
Harvey VJ, Evans BD, Mitchell PLR, et al. Reduction of carboplatin induced emesis by ondansetron. British Journal of Cancer. 1991;63(6):942-944.	2
Henriksson R, Lomberg H, Israelsson G, Zackrisson B, Franzen L. The effect of ondansetron on radiation-induced emesis and diarrhoea. Acta Oncologica. 1992;31(7):767-769.	2
Hesketh PJ, Gandara DR, Hesketh AM, et al. Dose-ranging evaluation of the antiemetic efficacy of intravenous dolasetron in patients receiving chemotherapy with doxorubicin or cyclophosphamide. Supportive Care in Cancer. 1996;4(2):141-146.	2
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Honkavaara P, Pyykko I, Rutanen EM. Increased incidence of retching and vomiting during periovulatory phase after middle ear surgery. Canadian Journal of Anaesthesia. 1996;43(11):1108-1114.	2
Hunter AE, Prentice HG, Pothecary K, et al. Granisetron, a selective 5-HT3 receptor antagonist, for the prevention of radiation induced emesis during total body irradiation. Bone Marrow Transplantation. 1991;7(6):439-441.	6
Jacobson SJ, Shore RW, Greenberg M, Spielberg SP. The efficacy and safety of granisetron in pediatric cancer patients who had failed standard antiemetic therapy during anticancer chemotherapy. American Journal of Pediatric Hematology/Oncology. 1994;16(3):231-235.	2
Jantunen IT, Kataja VV, Uhonen TT, Parviainen T. Effects of granisetron with doxorubicin or epirubicin on ECG intervals. Cancer Chemotherapy and Pharmacology. 1996;37(5):502-504.	2
Jichang Z, Binghe X, Aiping Z. Phase III clinical studies with ondansetron (Qilu) in the prophylaxis of nausea and vomiting induced by non-cisplatin chemotherapy. Chinese Journal of Oncology. 1997;19(6):460-462.	1
Jurgens H, McQuade B. Ondansetron as prophylaxis for chemotherapy and radiotherapy-induced emesis in children. Oncology. 1992;49(4):279-285.	6
Kris MG. Phase II trials of ondansetron with high-dose cisplatin. Seminars in Oncology. 1992;19(4 SUPPL. 10):23-27.	2
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Kris MG, Grunberg SM, Gralla RJ, et al. Dose-ranging evaluation of the serotonin antagonist dolasetron mesylate in patients receiving high-dose cisplatin. Journal of Clinical Oncology. 1994;12(5):1045-1049.	2

Excluded Studies	Exclusion code #
Lemerle J, Amaral D, Southall DP, Upward J, Murdoch RD. Efficacy and safety of granisetron in the prevention of chemotherapy-induced emesis in paediatric patients. European Journal of Cancer. 1991;27(9):1081-1083.	2
Lippens RJJ, Broeders GCJM. Ondansetron in radiation therapy of brain tumor in children. Pediatric Hematology and Oncology. 1996;13(3):247-252.	2
Martin AR, Carides AD, Pearson JD, et al. Functional relevance of antiemetic control. Experience using the FLIE questionnaire in a randomised study of the NK-1 antagonist aprepitant. European Journal of Cancer. 2003;39(10):1395-1401.	2
Martini F, Milandri C, Turci P, Gentilini P. Vascular complications in patients receiving chemotherapy: What role do third generation antiemetics play? Oncology Reports. 1995;2(4):553-555.	2
McQueen KD, Milton JD. Multicenter postmarketing surveillance of ondansetron therapy in pediatric patients. Annals of Pharmacotherapy. 1994;28(1):85-92.	2
Merrouche Y, Catimel G, Rebattu P, et al. A phase I antiemetic study of MDL 73,147EF, a novel 5-hydroxytryptamine antagonist in cancer patients receiving emetogenic chemotherapy. Annals of Oncology. 1994;5(6):549-551.	2
Parikh PM, Shah SR, Shah SC, et al. Preliminary experience with use of a selective 5HT3 receptor antagonist (ondansetron) to prevent high dose chemotherapy induced emesis. Indian Journal of Cancer. 1996;33(1):17-20.	2
Peters II MD, Long KS, Patel HS, Reitz JA, Jessen LM, Emhart GC. Multicenter evaluation of ondansetron use in hospitalized oncology patients. American Journal of Hospital Pharmacy. 1993;50(6):1164-1170.	2
Roberts JT. Ondansetron in the control of refractory emesis following radiotherapy. Clin Oncol (R Coll Radiol). Jan 1992;4(1):67-68.	2
Roila F, Bracarda S, Tonato M, et al. Ondansetron (GR38032) in the prophylaxis of acute and delayed cisplatin-induced emesis. Clin Oncol (R Coll Radiol). Sep 1990;2(5):268-272.	2
Rosso R, Campora E, Cetto G, Fosser V, Marangolo M, Oliva C. Oral ondansetron (GR 38032F) for the control of acute and delayed cyclophosphamide-induced emesis. Anticancer Research. 1991;11(2):937-939.	2
Schwella N, Konig V, Schwerdtfeger R, et al. Ondansetron for efficient emesis control during total body irradiation. Bone Marrow Transplantation. 1994;13(2):169-171.	2
Seynaeve C, de Mulder PH, Lane-Allman E, van Liessum PA, Verweij J. The 5-HT3 receptor antagonist ondansetron re-establishes control in refractory emesis induced by non-cisplatin chemotherapy. Clinical Oncology (Royal College of Radiologists). 1991;3(4):199-203.	2
Smith DB, Newlands ES, Rustin GJS, et al. A phase I/II study of the 5-HT3 antagonist GR38032F in the anti-emetic prophylaxis of patients receiving high-dose cisplatin chemotherapy. Cancer Chemotherapy and Pharmacology. 1990;25(4):291-294.	2

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Smith DB, Rustin GJ, Howells N, Lambert HE, McQuade B. A phase II study of ondansetron as antiemetic prophylaxis in patients receiving carboplatin for advanced ovarian cancer. The North Thames Ovary Group. Ann Oncol. Sep 1991;2(8):607-608.	2
Sohara N, Takagi H, Abe T, et al. Nausea and vomiting induced by arterial chemo-embolization in patients with hepatocellular carcinoma and the antiemetic effect of ondansetron hydrochloride. Supportive Care in Cancer. 1999;7(2):84-88.	2
Steiner M, Yorgason RZ, Vermeulen LC, Theisen J. Patient outcomes after therapeutic interchange of dolasetron for granisetron. American Journal of Health-System Pharmacy. 2003;60(10):1023-1028.	2
Stoltz R, Cyong J-C, Shah A, Parisi S. Pharmacokinetic and Safety Evaluation of Palonosetron, a 5-Hydroxytryptamine-3 Receptor Antagonist, in U.S. and Japanese Healthy Subjects. Journal of Clinical Pharmacology. 2004;44(5):520-531.	4
Togo S, Akiyama H, Yamaguchi S, Ichikawa Y, Ike H, Shimada H. Clinical evaluation of granisetron as an inhibitor of nausea and vomiting induced by oral anticancer drugs. Oncology Reports. 2002;9(2):277-282.	2
Tolan MM, Fuhrman TM, Tsueda K, Lippmann SB. Perioperative extrapyramidal reactions associated with ondansetron. Anesthesiology. 1999;90(1):340-341.	6
Tzekova VI, Velikova MT, Koynov KD. Granisetron in repeated cycles of chemotherapy with platinum. Neoplasma. 1998;45(1):46-49.	2
Veneziano M, Framarino dei Malatesta M, Bandiera AF, Fiorelli C, Galati M, Paolucci A. Ondansetron-induced headache Our experience in gynecological cancer. European Journal of Gynaecological Oncology. 1995;16(3):203-207.	2
Walker JB. Efficacy of single-dose intravenous dolasetron versus ondansetron in the prevention of postoperative nausea and vomiting. Clinical Therapeutics. 2001;23(6):932-938.	2
Witherow P, Wilson K. Using ondansetron with pediatric patients undergoing total body irradiation. Oncol Nurs Forum. Nov-Dec 1991;18(8):1416-1417.	5
Systematic Reviews	
Antonarakis ES, Evans JL, Heard GF, Noonan LM, Pizer BL, Hain RDW. Prophylaxis of acute chemotherapy-induced nausea and vomiting in children with cancer: What is the evidence? Pediatric Blood and Cancer. 2004;43(6):651-658.	8
Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: A review of published trials. British Medical Journal. 1995;311(7009):844-846.	8
Carlisle J, Schousboe BMB, Moller A, Pedersen T. Drugs for preventing postoperative nausea and vomiting. Cochrane Database of Systematic Reviews. 2004;4.	2
Constenla M. 5-HT3 receptor antagonists for prevention of late acute-onset emesis. Annals of Pharmacotherapy. 2004;38(10):1683-1691.	8

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Cox F. Systematic review of ondansetron for the prevention and treatment of postoperative nausea and vomiting in adults. British Journal of Theatre Nursing. 1999;9(12):556-566.	8
Del Giglio A, Soares HP, Caparroz C, Castro PC. Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting: Results of a meta-analysis of randomized controlled trials. Cancer. 2000;89(11):2301-2308.	8
Figueredo ED, Canosa LG. Ondansetron in the prophylaxis of postoperative vomiting: A meta- analysis. Journal of Clinical Anesthesia. 1998;10(3):211-221.	8
Jewell D, Young G, Hall PF. Review: Antiemetic drugs reduce nausea in early pregnancy. Evidence-Based Medicine. 2002;7:155%N 155.	5
Kazemi-Kjellberg F, Henzi I, Tramer MR. Treatment of established postoperative nausea and vomiting: A quantitative systematic review. BMC Anesthesiology. 2001;1(-).	8
Laplanche A, Gerondeau N. Role of ondansetron in cancerology PLACE DE L'ONDANSETRON EN CANCEROLOGIE. Bulletin du Cancer. 1993;80(7):568-576."	1
Loewen PS, Marra CA, Zed PJ. 5-HT3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting. Canadian Journal of Anesthesia. 2000;47(10):1008-1018.	3
Massaro AM, Lenz KL. Aprepitant: a novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother. Jan 2005;39(1):77-85.	8
Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine3 receptor antagonists. Annals of Pharmacotherapy. 2003;37(9):1276-1286.	8
Pham L, Langford J, Williams K. 5-HT3 Antagonists in the Treatment of Postoperative Nausea and Vomiting. Journal of Pharmacy Practice and Research. 2003;33(4):275-278.	8
Smith E, Wasiak J, Boyle M. Prophylactic antiemetic therapy in the emergency and ambulance setting for preventing opioid induced nausea and vomiting. Cochrane Database of Systematic Reviews. 2004;4.	4
Tramer MR, Moore RA, Reynolds DJM, McQuay HJ. A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting. British Medical Journal. 1997;314(7087):1088-1092.	2
Warr D, Bramwell V, Anderson D, Charette M. Use of 5-HT3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapy. Current Oncology. 2001;8(2):69-82.	8

Excluded Studies: Update 1

Excluded studies	Exclusion code #
Head-to-head trial	
Buyukavci M, Olgun H, Ceviz N. The effects of ondansetron and granisetron on electrocardiography in children receiving chemotherapy for acute leukemia. American Journal of Clinical Oncology. Apr 2005;28(2):201-204.	2
Active Control trials	
Bolton CM, Myles PS, Carlin JB, Nolan T. Randomized, double-blind study comparing the efficacy of moderate-dose metoclopramide and ondansetron for the prophylactic control of postoperative vomiting in children after tonsillectomy. British Journal of Anaesthesia. Nov 2007;99(5):699-703.	2
Boonmak P, Boonmak S, Bunsaengjaroen P, Srichaipanha S, Poomsawat S, Nonlhaopol D. Antiemetic effect of ondansetron 0.2 mg mL-1 in PCA morphine solution. European Journal of Anaesthesiology. 2007;24(8):664-667.	6
Khamales S, Bethune-Volters A, Chidiac J, Bensaoula O, Delgado A, Di Palma M. A randomized, double-blind trial assessing the efficacy and safety of sublingual metopimazine and ondansetron in the prophylaxis of chemotherapy-induced delayed emesis.[erratum appears in Anticancer Drugs. 2006 Jun;17(5):599 Note: Khamales, Slimane]. Anti-Cancer Drugs. Feb 2006;17(2):217-224.	3
Lee Y, Wang PK, Lai HY, Yang YL, Chu CC, Wang JJ. Haloperidol is as effective as ondansetron for preventing postoperative nausea and vomiting. Canadian Journal of Anaesthesia. May 2007;54(5):349-354.	2
Luisi FA, Petrilli AS, Tanaka C, Caran EM. Contribution to the treatment of nausea and emesis induced by chemotherapy in children and adolescents with osteosarcoma. Sao Paulo Medical Journal = Revista Paulista de Medicina. 2006;124(2):61-65.	2
Peixoto AJ, Celich MF, Zardo L, Peixoto Filho AJ. Ondansetron or droperidol for prophylaxis of nausea and vomiting after intrathecal morphine. European Journal of Anaesthesiology. Aug 2006;23(8):670-675.	4
Rosow CE, Haspel KL, Smith SE, Grecu L, Bittner EA. Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. Anesthesia & Analgesia. of contents, 2008 May 2008;106(5):1407-1409.	2
Sarvela PJ, Halonen PM, Soikkeli AI, Kainu JP, Korttila KT. Ondansetron and tropisetron do not prevent intraspinal morphine- and fentanyl-induced pruritus in elective cesarean delivery. Acta Anaesthesiologica Scandinavica. Feb 2006;50(2):239-244.	2
Teran L, Hawkins JK. The effectiveness of inhalation isopropyl alcohol vs granisetron for the prevention of postoperative nausea and vomiting. AANA Journal. Dec 2007;75(6):417-422.	2
Placebo-controlled trials	

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
Cohen IT, Joffe D, Hummer K, Soluri A. Ondansetron oral disintegrating tablets: acceptability and efficacy in children undergoing adenotonsillectomy. Anesthesia & Analgesia. of contents, 2005 Jul 2005;101(1):59-63.	2
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
Davis PJ, Fertal KM, Boretsky KR, et al. The effects of oral ondansetron disintegrating tablets for prevention of at-home emesis in pediatric patients after ear-nose-throat surgery. Anesthesia & Analgesia. of contents, 2008 Apr 2008;106(4):1117-1121.	2
Freedman SB, Adler M, Seshadri R, Powell EC. Oral ondansetron for gastroenteritis in a pediatric emergency department. New England Journal of Medicine. Apr 20 2006;354(16):1698-1705.	4
Hartsell T, Long D, Kirsch JR. The efficacy of postoperative ondansetron (Zofran) orally disintegrating tablets for preventing nausea and vomiting after acoustic neuroma surgery. Anesthesia & Analgesia. Nov 2005;101(5):1492-1496.	2
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Drug Class Review

Newer Antiemetics

Final Report Update 1
Evidence Tables

January 2009

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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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.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Children						
Jaing **2004** Multicenter 3	Open RCT Crossover	Children, females	granisetron po 0.5 or 1.0mg ondansetron iv 0.45mg/kg once	no other antiemetics allowed.	4 wk run-in with antiemetics acc. to rand. scheme/NR	7.8 64%male NR
Forni **2000** Not specified 5	DB RCT Parallel	Children	Ondansetron iv 5.3mg/m2 Granisetron iv 2mg/m2 Tropisetron iv 3.3mg/m2	Antiemetics were given with dexamethasone 8 mg/m2 iv.	NR/NR	16.9 69%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Children			
Jaing **2004** Multicenter 3	35/33/33	0/0/33	Acute lymphoblastic leukemia: 100%
Forni **2000** Not specified 5	NR/NR/90	NR/0/90	NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Children	
Jaing **2004** Multicenter 3	Granisetron vs Ondansetron Complete response: no emetic episodes and no need for rescue medication: Within 24h: 60.6% vs 45.5%, NS Incomplete response: 39.4% vs 54.5%, NS Therapeutic success: 84.8% vs 87.9%, NS Failure: ≥ 3 vomiting episodes in 24h study period: 15% vs 12%, NS
Forni **2000** Not specified 5	Results given as Ondansetron vs Granisetron vs Tropisetron Complete response (no vomiting or retching) Complete response : 58.3% vs 62.9% vs 57.1%, NS Complete response: broken down by chemo regimen, not by study drug: 69% vs 44%, 0.0001 for ifos pts vs. cisplatin pts Partial response, % of patient days (1-4 episodes of vomiting/day): 34.2% vs 28.2% vs 38.3%, NS Failure (≥5 episodes of vomiting/day) % of patient days: 7.5% vs 8.9% vs 4.6%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Children		
Jaing **2004** Multicenter 3	"The most frequently reported AEs were mild headache and constipation. The AEs were the same in both groups."	No concomitant antiemetic therapy apart from the study drugs was given to the patients.
Forni **2000** Not specified 5	All patient days Headache: 3.9% of 717 pt days, NR Headache was the only AE the authors reported; they stated that it was of mild intensity and its frequency was the same in all 3 treatment groups.	Population stratified by age owing to rarity of osteosarcoma; both pediatric and adult pts entered study. Nausea data not collected because pediatric pts deemed not able to give reliable nausea data. Withdrawal data: No cases of dose reduction of antiblastics; in 2 pts the ifosfamide (ifo) cycle was stopped (on days 4 & 5 of infusion) because of neurotoxicity. 717 pt-days of treatment evaluated for 90 pts; results were given in terms of pt days. 3 pt days not evaluable: 2 Gran pts were not given ifo for 3 days total due to neurological problems. Children not analyzed as a subpopulation. In cisplatin-Adriamycin cycles the complete protection (CP) rate decreased from 61% on day 1 to 27% on day 2. On the third day when Adriamycin was given, the total protection=44% (P<0.0001). During ifo cycles CP decreased from 95.5% on day1 to 43% on the last (P<0.0001). 10% of pts experienced CP on all treatment days during both chemo types. CP was achieved in 19% only for one type of chemo cycle; the remaining 71% experienced emesis in both cycles for at least 1 day.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Sepulveda-Vildosola 2008 Single Center 2-5	RCT, DB, Parallel	None	Ondansetron IV 8mg/m^2 Palonosetron IV 0.25mg	NR	NR/NR	Mean age: 11years Range: 2-15 69% males Ethnicity: NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Sepulveda-Vildosola 2008 Single Center 2-5	NR/NR/100	NR/NR/100	Previous treatment with chemotherapy: 86% Nausea or vomiting in previous chemotherapy: 76%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Sepulveda-Vildosola 2008 Single Center 2-5	Palonosetron vs Ondansetron Complete control of emetic events at day 1: 92% vs 72% Complete control of emetic events at day 2: 72% vs 46% Complete control of emetic events at day 3: 78% vs 54% Complete control of emetic events at day 4: 88% vs 84% Complete control of emetic events at day 5: 98% vs 90% Complete control of emetic events at day 6: 100% vs 94% Complete control of emetic events at day 7: 100% vs 96% Absence of nausea at day 1: 74% vs 38% Absence of nausea at day 2: 62% vs 18% Absence of nausea at day 3: 72% vs 30% Absence of nausea at day 4: 88% vs 58% Absence of nausea at day 5: 98% vs 88% Absence of nausea at day 6: 98% vs 92% Absence of nausea at day 7: 98% vs 94%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Sepulveda-Vildosola 2008 Single Center 2-5	NR	

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
White **2000** Multicenter 4, 5	DB RCT Parallel	Children, kinetosis	Ondansetron iv 5mg/m2 Ondansetron po 8mg	Dexamethasone 2-4 mg po was given along with study antiemetics	No/NR	8 58%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
White **2000** Multicenter 4, 5	NR/438/428	0/0/428	Mean weight (+/- SD) = 28.6 (+/- 12.2) kg Mean body surface area: (+/- SD) = 1.01 (+/- 0.30)m2 Previous motion sickness: yes: 3%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
White **2000** Multicenter 4, 5	Ond iv vs Ond po Complete control of emesis (0 episodes) Treatment phase A: 73% vs 71%, NS Overall (A+B): 62% vs 62%, NS Treatment Day 1: 81% vs 78%, NS Major control of emesis (1-2 episodes): Treatment A: 16% vs 17%, NS Overall (A+B): 23% vs 20%, NS Treatment Day 1: 10% vs 13%, NS Mild Nausea Treatment Day 1: 21% vs 21%, NS Phase A (a little bit nauseous): 26% vs 26%, NS Overall (A+B): 36% vs 33%, NS No nausea experienced: Treatment Day 1: 73% vs 70%, NS Overall (Phases A + B): 52% vs 56%, NS Phase A: 64% vs 64%, NS % with reduced appetite during treatment: increased by 7% from baseline vs increased by 12% from baseline, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
White **2000** Multicenter 4, 5	Ond iv vs Ond po All Adverse Events: 20% vs 19%, NS Abdominal/ gastrointestinal discomfort and pain: 4% vs 3%, NS Fever/pyrexia: 3% vs 3%, NS Diarrhea and headaches: 2% vs 2%, NS Serious AEs: ≤2% vs ≤2%, NS	Ond po administered as an oral syrup, not a tablet. Study medication administered during 2 phases: phases A and B. Treatment phase A involved each of the days (max. 8 days) during which pts received moderately/highly emetogenic chemo. Pts allowed to receive 1 or 2 single days of no or low emetogenic chemo in between the days that they received moderately/highly emetogenic chemo. interventions are given for Phase A. Treatment phase B defined as the 2 days immediately following cessation of moderately/highly emetogenic chemo (or if pts received chemo of low emetic potential for ≥2 consecutive days). All pts received Ond 4 mg po during phase B. All pts received Ond 4 mg po + Dex 2-4 mg po 6-8 h after receiving the IV. Dex given according to the body surface area (BSA): 4mg/d for pts with BSA≤ 0.6 m2 and 8 mg/d for BSA >0.6 m2. This regimen was followed each day of moderate or highly emetogenic chemo. 483 pts originally enrolled; 9 did not receive mod./highly emetogenic chemo and another did not receive Ond iv; so 482 were considered the ITT population.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Orchard 1999 Single Center 5	DB RCT Parallel	children, BMT, TBI	Ondansetron iv mg Granisetron iv mg 7 days	All received dexamethasone iv 10 mg/m2/day (max 10 mg/day) for patients <18; and 10 mg/day IV for pts ≥18.	NR/NR	38.4 57%male NR
Corapcioglu 2005 NR 5	Randomized, DB	None	Ondansetron IV 5mg/m^2 Ondansetron ODT 4mg	Corticosteroids, only in patients with leukemia and lymphoproliferative malignancy	No/no antiemetics 24 hours before surgery	Median age: 9.4 years Range: 3-17 years 50% male Ethnicity: NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Orchard **1999** Single Center 5	NR/NR/193	4/2/187	Conditioning regimen: Chemo only: 22% Chemo plus radiation: 75% Weight (range) = 72 kg (11-132 kg) Autologous transplant: 35% Allogeneic transplant: 26% Unrelated transplant: 35% Non malignancy: 16% Aplastic anemia: 7% Immune deficiency: 2% Metabolic disorder: 8% Acute lymphocytic leukemia: 3% AML/MDS: 21% Chronic myeloid leukemia: 25% Lymphoma: 10% Breast cancer: 6% Other malignancy: 15%
Corapcioglu 2005 NR 5	NR/NR/22	NR/NR/22	NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Orchard **1999** Single Center 5	Ondansetron vs Granisetron Mean no. of emetic episodes: Day 0 of study (transplantation): 0.70 vs 0.75, NS Adults: pts ≥ 18 yrs, overall (Days -7 to Day +2 of study): 0.86 vs 0.80, NS No. of emetic episodes: Day -6 of study: 0.75 vs 0.65, NS Children: pts Day +2 of study: 1.30 vs 1.20, NS Day -7 of study: 0.50 vs 0.60, NS Episodes of emesis: All patients, overall (Days -7 to Day +2 of study): 0.86 vs 0.73, NS Major control of emesis: 1-2 emetic episodes in 24h of pt days: 27% pt days vs 27% pt days, NS Failure of control for emesis: >5 emetic episodes in 24h of pt days: 4% pt days vs 3% pt days, NS Minor control : 3-5 emetic episodes in 24h of pt days: 8% pt days vs 7% pt days, NS Complete control of emesis: No emetic episodes in 24h of pt days: 61% pt days vs 63% pt days, NS Mean nausea scores All patients, overall (Days -7 to Day 0): 1.29 vs 1.17, NS Day 0 of study: 1.30 vs 1.45, NS Day -1 of study: 1.45 vs 1.10, NS Day -6 of study: 1.30 vs 1.00, NS Adults: pts ≥ 18yrs, overall (Days -7 to Day 0): 1.36 vs 1.29, NS Children: pts Day -7 of study: 0.75 vs 0.75, NS Day -5 of study: 1.20 vs 0.9, NS Number of Daily Requests for Rescue Drugs 0 requests: 41% vs 40%, NS 1 request: 37% vs 38%, NS 2 requests: 20% vs 19%, NS 3 requests:1% vs 2%, NS
Corapcioglu 2005 NR 5	IV vs ODT Response Rate Complete: 82% vs 85% Major: 10% vs 8% Minor: 4% vs 3% Failure: 4% vs 4% Pts <10y - complete: 94% vs 95% Pts ≥10y - complete: 65% vs 74%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Orchard 1999 Single Center 5	Ondansetron vs Granisetron Headache: 13.4% vs 14.4%, NR Diarrhea: 2.1% vs 6.7%, Dizziness: 2% vs 4%, Joint pain: 1.0% vs 5.5%,	Patients were undergoing hematopoietic cell transplants; results were stratified by age (<18, n=51; ≥ 18 n=136) and analyzed. Of the 193 pts randomized, 4 withdrew within 48 h of randomization and 2 had inadequate data for analysis. The pediatric population of this study was receiving HSCT for nonmalignant conditions at a much higher percentage (51% vs. 4%) than the adult population; they also had a higher proportion of transplants from an unrelated donor than adults did (68% vs. 24%)
Corapcioglu 2005 NR 5	None attributed to study drug	Had 22 patients, but 95 chemotherapy courses (approximately 3 courses per patient)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Adult						
Aprepitant vs ondansetron						
Schmoll 2006 NR ≥3	RCT, DB, Parallel	None	Aprepitant group: Aprepitant 125mg on day 1; aprepitant 80mg days 2 -3 Control group: ondansetron 32mg on day 1; oral placebo days 2-3	All received dexamethasone days 1-4 Those taking rescue medications were considered treatment failures	NR/No 5-HT_3 RAs within 48 hours of day 1	59 63% male Asian: 17.5% Black: 3% Hispanic: 12.5% White: 61% Other: 6%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Adult			
Aprepitant vs ondansetron			
Schmoll 2006 NR ≥3	516/NR/489	29/3/484	History of motion sickness: 5.5% History of vomiting associated with pregnancy (females only): 26.5% History of CINV: 5% Type of Cancer Respiratory: 45% Urogenital: 19% Gastrointestinal: 12% Eyes/ears/nose/throat: 10% Other: 14%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Adult	
Aprepitant vs ondansetron	
Schmoll 2006 NR ≥3	Aprepitant group vs control group Complete response 0-120h after surgery: 72% vs 60.6% (p=0.003) Complete response 0-24h after surgery: 87.7% vs 79.3% (p=0.005) Complete response >24-120h after surgery: 74.1% vs 63.1% (p=0.004) No vomiting 0-120h after surgery: 76.5% vs 62.2% (p<0.001) No vomiting 0-24h after surgery: 88.9% vs 80.5% (p=0.004) No vomiting >24-120h after surgery: 79% vs 64.3% (p<0.001) No significant nausea 0-120h after surgery: 73.1% vs 69.7% (NS) No significant nausea 0-24h after surgery: 92.1% vs 89.5% (NS) No significant nausea >24-120h after surgery: 75.9% vs 72.1% (NS) No use of rescue therapy 0-120h after surgery: 82.3% vs 79.7% (NS) No use of rescue therapy 0-24h after surgery: 94.2% vs 92.9% (NS) No use of rescue therapy >24-120h after surgery: 83.5% vs 81.7% (NS)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Adult		
Aprepitant vs ondansetron		
Schmoll 2006 NR ≥3	Aprepitant group vs Control group Overall incidence of AEs: 79% vs 81.6% Anorexia: 14% vs 14.8% Asthenia: 13.6% vs 15.2% Constipation: 15.6% vs 22.1% Diarrhea: 12.8% vs 9.4% Dyspepsia: 13.6% vs 11.1% Fatigue: 9.1% vs 6.1% Hiccups: 9.9% vs 9.8% Nausea: 15.6% vs 9.8% Vomiting: 9.1% vs 9.8%	

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Granisetron vs Ondansetron						
Abali 2007 NR 4,5	Open-label observation	None	Ondansetron 8 mg Granisetron 3 mg iv Tropisetron 5 mg iv	All received 8 mg dexamethasone iv in addition to antiemetic	NR/NR	48 27.2% male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Granisetron vs Ondansetron			
Abali 2007 NR 4,5	NR/NR158	NR/NR/158	Previous history of chemotherapy: 76% Chemotherapy-naïve: 23% Received cisplatin containing combination chemotherapy: 24% Received moderately emetogenic chemotherapy: 76%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Granisetron vs Ondansetron	
Abali 2007 NR 4,5	Ondansetron 8 mg vs Granisetron 3 mg iv vs Tropisetron 5 mg iv Acute Phase Complete Response: 72.1% vs 71.1% vs 80.4% Major Response: 18% vs 21.7% vs 13.7% Minor Response: 4.9% vs 2.2% vs 3.9% Delayed Phase Complete Response: 68.9% vs 76.1% vs 68.6% Major Response: 11.5% vs 10.9% vs 19.6% Minor Response: 11.5% vs 4.3% vs 7.8% Nausea- Acute Phase Severe: 14.8% vs 10.9% vs 11.8% Moderate: 14.8% vs 13% vs 13.7% Mild: 34.4% vs 39.1% vs 35.3% Nausea- Delayed Phase Severe:19.7% vs 19.6% vs 23.5% Moderate: 19.7% vs 17.4% vs 13.7% Mild: 23% vs 23.9% vs 25.5%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Granisetron vs Ondansetron		
Abali 2007 NR 4,5	Ondansetron 8 mg vs Granisetron 3 mg iv vs Tropisetron 5 mg iv Incidence of AEs: 70.5% vs 73.9% vs 82.4% Headache: 39.3% vs 52.2% vs 47.1% Dizziness: 18% vs 26.1% vs 23.5% Diarrhea: 4.9% vs 10.9% vs 5.9%	

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Barrajon **2000** Single Center 5	DB RCT Crossover	women, alcoholics, prior chemo	Tropisetron iv 5mg Granisetron iv + 3mg Ondansetron iv 24mg 10 min	All received 20 mg dexamethasone iv with the antiemetic; and then received it on a tapering oral schedule of 2mg bid for 2 days and then 1 mg bid for two days.	NR/NR	61 32%male NR
Chiou **2000** Single Center 4, 5	Open RCT Parallel	none	Ondansetron iv 24mg Granisetron po 2mg 24hr	Initial dose given with dexamethasone iv 10 mg; dex not given with other doses	No/NR	56.5 63%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Barrajon 2000 Single Center 5	NR/NR/136	16/0/120	Primary Tumor: Breast: 54% Primary Tumor: Lung: 12% Primary Tumor: Head and neck: 12% Primary Tumor: Gynecological: 9% Primary Tumor: Digestive: 6% Primary Tumor: Other: 8% Ethanol consumption >120g/day: 13% Previous chemo: 30% Chemo: CDDP + TAX: 26% Chemo: CDDP+5FU+/-MTX: 20% Chemo: CEI/PEI+/-VNR: 10% Chemo: FAC/FEC: 15% Chemo: CMF: 16% Chemo: Other: 13% Mean cisplatin dose = 74.7 Pts receiving Platinum-based chemo: 54% Pts receiving chemo for >24h: 29%
Chiou 2000 Single Center 4, 5	NR/NR/51	0/0/51	severely emetogenic chemo: 57% moderately emetogenic chemo: 43% Primary Tumor: Non-Hodgkin's lymphoma: 35% Unknown: 12% Urologic: 12% Gastrointestinal: 12% Breast: 6% Non-small-cell lung cancer: 10% Head and neck: 14%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Barrajon 2000 Single Center 5	Ondansetron vs Granisetron vs Tropisetron Degree of nausea: (first cycle only) grades 0-3 1: 15.0% vs 13.0% vs 20.0%, NS 2: 20.0% vs 28.0% vs 13.0%, NS 3 (severe): 15.0% vs 18.0% vs 15.0%, NS No nausea (grade 0): 50.0% vs 43.0% vs 53.0%, NS Emesis: Complete control (for first cycle only) No emetic episodes experienced: 60% vs 63.0% vs 55.0%, NS Emesis: number of patients with ≥1 episodes (first cycle only): 40.0% vs 37.5% vs 45.0%, NS Emesis: number of episodes and mean (for the first cycle only) Total number of episodes of emesis per each treatment group: 84 vs 87 vs 100, NS Mean number of episodes (per pt experiencing emesis): 2.1 vs 2.18 vs 2.5, NS Emesis: days with emesis and mean (first cycle only) Total days with emesis per treatment group: 33 vs 40 vs 44, NS Mean number of days with emesis per patient: 0.83 vs 1.0 vs 1.1, NS Patient preference (after crossovers): 45% vs 30% vs 25%, p
Chiou 2000 Single Center 4, 5	Ondansetron vs Granisetron Complete control of vomiting/retching (no emesis) and nausea: acute and delayed No nausea in 24h (acute): 38.5% vs 56%, NS No nausea over 2-7 days (delayed): 34.6% vs 16%, NS No emesis in 24h (acute): 84.6% vs 84%, NS No emesis over 2-7 days (delayed): 19.2% vs 16%, NS Need of rescue medication Within 24h: 11.5% vs 12.0%, NS Within 2-7 days: 38.5% vs 56.0%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Barrajon 2000 Single Center 5	Ond vs Gran vs Trop % with headache, first cycle only: 10% vs12.5%vs 40%; NR Fluid administration all 3 courses: 8.3% vs 8.3% vs 8.3%; NR Need for rescue antiemetic (metoclopramide) No. of patients needing rescue: 6 vs 4 vs 6; NR Trop emergency admission for less than 24h: probably due to fluid loss: 2.5%	No stratification implemented. No correction made for paired data or for continuity. Rescue antiemetic was metoclopramide. 16 of 136 pts included in the initial rounds of randomization were not evaluable because they were not able to complete the anticipated treatment owing to progression of disease or intolerable toxicity that prevented further chemo at the same initial doses. Subgroup analysis: NSD in emesis depending on these risk factors: age, gender, chemo with cisplatin, or alcohol consumption. The factor clearly associated to a significant increase in emesis was chemo regimens >1day (complete protection for those with only 1 day chemo = 69% vs. 4% for >1day chemo, p<0.001).All efficacy measures are reported from the first cycle only, before any crossover occurred, unless otherwise noted. The authors state: an ITT analysis after the first course [i.e., cycle] was not considered possible, as data were not available for 8 of 16 included pts. The preference for ondansetron appeared at the start of the trial and was maintained throughout the study. Cumulative preferences for Gran and Trop crossed each other throughout the study.
Chiou 2000 Single Center 4, 5	Granisetron vs Ondansetron Diarrhea: 12.0% vs 0%, NR Constipation: 4.0% vs 23.1%, NR Headache: 4.0% vs 3.8%, NR Dizziness: 8.0% vs 3.8%, NR Restlessness: 8.0% vs 3.8%, NR	Moderate emetogenicity including non-cisplatin-based regimens, (CHOP, FAC, FEC). Sever emetogenicity including cisplatin (> 50 mg/m2)-based chemotherapy (CMV, EP, FP, FEP, and one case of high-dose chemotherapy with 4 g/m2 of cyclophosphamide.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Chua **2000** Single Center 5	Open RCT Crossover	none	granisetron iv 3mg tropisetron iv 24mg ondansetron iv 5mg	dexamethasone 20 mg iv given with study antiemetics on day 1,	NR/NR	NR 87%male Asian (Chinese), n= 89 (100%)
deWit **2001** NR 5	DB RCT Crossover	none	Granisetron iv 3mg Ondansetron iv 8mg once	dexamethasone 10 mg iv given with study medication	No/NR	46 10%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Chua **2000** Single Center 5	94/89/89	0/0/89	GRADEX vs TRODEX: 65% GRADEX vs ONDEX: 73% TRODEX vs ONDEX: 72% Primary Tumor: Nasopharnyx: 80%; Oral Cavity: 10%; Hypopharnx: 8%; Larnyx: 1%; Ear: 1% Chemo as part of : primary treatment: 55%; induction: 39%; adjuvant: 11%; concomitant chemoirradiations: 4% Chemo : as palliative: 45% Chemo : in combo w/radiation: 55% Chemo Cycle 1: 100% Chemo Cycle 2: 82% Chemo Cycle 3: 64% Antiemetic regimens: GRADEX: 76% Antiemetic regimens: TRODEX: 80% Antiemetic regimens: ONDEX: 90% Crossed over once: 18%; Crossed over twice: 64%
deWit **2001** NR 5	NR/45/40	0/0/40	cisplatin-based chemo: 33% cyclophosphamide-based chemo: 68% previous cycles: 10% Primary Tumor- Breast: 63% Primary Tumor- Ovarian: 10% Primary Tumor- Lung: 10% Primary Tumor- Other: 18%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Chua **2000** Single Center 5	Ondansetron vs Granisetron vs Tropisetron Complete response: no nausea or vomiting, or mild nausea only in the 24h after starting chemo First cycle only: 74% vs 81% vs 75%, NS Pt preference: Gran vs Onda vs Trop vs no drug preference post-crossover: 14% vs 17.8% vs 15% vs 53%, NS
deWit **2001** NR 5	Ondansetron vs Granisetron Results for Cisplatin-based chemotherapy pts Partial: 34% vs 34%, NS Failure: 67% vs 43%, NS Complete: 0% vs 29%, NS Results for Cyclophosphamide-based chemotherapy pts Failure to respond: 73% vs 25%, NS Partial response: 20% vs 17%, NS Complete response : 7% vs 58%, NS Ond iv 8 vs Gran iv 3 Complete protection to failure to respond for total population Complete response: no vomiting and no/mild nausea : 4.8% vs 47.4%, 0.005 for Gran vs. Ond Failure to respond: ≥ 2 vomits or severe nausea (no significant intake possible), or nausea >4 hours : 67% vs 37%, NR Partial response: 0-1 vomits and/or moderate nausea during a max. of 4 hours: 29% vs 16%, NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Chua **2000** Single Center 5	Headache vs Diarrhea vs Constipation All adverse events Patient: 14% vs 7% vs 4%, NS	Study antiemetics given on Day 1 only; the antiemetic regimen for days 2-6 was metoclopramide 80 mg/d + dex 8mg/d + alprazolam 500 micrograms/d. GRADEX= granisetron + dexamethasone; TRODEX= tropisetron + dexamethasone; ONDEX= ondansetron + dexamethasone. Data abstracted for Cycle 1 of the crossover study; this portion represented a parallel study. Chemo regimen: DAY 1: cisplatin 100 mg/m2 and DAYS 1-3: 5-FU 1000 mg/m2. All had prehydration with iv fluids for 1 day before chemo. Cisplatin was a 4-hr infusion, and 5-FU was administered as a continuous infusion.
deWit **2001** NR 5		45 pts randomized; 5 pts excluded at the study cycle: 2 had nausea prior to chemo; 2 had chemo dose reductions; and 1 used other antiemetics. The patients on cisplatin were in a highly emetogenic category (defined by Hesketh 1997); but the patients on cyclophosphamide had dosages ≥ 500 mg/m2, which can range from moderate (500-750 mg/m2 and 750-1500 mg/m2) emetogenicity to high emetogenicity (≥ 1500 mg/m2) per Hesketh 1997. The study did not specify which dosage the cyclophosphamide pts were receiving.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Del Favero 1995 Multicenter 5	DB RCT Parallel	kinetosis	Ondansetron iv 8mg Granisetron iv 3mg	all given dexamethasone (dex) 20 mg iv as a 15-min infusion 45 min before administration of cisplatin. All pts received Dex im and metoclopramide po on days 2-4.	NR/NR	61 68%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Del Favero 1995 Multicenter 5	NR/NR/973	6/1/966	Median dose of cisplatin (mg per square meter): 8% Dose of cisplatin: < 90 mg/m2: 63% ≥ 90 mg/m2: 37% Performance Status: 50-80: 35% 90-100: 65% Previous non-cisplatin chemo: Yes 7% No 92% Primary tumor: Ovary: 14% Lung: 38% Head-neck: 12% Bladder: 14% Other: 21% Kinetosis: Yes: 10% No: 89% Concomitant medications: Opioids: 4% H2 antagonists: 14% Benzodiazepines: 4% NSAID: 9%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Del Favero **1995** Multicenter 5	*Data given as ond vs gran* Complete response: acute: no nausea and no vomiting, and no nausea+no vomiting No nausea: acute : 72.1% vs 71.8%, NS Complete response: Acute: 66.5% vs 67.3%, NS No vomiting: acute: 79.3% vs 79.9%, NS Mean number of emetic episodes: acute Only in patients who had vomiting: 4.04 vs 3.91, NS Acute (only in pts who had nausea; scale = 0:none to 3:severe) score: 1.47 vs 1.48, NS Complete protection from nausea: acute: 72.1% vs 71.8%, NS Complete protection from vomiting, days 2-6 Day 2: 81.9% vs 81.9%, NS Day 3: 82.8% vs 86.9%, NS Day 4: 85.5% vs 87.8%, NS Day 5: 88.5% vs 88.6%, NS Day 6: 92.0% vs 90.7%, NS Complete protection from nausea, Days 2-6 Day 2: 66.6% vs 63.1%, NS Day 3: 63.7% vs 67.5%, NS Day 4: 65.8% vs 70.7%, NS Day 5: 70.4% vs 73.4%, NS Day 6: 72.5% vs 75.7%, NS Complete protection from nausea and vomiting, days 2-6 Day 2: 61.8% vs 59.9%, NS Day 3: 60.3% vs 65.4%, NS Day 4: 63.0% vs 68.4%, NS Day 5: 68.3% vs 71.3%, NS Day 6: 71.4% vs 74.5%, NS Kinetosis pts vs Non-Kinetosis pts Kinetosis vs. non-kinetosis afflicted pts Efficacy in Gran pts not protected vs. emesis: 43% vs 16.9%, NR Efficacy in Ond pts not protected vs. emesis (Range): 12(30) vs 88(19.9), NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Del Favero 1995 Multicenter 5	granisetron vs ondansetron constipation:0.6% vs 0.4%, NS headache: 3.1% vs 3.1%; NS heartburn: 0.8% vs 0.2%, NS weakness: 2.3% vs 0.8%, NS epigastric pain: 1.0% vs 0.8%, NS nervousness: 0.2% vs 0.8%, NS hot flush: 2.9% vs 2.1%, NS hiccup: 2.3% vs 3.3%, NS sedation: 1.0% vs 0.4%, NS other AEs (not specified) : 4.1% vs 4.3%, NS	15 min after study drug administration finished, cisplatin infusion began and was given over 30 min. The other chemo agents were given immediately after the end of the cisplatin infusion. Food intake was not permitted until 8 hrs after cisplatin. To prevent cisplatin-induced delayed emesis, all pts received metoclopramide (meto) 20 mg po every 6 hrs on days 2 to 4, together with intramuscular dex 8 mg bid on days 2 and 3, and 4 mg bid on day 4. Gran and Ond given to patients on day 1 only; so day 1 was the head-to-head part of the trial for the study medication. The number of evaluable pts went from 483/group to Ond N= 476 and Gran N=474 (Total N=950). Causes of non-availability were: 2 pts died; 7 pts had failure of antiemetic treatment on day 1; 1 pt had failure of antiemetic treatment on day 2; 3 were lost to followup; 1 refused antiemetic therapy; 1 had AEs on day 1; 1 had AEs on day 2. By group: Ond: 1 pt: error in administered antiemetic treatment and case report form not completed; 1 pt refused chemo; 1 pt the administered chemo was different after randomization. Gran: 1 pt died during first 24 hours; 2 pts failed to receive antiemetic therapy after randomization; 1 pt was lost t

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Fox-Geiman 2001 Single Center 5	DB RCT Parallel	BMT; TBI	Ondansetron po 24mg (8 mg Q8) Ondansetron iv 32mg qd Granisetron po 2mg (1 mg Q12)	Yes; all received dexamethasone 10 mg iv qd while receiving the 5-HT3 antagonist; also, benzodiazepines were allowed as needed for sleep.	NR/NR	47 28%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Fox-Geiman 2001 Single Center 5	NR/NR/102	6/0/102	Mean weight, kg: 78kg allogenic transplant 3% autologous transplant 97% Inpatient treatment setting 73% Outpatient treatment setting 27% History of moderate/severe nausea 72% History of vomiting: 57% History of anticipatory nausea/vomiting 12% Conditioning regimens: TBI-containing 26% Conditioning regimens: Chemo only 74% preparative regimen: STAMP V: 33% TBI/VP/CY: 25% TANC: 15%; BU/CY: 11% BEAM: 4%; BCNU/VP/CY: 2% ICE: 2% Carboplatin/VP: 2% Carboplatin/MTZ/CY: 2% MMT: 2% Thiotepa/CY: 1% TBI/CY: 1%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Fox-Geiman 2001 Single Center 5	Ond po 24 vs Ond iv 32 vs Gran po 2 Complete response (CR: no or mild nausea (pt able to eat; reasonable intake) and no rescue antiemetics used) Day 1: 95% vs 92% vs 92%, NS Day 2: 69% vs 69% vs 77%, NS Day 3: 73% vs 75% vs 81%, NS Day 4: 35% vs 32% vs 45%, NS Day 5: 27% vs 30% vs 25%, NS Day 6: : 32% vs 32% vs 25%, NS Day 7: 45% vs 31% vs 15%, NS Day 8: 35% vs 10% vs 8%, NS Composite score (overall - Days 1-8): 48% vs 49% vs 47%, NS Major Response score (1 vomiting episode or if no vomiting, moderate nausea (intake significantly decreased; pt can eat) with rescue allowed: Normalized for 8 days: 82% vs 81% vs 84%, NS Major response (MR): 1 episode of vomiting or moderate nausea (intake significantly decreased, but patient can eat) with rescue allowed Day 1: 2% vs 6% vs 8%, NS Day 2: 31% vs 24% vs 17%, NS Day 3: 21% vs 19% vs 11%, NS Day 4: 42% vs 42% vs 47%, NS Day 5: 58% vs 47% vs 55%, NS Day 6: 46% vs 41% vs 60%, NS Day 7: 28% vs 54% vs 57%, NS Day 8: 44% vs 65% vs 70%, NS Failure (>4 episodes of nausea regardless of nausea or rescue antiemetic use) Composite score: 4.0% vs 2.6% vs 3.3%, NS No. of patients requiring rescue antiemetics On ≥1 day of their antiemetic regimen: 91% vs 79% vs 85%, NS Nausea VAS score (0= no nausea to 100=extreme nausea): 32 vs 27 vs 32, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Fox-Geiman 2001 Single Center 5	Total po pts vs Ond IV Total withdrawals: 7.3% vs 2.9%, NR Ond iv vs Ond po vs Gran po Withdrawals due to AEs: blurred vision: 2.9% vs 0% vs 0%, NR Blurred vision: 2.9% vs 0% vs 0%, NR No AEs discussed other than the iv pt who withdrew due to blurred vision on 2 occasions "attributed to dexamethasone". The additional 5 withdrawals "refused to continue the protocol due to poor nausea and/or emesis control."	Patients were stratified by gender and by TBI-containing vs. non-TBI-containing preparative regimens. Pt population were to receive chemo or chemoradiotherapy treatments prior to stem cell transplantation. Chemo regimens: Preparative regimens included STAMP V; TBI/etoposide (VP)/cyclophosphamide (CY); TANC (paclitaxel 700 mg/m^2 IV over 24 hours on day -9; mitoxantrone 30 mg/m^2 IV bolus on days -8, -6, and -4; and carboplatine [total area under curve (AUC)=28] continuous IV over 5 days on days -8, -7, -6, -5, and -4); busulfan (BU)/CY; BEAM (carmustine, etoposide, cytosine arabinoside, and melphalan); carmustine (BCNU)/VP/CY; ICE (ifosfamide, carboplatin, VP-16) (carboplatine dose modified to total AUC = 28); carboplatin/VP (carboplatin dose modified to a total AUC = 30; carboplatine/mitoxantrone (MTZ)/CY; MMT (paclitaxel 150 mg/m^2 per day continuous IV infusion [CIV] over 96 hours on days -6, -5, -4, and -3; mitoxantrone 30 mg/m^2 IV over 15 minutes on days -6, -5, and -4; and melphalan 90 mg/m^2 IV over 20 minutes on days -6 and -5); thiotepa/CY; and TBI/CY.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Gebbia 1994a Single Center 5	Open RCT Parallel	none	ondansetron iv 24mg granisetron iv 3mg	No	NR/NR	59 64%male NR
Gebbia 1994b Single Center 3	Open RCT Parallel	none	ondansetron iv 16mg Granisetron iv 3mg	No	NR/NR	56 21%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Gebbia 1994a Single Center 5	NR/NR/182	16/0/166	Delayed: 91% Primary tumor: head and neck 47% lung 16% urinary bladder 7% ovary 7% stomach 6% endometrium 6% vulva 7% breast 3% testis 1% sarcoma 1%
Gebbia 1994b Single Center 3	NR/NR/164	8/0/158	Primary Tumor: Breast 60% Lung 15% Ovary 8% Stomach 6% Non-Hodgkin lymphoma 9% Melanoma 1%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Gebbia 1994a Single Center 5	Ondansetron vs Granisetron Acute emesis response rates: complete, major, minor, and failure Major response: 29% vs 24%, NS Minor response: 14% vs 12%, NS Failure: 5% vs 15%, NS Complete response: no emesis(acute): 52% vs 49%, NS Delayed emesis response rates: complete, major, minor, and failure Complete response : 39% vs 36%, NS Major response : 24% vs 22%, NS Minor response : 21% vs 28%, NS Failure: 16% vs 14%, NS Nausea severity No nausea: acute: 74% vs 79%, NS No or mild nausea: delayed: 53% vs 45%, NS Complete response in pts undergoing fractionated chemo No emesis in pts undergoing fractionated chemo: Days 2-5 : 43% vs 35%, NS
Gebbia 1994b Single Center 3	Ondansetron vs granisetron Acute emesis response rates: Complete, major, minor, failure Failure: ≥ 6 emetic episodes: 3% vs 4%, NS Minor response: 3-5 emetic episodes: 6% vs 10%, NS Major response: 1-2 emetic episodes: 22% vs 19%, NS Complete response: no emetic episodes: 69% vs 67%, NS Delayed emesis response rates: Complete, major, minor, failure Major response, days 2-5: 15% vs 20%, NS Complete response: no emesis days 2-5: 45% vs 52%, NS Pts experiencing no nausea: Acute: 50% vs 45%, NS Delayed: 31% vs 37%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Gebbia 1994a Single Center 5	*data given as Ond iv 24 vs Gran iv 3* Headache:9% vs 4%, NS Constipation: 17% vs 7%, NS	Pts stratified according to length of chemo (single day vs. fractionated). Cisplatin was given as a single dose on day 1. Pts with fractionated chemo received Ond po 8 mg bid (total= 16 mg) or Gran iv 3 mg on the days with chemo after day 1.
Gebbia 1994b Single Center 3		All pts were required to receive epidoxorubicin ≥ 75 mg/m2, doxorubicin ≥ 40 mg/m2, cyclophosphamide ≥ 600 mg/m2 iv, IFX ≥ 3 g/m2 (study 2). In Study 2, most patients received a CMF regimen (cyclophosphamide 600 mg/m2, methotrexate 40 mg/m2, and 5-fluorouracil [5-FU] 600 mg/m2), FAC/FEC regimen (5-FU 600 mg/m2, cyclophosphamide 600 mg/m2, epidoxorubicin 75-90 mg/m2 or doxorubicin 40-60 mg/m2), or ifosfamide 3-5 g/m2 plus vinorelbine 25-30 mg/m2.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Gralla **1998** Multicenter 5	DB RCT Parallel	corticosteroids	Ondansetron iv 32mg + dex or m-prednisolone Granisetron po 2mg + dex or m-prednisolone	Corticosteroids (dexamethasone or methylprednisolone) could be given as replacement or maintenance therapy up to an equivalent total daily dose of 10mg prednisone, or as part of prophylactic antiemetic pretherapy ≤ 8 hours before chemo with cisplatin.	NR/NR	61.7 66%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Gralla **1998** Multicenter 5	NR/NR/1054	13/0/1054	Mean body weight = 74 kg Mean alcohol units/week = 6.7 units/wk Pts using corticosteroids: 79% Respiratory and intrathoracic cancers: 61% Genitourinary cancers: 13% Other cancers (incl. head and neck): 9%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Gralla **1998** Multicenter 5	Ondansetron vs Granisetron Total control (no emesis, no nausea of any severity, and no use of antiemetic rescue medication) over 24h post cisplatin administration) For all patients: 58.3% vs 54.7%, NS Females only: 52.0% vs 46.3%, NS Patients using corticosteroids: 61.5% vs 58.8%, NS Patients not using corticosteroids: 45.8% vs 40.2%, NS Males only: 61.5% vs 59.3, NS Complete control of emesis Total population: 61.2% vs 67.1%, NS No Corticosteroid Added: 57.9% vs 46.2%, NS Corticosteroid Added: 69.5% vs 65.5%, NS Females: 60.0% vs 53.7%, NS Males: 70.7% vs 65.3%, NS Complete control of nausea Total population: 59.0% vs 55.4%, NS Females: 53.1% vs 46.8%, NS Corticosteroid Added: 62.0% vs 59.5%, NS Males (Ond n = 345; Gran n = 346): 62.0% vs 60.1%, NS No Corticosteroid Added: 47.7% vs 41.0%, NS Use of antiemetic rescue medication Total % of patients (both study drugs combined): 28.2% Use of antiemetic rescue medication Total % of patients: 25.2% vs 31.1%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Gralla **1998** Multicenter 5	Ondansetron vs Granisetron Asthenia: 18.5% vs 18.0%, NS Constipation: 12.1% vs 15.7%, NS Headache: 14.0% vs 15.5%, NS Decreased Appetite: 13.7% vs 12.5%, NS Diarrhea: 9.8% vs 10.7%, NS Patients experiencing any AE: 85.8% vs 87.1%, NS Total withdrawals: 1.4% vs 0.94%, NR Both drugs Withdrawals due to AEs: not stratified by drug: 0.38%, NA	Patients were required to receive IV cisplatin of ≥ 60 mg/m2 over a period not exceeding 3 hours. No additional cisplatin was administered until 24 hours had elapsed. The timing of all post-chemo assessments and procedures was based on the time when cisplatin administration began. All patients had the same drug schedule: if they received Ond iv, they also received 2 placebo tablets at the same time as the Gran pts; and if they received Gran tablets, they received placebo (i.e., saline) via iv 30 minutes before chemo like the Ond pts. This study only reported numbers for AEs that occurred in at least 10% of each drug's population. They state that "there were no notable difference between the treatment groups in the types of events reported or their incidences". The two most commonly used antiemetic rescue medications used were prochlorperazine and dexamethasone, respectively. 1053 of 1054 pts received cisplatin (one ineligible pt was enrolled in error and received Gran but not cisplatin).

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Herrington 2000 Multicenter 4	Open RCT Parallel	women	Ondansetron po 16mg Granisetron po 1mg	Yes: study drug given concomitantly with dexamethasone (dex) 12 mg po	No/NR	60.6 25%male NR
Jantunen 1993 Multicenter 3, 4	Open RCT Crossover	none	Ondansetron iv 8mg Granisetron iv 3mg Tropisetron iv 5mg	First 24h: no other medication allowed; but from Day 2 onward, pts received metoclopramide (10 mg 6-hourly po) if experiencing nausea.	no/no	50.6 16%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Herrington 2000 Multicenter 4	65/61/61	0/0/61	Primary Tumor- Breast: 63%; Lymphoma: 20%; Multiple myeloma: 7%; Other: 12% Chemo: cyclophosphamide-doxorubicin: 66%; cyclophosphamide: 21%; doxorubicin: 7%; other: 7%
Jantunen 1993 Multicenter 3, 4	NR/NR/166	34/2/130	Previous Chemo: yes: 70% Previous Chemo: no: 30% Breast cancer: 64% Gastrointestinal cancer: 16% Lymphoma: 9% Lung cancer: 4% Head and neck cancer: 2% Mesothelioma: 2% Other malignancies: 2% Chemo: CMF: 34% Chemo: FAC/FEC: 14% Chemo: C+mitoxantrone+5-FU: 5% Chemo: other cyclophosphamide containing: 7% Chemo: A/E+MTX+5-FU: 14% Chemo: other anthracycline-containing: 9% Chemo: carboplatin-containing: 5% Chemo: Mitomycin + MTX mitoxantrone: 5% Chemo: DTIC-containing: 2% Chemo: cisplatin Chemo: other: 4%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Herrington 2000 Multicenter 4	ond po 16 vs gran po 1 Total control of nausea and emesis Total control of nausea and emesis (over 24 hours): 45% vs 46%, NS Severity of nausea Severe: 9% vs 14%, NS Mild: 18% vs 25%, NS Moderate: 15% vs 14%, NS None: 58% vs 46%, NS Emetic episodes None: 76% vs 82%, NS 1: 12% vs 14%, NS 2-3: 3% vs 4%, NS 4 or more: 9% vs 0%, NS Rescue antiemetics administered: 42% vs 54%, NS
Jantunen 1993 Multicenter 3, 4	Ondansetron vs Granisetron vs Tropisetron Control of vomiting during the first 24h (for Cycle 1 of 3) Complete control: no vomiting or retching; Cycle 1 (N = 161 of 166) (p-value gran vs. other drug): 60.7% (<0.01 Partial control: 1-2 episodes of vomiting or retching: Cycle 1 (N = 161 of 166) (p-value gran vs. other drug): 21.4% (NS) vs 14.0% (NA) vs 12.7%(NS), NS Failure: >2 episodes of vomiting or retching: Cycle 1 (N = 161 of 166)(p-value gran vs. other drug): 17.9%(<0.01 Ondansetron vs Granisetron vs Tropisetron vs no preference Patient preference (after all 3 cycles (i.e., everyone had tried all 3 drugs) were completed): 16.9% vs 41.5% vs 15.4% vs 26.2%, NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Herrington 2000 Multicenter 4	ondansetron vs granisetron Overall AEs constipation: 3.0% vs 7.1%, NS flushing: 6.1% vs 10.7%, NS diarrhea: 12.1% vs 3.6%, NS dry mouth: 15.1% vs 7.1%, NS headache: 27.2% vs 42.8%, NS no adverse event: 52% vs 32%, NS	65 patients were enrolled, but only 61 were analyzed: 2 pts took prophylactic phenothiazines although they experienced no nausea or emetic symptoms, and 2 pts received drugs listed in the exclusion criteria before receiving study drugs.
Jantunen 1993 Multicenter 3, 4	Ondansetron vs Granisetron vs Tropisetron Headache (no. of pts analyzed not given, nor is it stated if these are for all 3 cycles): 35% vs 35% vs 34%,	Patients crossed over twice after receiving their original study drug; only the results from Cycle 1 are given in this evidence table (130/166 patients were analyzed for all 3 cycles; 161/166 were in analyzed for Cycle 1). C=cyclophosphamide; M=methotrexate; F or 5-FU = 5-fluourouracil; A = doxorubicin; E = epirubicin MTX - methotrexate; DTIC - ductual carcinoma in situ. Withdrawal information: In cycle 1, data was given for 161 of 166 pts (no reasons given as to why those 5 not accounted for); for all 3 cycles, there were 36 pts total who could not evaluated in the cross-over analysis of response. Of these, 18 had their chemo changed due to progressive disease and no longer fit the inclusion criteria; 4 had chemo dose reductions due to low blood counts; 5 had incomplete data on emesis; 4 requested to be withdrawn after Cycle 1 due to inadequate control of emesis (2 in Ond, 2 in Trop); 2 emigrated and were lost to F/u; 1 did not fit inclusion criteria (astrocytoma); 1 received Trop 2X which was considered to be a major violation of study protocol; 1 requested to be withdrawn after random

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Kalaycio **1998** NR 5	DB RCT Parallel	ASCT, women	Granisetron iv 0.5mg Ondansetron iv 8mg 8 days	All pts received dexamethasone 10 mg iv for 7 days	NR/NR	43 0%male NR
Leonardi **1996** Multicenter 3, 4, 5	NR RCT Crossover	none	Ondansetron iv 0.45mg/kg Granisetron iv 0.04mg/kg	No	NR/NR	51 41%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Kalaycio **1998** NR 5	48/48/48	3/45/45	Primary Tumor: Breast: 100% Chemotherapy Non-Naïve: 100% History of alcohol use: 18% History of emesis: 38% History of ondansetron: 62% History of granisetron: 31%
Leonardi **1996** Multicenter 3, 4, 5	NR/NR/118	3/0/118	Patients receiving moderately emetogenic chemo: 41% Pts receiving highly emetogenic chemotherapy: 59% ECOG Performance Status 0-3: 100% Breast cancer: 36% Lung cancer: 24% Hodgkins or non-Hodgkins lymphoma: 16% Other malignancies: 24%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Kalaycio **1998** NR 5	Granisetron vs Ondansetron Mean number of salvage anti-emetics: 15.8 vs 15.8, NS Mean days to first salvage anti-emetic: 2.8 vs 2.9, NS Mean emetic episodes per day: 5.6 vs 7.0, NS No emetic episodes: 17.4% vs 9.1%, NS
Leonardi **1996** Multicenter 3, 4, 5	Ondansetron vs Granisetron Complete control: no vomiting and no nausea, or only mild nausea after initial administration of antiemetic therapy Pts receiving highly emetogenic chemo:54.3% vs 61.7%, NS Pts receiving moderately emetogenic chemo: 67% vs 72.8%, NS All patients combined: 62.1% vs 68.4%, NR Major control: moderate to severe nausea, or just one episode of vomiting All patients: 15.5% vs 12.8%, NR Pts receiving highly emetogenic chemo: 13% vs 12.7%, NS Pts receiving moderately emetogenic chemo: 17% vs 12.8%, NS Minor control: 2-5 episodes of vomiting, regardless of nausea rating All patients: 16.4% vs 14.5%, NR Pts receiving moderately emetogenic chemo: 12.8% vs 10%, NS Pts receiving highly emetogenic chemo: 21.7% vs 21.2%, NS Failure: >5 vomiting episodes, regardless of nausea rating Pts receiving highly emetogenic chemo: 8.7% vs 2.1%, NS Pts receiving moderately emetogenic chemo: 2.8% vs 4.3%, NS All patients: 5.2% vs 5.1%, NR No. of cycles with vomiting episodes Pts receiving highly emetogenic chemo: 41.3% vs 38.3%, NS Pts receiving moderately emetogenic chemo: 31.4% vs 27.1%, NS All patients: 35.3% vs 31.6%, NR Patient preference: Preference: 22% vs 38%, 0.05 No preference: 40%, NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Kalaycio **1998** NR 5	Granisetron vs Ondansetron headache: 36% vs 39%, NS diarrhea: 36% vs 39%, NS creatinine (mean): 0.73 vs 0.60, NS bilirubin (mean): 0.60 vs 0.59, NS	All pts received an infusion of autologous stem cells 3 days after the chemo regimen was complete. All pts received hematopoietic growth factors after ASCT until engraftment was achieved. 2 pts were disqualified for being on antiemetics at the time of study entry and 1 pt was excluded for absence of her chart.
Leonardi **1996** Multicenter 3, 4, 5	Death: Both drugs:1.7% Ondansetron vs Granisetron Headache: 24% vs 23%, NS Lightheadedness: 13% vs 18%, NS Constipation: 11% vs 6%, NR Other AEs (not specified): 6% vs 6%, NR Number of cycles without any AEs: 62% vs 68%, NS	Moderately emetogenic (ME) chemo: a regimen containing Adriamycin >25 mg/m2 or epidoxorubicin >40 mg/m2 and/or cyclophosphamide >500 mg/m2 in combination with other agents except cisplatin. Highly emetogenic (HE) chemo: a regimen containing cisplatin >50 mg/m2 alone or in association with other antiblastic agents. Data is presented as a result of cycles, not patients; Ond was first administered in 65 patients and Gran in 53 patients. There were a total of 233 cycles (3 patients did not complete a second cycle - 2 died before the second cycle began and one refused a second cycle) evaluated for the 118 patients. There were 93 HE cycles (40%) and 140 ME cycles (60%); and there were 116 cycles with Ond and 117 with Gran.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Mantovani **1995** Single Center 5	Open RCT Parallel	none	Ondansetron iv 24mg Granisetron iv 3mg Tropisetron iv 5mg	Not explicitly stated unless pt had severe nausea.	NR/NR	58.2 97%male NR
Martoni **1995** Single Center 5	Open RCT Crossover	none	Ondansetron iv 24mg Granisetron iv 3mg	No other antiemetic drugs allowed, including corticosteroids.	NR/NR	62 75%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Mantovani **1995** Single Center 5	NR/NR/117	0/0/117	No. of cycles with Gran. used = 165 cycles No. of cycles with Ond. used = 150 cycles No. of cycles with Trop. used = 148 cycles ECOG performance status = 0: 60% ECOG performance status = 1: 31% ECOG performance status = 2: 8% ECOG performance status =3: 2% Cancer Stage II: 5% Cancer Stage III: 25% Cancer Stage IV: 70% Site of primary tumor: oral cavity: 27%; oropharynx; 24%; hypopharynx: 9%; Larynx: 37%; maxillary sinus: 2%; upper esophagus: 2% Crossed over once (i.e., to a second drug): 16% Crossed to a third drug: 2% Mean no. of chemo cycles/patient = 3.9
Martoni **1995** Single Center 5	NR/NR/124	0/0/124	Outpatients: 20% Inpatients: 80% Karnofsky perfm score median (range) = 80 (50-100) Primary tumor: NSCLC: 61% Primary tumor: Bladder: 27% Primary tumor: Ovary: 6% Primary tumor: Others: 6% Previous emesis (kinetosis, during pregnancy): 5% Alcohol use: 20% Chemo: CP (60) + VNR (25): 44% Chemo: CP (60) + EPI (120): 18% Chemo: CP (60) + EPI (60): 6% Chemo: CP (50) + EPI (50) + CTX (500): 6% Chemo: CP (70) + EPI (60) + MTX (40): 27%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Mantovani **1995** Single Center 5	Ondansetron vs Granisetron vs Tropisetron Complete response (CR): no nausea of vomiting or only mild nausea in the 24h after starting chemo: 82.4% vs 84.2% vs 72.5%, NS Major response (MR): single vomiting episode in the 24h after chemo; or no vomiting but moderate to severe nausea: 17.9% vs 10.5% vs 15.0%, NS Major efficacy (CR+MR): Complete and Major response combined: 100.0% vs 94.7% vs 87.5%, Minor response (MiR): 2-4 vomiting episodes in the 24h after starting chemo: 0.0% vs 2.6% vs 7.5%, Failures (F): >4 vomiting episodes in the 24h after starting chemo: 0.0% vs 2.6% vs 5.0%,
Martoni **1995** Single Center 5	Ondansetron vs Granisetron First cycle outcomes, including complete response (no nausea and no vomiting) No nausea: 60% vs 64%, NS No vomiting: 74% vs 76%, NS Complete response: No nausea and no vomiting: 59% vs 62%, NS Patient preference For study drug: 24.8% vs 44.6%, 0.003 Neither drug preferred: 30.6%, NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Mantovani 1995 Single Center 5	All 3 drugs were well tolerated and no severe AEs were observed during treatment. Headache, a common complaint among pts receiving 5-HT3 antagonists, was <10% and not significantly different in any of the 3 treatment arms. No other relevant side effects were observed in any of the pts during treatment	All pts were on study drugs for multiple courses of chemotherapy. 40 pts had al-Sarraf's classical chemo: 100 mg/m2 cisplatin (CDDP) iv over 2h using a standard pre- and post- hydration protocol with forced diuresis by 250 cc of 18% mannitol on Day 1 + 1000 mg/m2 of 5-fluourouracil (5-FU) iv, continuous infusion for 120H on Days 1-5. 77 pts had: 80 mg/m2 CDDP iv over 2 h according to standard pre- and post- hydration protocol with forced diuresis by 250 cc of 18% mannitol on Day 1; 600 mg/m2 of 5-FU infused during a period of 4h on days 2-5; and 20 mg/m2 of vinorelbine iv over 20 min on days 2 and 8. Response data given for the first chemo cycle only (data for all 3 cycles given in paper). Pts did not know to which antiemetic they had been assigned, even if they were crossed over to a different antiemetic due to failure. Significance was between Ond vs. Trop for CR+MR and Gran and Ond vs.Trop for MiR. P-values for all other comparisons were NS. Data was given mostly in terms of number of cycles, not number of pts. It appears there were 117 pts in cycle 1, 104 pts in cycle 2, and 87 pts in cycle 3; but withdrawal rates and reasons not given.
Martoni 1995 Single Center 5	Ondansetron vs Granisetron Headache: Data from both cycles combined/after crossover: 18.3% vs 12.7%, NS First cycle only: 15.5% vs 13.6%, NS Constipation: data for both cycles/ after crossover: 4.3% vs 2.7%, NS Diarrhea: data from both cycles combined (i.e., after crossover): 0.87% vs 2.7%, NS	Eligible pts randomized to Ond or Gran at the first cycle; they crossed over to second drug at the second cycle. Just before the third cycle, they were asked which antiemetic they preferred. We report only data from the first antiemetic drug used for the first cycle. Chemo included 5 different regimens containing CP (median dose = 60 mg/m2; dose range = 50-70 mg/m2) and 1 or 2 other drugs including epirubicin (EPI; 50-120 mg/m2) or cyclophosphamide (CTX; 500 mg/m2) or methotrexate (MTX; 40 mg/m2) or vinorelbine (VNR; 25 mg/m2). All regimens were administered IV on Day 1 and repeated every 21-28 days. Alcohol use ≥0.75 liters/day of wine. Pt preference for drugs was conditioned by which antiemetic the pt first received: only 7 (13%) patients preferred Ond vs. 25 (48%) who preferred Gran and 20 (38%) who had no preference when Gran was administered as the first cycle (p=0.019). 23 pts not evaluable at the 2nd cycle: 13 (6 on Gran and 7 on Ond) had a reduced dose of cytotoxic drugs; 9 (2 on Gran and 7 on Ond) did not receive the 2nd cycle at all; and 1 Gran had protocol violation. Cross-over analysis carried out on 101 pts who received both cycles.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Massidda 1996b NR 3	NR RCT Parallel	women	Ondansetron iv 8mg Granisetron iv 3mg Tropisetron iv 5mg short	No	NR/NR	51.7 0%male NR
Navari 1995 Multicenter 5	DB RCT Parallel	women	Ondansetron iv 0.45 mg/kg Granisetron iv 10 mcg/kg Granisetron iv 40 mcg/kg 15min	No	NR/NR	62.3 64%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Massidda 1996b NR 3	NR/NR/60	NR/NR/60	Performance status: 0: 42% Performance status: 1: 58% Kinetosis: yes: 7%; no: 93% Alcohol use: > 150ml of table-wine or equivalent: 57% Benzodiazepines concomitant use: 10% H2 antagonists concomitant use: 5% Chemo: Epirubicin high dose: 27%; mitomycin C + methotrexate + mitoxantrone: 15%; cyclophosphamide regimens: 58%
Navari 1995 Multicenter 5	NR/NR/994	7/0/987	Mean weight - 73.43 kg Weight range = 36.3 to 148.8 kg: 0% Mean alcohol consumption = 15.2 units/wk Mean body surface area (m2) = 1.84 Mean cisplatin dose = 81.5 mg/m2 Range of cisplatin doses = 50 to 126 mg/m2 Patients receiving a high dose of cisplatin ≥100mg: 27%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Massidda 1996b NR 3	Ond iv 8 vs Gran iv 3 vs Trop iv 5 Complete response: absence of vomiting and none or mild nausea Acute (within 24 h of chemo): 74% vs 58.6% vs 50.8%, NR Delayed (within days 2-5 of chemo): 64% vs 63.7% vs 47.3%, NR Complete protection from nausea: no episodes of nausea Delayed: 50% vs 35% vs 27%, ond. vs gran; p=0.104 Acute: 56% vs 37% vs 20%, ond vs gran: p=0.018 Complete protection from vomiting: no episodes of vomiting Acute: 75% vs 70% vs 72%, NS Delayed: 70% vs 82% vs 27%, NS
Navari 1995 Multicenter 5	Ondansetron vs Granisetron 10 vs Granisetron 40 Total control rate (TCR) (pts did not experience any vomiting, retching, or nausea of any severity and who received no rescue med) Total N of patients: 39% vs 38% vs 41%, NS Females: 28% vs 33% vs 28%, NS High dose of Cisplatin patients: 25% vs 28% vs 33%, NS Males: 46% vs 48% vs 40%, NS No emesis - pts who did not vomit, retch, or receive any rescue medication Total N of patients: 51% vs 47% vs 48%, NS High dose of Cisplatin patients: 35% vs 38% vs 37%, NS Males: 59% vs 50% vs 56%, NS Females: 37% vs 42% vs 34%, NS No nausea - pts who did not experience nausea and did not receive rescue med Total N of patients: 25% vs 28% vs 33%, NS Females: 28% vs 33% vs 29%, NS High dose of Cisplatin patients: 28% vs 28% vs 36%, NS Number of Males: 47 vs 42 vs 49, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Massidda 1996b NR 3	AE data given: "AEs correlated with the 3 antiemetics were mild and reversible and essentially represented by constipation, headache, and diarrhea."	The only p-values of significance were for Ond vs. Gran (p=0.018) and Ond vs. Trop (p=0.05) in acute nausea; and in delayed nausea: Ond vs. Gran (p=0.104) and Ond vs. Trop (p=0.01).
Navari 1995 Multicenter 5	All treatment groups, data recorded day of treatment and throughout the 5-11 day follow-up period Headache: for total N: 20%, NS Diarrhea: for total N: 17%, NS Constipation: for total N: 14%, NS Fever: for total N: 12%, NS Anorexia: for total: 11%, NS Fatigue: for total: 10%, NS There were no significant differences between treatment groups for incidence or type of AE reported. Changes in vital signs and clinical lab parameters were comparable across study groups and were considered the result of the underlying disease or cytotoxic treatment rather than a consequence of the study drugs.	To maintain blinding, placebo administered as iv 4 & 8 h after chemo in both gran groups. All iv administrations occurred over a 15 min infusion rather than recommended 5-min infusion for granisetron. Alcohol unit - 150 mL wine, 0.25L beer, or 50 mL liquor. Mean values are average units/week over the previous 12 months. The outcomes for the subgroup of patients receiving a high cisplatin dose were further stratified by gender (but we do not report these results in our tables). There were no differences in % of pts who received rescue medication; in each group 43% of patients received additional antiemetics. Time to first nausea and time to first emesis were similar for all treatment groups (data given as graphical representation).

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Noble **1994** Multicenter 3	DB RCT Crossover	none	Ondansetron iv 24mg/d (8 mg tid) Granisetron iv 3mg/d 5 days	no	none/NR	51.8 77%male NR
Oge **2000** NR 4, 5	NR RCT Parallel	none	ondansetron iv 8mg granisetron iv 3mg Tropisetron iv 5mg	No other antiemetics were given within the first 24 h; after Day2, pts experiencing nausea received metoclopramide 10mg/6hr po.	NR/NR	50.17 64%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Noble **1994** Multicenter 3	NR/NR/359	0/0/359	Mean weight = 67.4 kg (range 39-118 kg) Head and neck cancer: 25% Lung cancer: 18% Ovarian and cervical cancer: 8% Testicle cancer: 17% Other cancer: 32% Pts receiving cisplatin in Cycle 1: 83% Mean cis. dose, C.1 (range) = 19.25 (11.3-37.9) Pts receiving ifosfamide in Cycle 1: 17% Mean ifo. dose, for C.1 (range) = 1392 (1018-2455)
Oge **2000** NR 4, 5	NR/NR/106	0/0/106	Primary Tumor: __ Lung: 29%; Nasopharynx: 20% Metastatic carcinoma: 12% Cervix: 8% Larynx: 4% Testis: 3% Adrenal: 3% Ovary: 3% Breast: 2% Thyroid: 2% Primary Tumor: Lymphoma: 2% Primary Tumor: Bladder: 2% Primary Tumor: Other: 11% Chemo: Cisplatin + 5FU: 33%; Cisplatin+ Etoposide: 18%; EAP: 11%; CIF: 7%; Cisplatin+Vinalbine: 5%; BEP: 4%; MIC: 4%; Cisplatin+Gemsitabine: 3%; Other chemo: 16%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Noble **1994** Multicenter 3	Granisetron vs Ondansetron vs undecided Patient preference: 34% vs 25.6% vs 39.2%, p=0.048 Ondansetron vs Granisetron Other efficacy results: No vomiting and treatment failure, cycle 1 No vomiting: (0-24h): 90.7% vs 94.9%, NS 0-5 days: 45.4% vs 44.3%, NS Treatment failure (>4 vomits): 0-24h: 2.2% vs 2.3%, NS 0-5 days: 21.3% vs 20.5%, NS
Oge **2000** NR 4, 5	*ond iv 8 vs gran iv 3 vs Tropisetron* Complete response (CR): no vomiting or retches Acute (24h): 51.4% vs 65.7% vs 61.1%, NS Delayed (24-72h): 48.5% vs 55.5% vs 48.5%, NS Partial response (PR): 1-2 vomits, or mild to moderate nausea, or 1-3 retches Acute (24h): 22.8% vs 22.8% vs 19.4%, NS Delayed (24-72h): 22.8% vs 25% vs 37.1%, NS Failure: >2 vomits or >3 retches or severe nausea Acute (24h): 25.7% vs 11.4% vs 19.4%, NS Delayed (24-72h): 28.5% vs 19.4% vs 14.2%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Noble **1994** Multicenter 3	Ondansetron vs Granisetron Any adverse event, cycle 1 Any serious AE (non-specific): 6.0% vs 6.3%, NS Any AE (non-specific): 67.8% vs 67.6%, NS Specific adverse events for Cycle 1 Pain: 12.0% vs 14.8%, NS Insomnia: 6.0% vs 5.1%, NS Headache: 19.1% vs 18.2%, NS Constipation: 18.0% vs 19.9%, NS Hypertension: 6.0% vs 4.5%, NS Decreased Appetite: 6.0% vs 2.8%, NS Diarrhea: 7.7% vs 4.5%, NS	Double dummy study. After cross-over, pts received other antiemetic therapy. 5% of patients in both groups discontinued treatment due to poor antiemetic efficacy at cycle 1 [approx. Ond = 9 pts (of 183) and Gran = 9 pts (of 176)]. Pts who experienced breakthrough nausea and/or vomiting received up to 2 further blinded doses of Gran 3mg iv (pts receiving gran) or placebo Gran (pts receiving Ond). Any subsequent uncontrolled nausea and vomiting was treated with a standard antiemetic of the MD's choice and the pt was withdrawn from that cycle. These pts were eligible for inclusion in the second treatment cycle. Pts were in hospital for each of the 5-day chemo cycles. Data for Cycle 1 and cycle 2 reported in study; we only looked at Cycle 1 data (i.e., pre-cross-over data). Cycle 1 contained 359 pts; cycle 2 contained 309 pts. Times to first vomiting episode and first use of rescue were significantly longer in Cycle 1 than cycle 2 (p=0.029 and p=0.036, respectively) and approached significance for time to first episode of moderate or severe nausea (p=0.074).
Oge **2000** NR 4, 5	All drugs combined Headache: 3.8%, NR Constipation: 0.94%, NR	E= etoposide; P= Cisplatin; B= Bleomycin; D= doxorubicin; I= Ifosfamide; M= mitomycin; C= cisplatin (?); F= 5-Fluourouracil. No pts were excluded from the study due to adverse effects. There were no differences in adverse effects in the 3 different drug groups.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Park **1997** Single Center 5	Open CT Parallel	none	Granisetron iv 3mg 1 day Ondansetron iv + po 24mg 5 day	No	No/NR	51 53%male NR
	DB RCT Parallel	women, corticosteroid use	Ondansetron iv 32mg Granisetron po 2mg 15min	Prednisone ≤ 10 mg daily (or other equivalent corticosteroid dose) was allowed at any time. Prophylactic dexamethasone and methylprednisolone were allowed as a component of pretherapy.	Dexamethasone and methylprednisolone was permitted/NR	

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Park 1997 Single Center 5	NR/NR/97	2/NR/95	Primary Tumor: Head and neck: 19% Stomach: 33% Esophagus: 3% Colorectal: 14% Breast: 20% Gynecologic: 2% Soft tissue sarcoma: 4% Pancreaticobiliary: 3% Other: 2% Chemo: Cisplatin 80mg/mean: 85% Cisplatin 100mg/mean: 67% Chemo: Adriamycin: 15% Chemotherapy naïve: 74% Chemotherapy non-naïve: 26% Breast cancer: 60%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Park **1997** Single Center 5	Ondansetron vs Granisetron Complete Response: no vomiting and no use of rescue medication Acute (within 24h): 45.8% vs 53.2%, NS Days 2-7: 27.1% vs 29.8%, NS Major response: 1-2 episodes of vomiting or moderate to severe nausea Acute (within first 24 hours): 27.1% vs 23.4%, NS Days 2-7: 27.1% vs 29.8%, NS Minor response: 2-4 vomiting episodes, regardless of nausea Acute (within first 24 hours): 20.8% vs 17.0%, NS Days 2-7: 33.3% vs 34.0%, NS Failure: >4 episodes of vomiting Days 2-7: 12.5% vs 14.9%, NS Acute (within first 24 hours): 6.3% vs 6.4%, NS Need for rescue treatment Acute: 14.6% vs 14.9%, NS Delayed: 27.7% vs 31.3%, NS
	Ondansetron iv vs Granisetron po Total control (no emesis (vomiting or retching), no nausea of any severity, and no use of any rescue medication: Total control for 0-24h after study period 0: Users of dexamethasone/methylprednisolone: 59.8% vs 61.9%, NS Males: 74.8% vs 75.0%, NS Carboplatin pts: 72.6% vs 74.0%, Cyclophosphamide pts: 54.2% vs 55.3% Nonusers of dexamethasone/methylprednisolone: 50% vs 48.5%, NS All pts: 58.0% vs 59.4%, NS Total control for 0-48h after study period 0: Cyclophosphamide pts: 39.8% vs 41.5%, NA Nonusers of dexamethasone/methylprednisolone: 40% vs 39.6%, NS Users of dexamethasone/methylprednisolone: 44.7% vs 48.3%, NS Females: 66.4% vs 65.2%, NS All pts: 43.8% vs 46.7%, NS Carboplatin pts: 57.5% vs 63.9%, NA Patients who were emesis free (i.e., incidence of emesis measurement) All pts (0-24h): 72.6% vs 71.0%, NS Females (0-24h): 69.7% vs 67.7%, Males (0-24h): 84.1% vs 83.9%, Use of corticosteroids (0-24h): 74.0% vs 73.2%, Cyclophosphamide (0-24h): 69.8% vs 67.2%, Carboplatin (0-24h): 85.0% vs 84.9%, N/A Non-use of corticosteroids (0-24h): 66.0% vs 61.4%, All pts (0-48h): 59.1% vs 58.7%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Park **1997** Single Center 5	Gran iv 3 vs Ond iv 32 All Adverse events Headache: 6.4% vs 8.3%, NS Dyspepsia: 4.3% vs 2.1%, NS Diarrhea: 4.3% vs 6.3%, NS Decreased Appetite: 0% vs 2.1%, NS Agitation: 0% vs 0%, NS Somnolence: 0% vs 0%, NS Constipation: 10.6% vs 8.3%, NS	Pts were to receive 80-100 mg/m2 of cisplatin or 40 mg/m2 doxorubicin.
	Ondansetron iv vs Granisetron po Any adverse event experienced: 76.2% vs 77.1%, NR Headache: 21.0% vs 20.6%, NR Asthenia: 18.0% vs 16.2%, NR Constipation: 10.9% vs 12.9%, NR	Double-dummy study. The prophylactic corticosteroid (dexamethasone or methylprednisolone) usage was equivalent between the two study groups. One alcohol unit = 5.07 oz wine; 8.46 oz beer; 1.69 oz spirits. Mild nausea = easily tolerated by pt, causing minimal discomfort and not interfering with

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Perez 1998 Multicenter 4						55.6 20%male NR
Perez 1998a Multicenter 3, 4	DB RCT Crossover	women, breast cancer	Granisetron iv 0.01mg/kg 30 sec Ondansetron iv 32mg 15 min	Dexamethasone (Dex) or methylprednisolone permitted at physician's discretion; if given in cycle1, the same medication and dose was required to be given in cycle 2.	No/NR	51.6 0%male White: 439 (76.6) Black: 85 (14.8) Asian: 11 (1.9) Other: 38 (6.6%)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Perez 1998 Multicenter 4	NR/NR/1085	16/1/1085	Lymphatic/hematologic malignancies: 13% Respiratory/intrathoracic malignancies: 13% IV Dexamethasone mean dose = 15.2 mg Oral dexamethasone mean dose = 15.3 mg Using prophylactic corticosteroids: 81%
Perez 1998a Multicenter 3, 4	NR/NR/623	//623	Mean body weight (+/- SD) = 75.3 kg (+/- 18.5) (Body weight range = 37.3 - 166.8 kg) Mean alcohol units/week = 2.00 units/week (range = 0 - 73.4 units/wk)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Perez **1998** Multicenter 4	All pts (0-48h): 59.1% vs 58.7%, NS Males (0-48h): 73.8% vs 73.2%, NS Females (0-48h): 55.5% vs 54.9%, Use of corticosteroids (0-48h): 60.5% vs 60.8%, Non-use of corticosteroids (0-48h): 53.0% vs 49.5%, Cyclophosphamide (0-48h): 56.8% vs 54.9%, Carboplatin (0-48h): 67.3% vs 71.4%, N/A Ond (0-24h) vs Ond (0-48h) vs Gran (0-24h) vs Gran (0-48h) vs <u>Maximum severity of nausea (none, mild, moderate, severe, unknown)</u> Unknown: 0.7% vs 1.1% vs 0.4% vs 0.6%, Severe: 3.9% vs 4.8% vs 5.7% vs 8.9%, Moderate: 8.8% vs 14.2% vs 9.8% vs 15.5%, Mild: 26.3% vs 33.0% vs 22.0% vs 25.8%, None: 60.2% vs 47.0% vs 62.2% vs 49.3%, Ondansetron vs Granisetron <u>Use of antiemetic rescue medication</u> % of patients who received at least one dose of antiemetic rescue medication: 48.4% vs 47.8%, <u>Patients who were nausea-free (24 and 48h)</u> Males (0-24h): 74.8% vs 75.9%, Females (0-24h): 54.4% vs 55.8% Corticosteroid users (0-24h): 60.1% vs 62.4%, No corticosteroid use (0-24h): 42.0% vs 40.6%, NS Cyclophosphamide (0-24h): 54.6% vs 55.6%, Carboplatin (0-24h): 72.6% vs 75.6%, N/A Total (0-24h): 58.4% vs 60.0%, NS Carboplatin (0-48h): 57.5% vs 64.7%, N/A Males (0-48h): 66.4% vs 67.9%, Females (0-48h): 39.0% vs 42.1%, Corticosteroid users (0-48h): 44.9% vs 49.0%, No corticosteroid use (0-48h): 42.0% vs 40.6%, NS
Perez **1998a** Multicenter 3, 4	Ondansetron vs Granisetron <u>Emesis-free and nausea-free patients at 24 h</u> Emesis free pts at 24h (both cycles combined): 62.7% vs 58.6%, NS Emesis free pts at 48h (both cycles combined): 45.0% vs 42.2%, NS Nausea free pts at 24h (both cycles combined): 48.5% vs 44.0%, 0.034 Nausea free pts at 48h (both cycles combined): 31.0% vs 26.7%, 0.021 <u>Patient preference for study medication</u> Patient preference for study medication: 50.9% vs 49.1%, NR <u>Total control during 48 h period: no nausea, emesis, or antiemetic rescue</u> Total emetic control at 24h (both cycles combined): no nausea, emesis, or antiemetic rescue: 48.3% vs 44.0%, 0.04 Total emetic control at 48h (both cycles combined): no nausea, emesis, or antiemetic rescue: 30.5% vs 26.2%, 0.024

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Perez **1998** Multicenter 4	Diarrhea: 6.3% vs 6.6%, NR Dizziness: 9.6% vs 5.4%, 0.011 Insomnia: 4.8% vs 5.2%, NR Dyspepsia: 5.2% vs 5.0%, NR Decreased Appetite: 5.0% vs 4.6%, NR Abnormal Vision: 4.2% vs 0.6%, p<0.001 Total withdrawals: 2.6% vs 0.55%, Withdrawals due to AEs: Total patients Withdrawals due to AEs - drug group not specified: 0.28%,	= easily tolerated by pt, causing minimal discomfort and not interfering with normal everyday activities. Moderate nausea = sufficiently discomforting to interfere with normal everyday activities. Severe nausea = incapacitating and prevented normal everyday activities. P-values are NS unless a value or NR ("not reported") is given. Withdrawals are given, but it is not stated when these withdrawals occurred, and if the total N=1085 includes these 17 withdrawals or not. Dexamethasone and methylprednisolone was permitted as a prophylactic component of pretherapy.
Perez **1998a** Multicenter 3, 4	Ondansetron vs Granisetron vs both drugs All adverse events >5% (excluding death) Diarrhea: 5.9% vs 7.7% vs 2.8%, Abnormal vision: 6.3% vs 0.4% vs 0%, p=0.001 Constipation: 6.3% vs 5.1% vs 3%, Dizziness: 14.0% vs 5.2% vs 2.8%, Fatigue: 14.3% vs 11.3% vs 5.2%, Headache: 14.3% vs 15.7%, Patients experiencing any AE: 75.4% vs 72.1% vs 42.9%, Anorexia: 5.4% vs 3.6% vs 0.9% An AE that began in cycle1 and continued unchanged was not considered an AE in cycle 2.	573/623 pts crossed over to both drugs. An alcohol unit is equivalent to 5.07 fl oz wine, 8.46 fl oz of beer, or 1.69 fl oz of spirits. Cycle 1: Dex and Pred were given to 82.3% of Gran pts and 79.8% of Ond pts; in cycle 2, those numbers were 80.1% and 82.1% Mean cyclophosphamide dose was 591.3 (Gran) and 575.1 (Ond) mg/m2 for cycle 1 and 572.2 (Gran) and 589.6(Ond) mg/m2 for cycle 2. Mean doxorubicin dose range was 53.7(Gran) and 53.9(Ond) mg/m2 for cycle 1 and 53.5(Gran) and 53.7(Ond) mg/m2 for cycle 2. A cycle effect was seen at 48 hours (p=0.024) with higher total control rates during Cycle 2 than during cycle 1.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Poon **1997** Single Center 4	DB RCT Crossover	women, breast cancer	Ondansetron iv 16mg Granisetron iv 3mg	Not allowed	NR/NR	47 0%male Chinese = 100%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Poon **1997** Single Center 4	NR/NR/20	0/0/20	Breast cancer: 100% Radical mastectomy: 90% Wide local excision plus axillary dissection: 10%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Poon **1997** Single Center 4	Ondansetron vs Granisetron Acute vomiting: complete, major, minor responses, and failure Failure (>5 vomiting episodes): 5% vs 5%, NS Complete response (no vomiting): 67.5% vs 72.5%, NS Minor response (3-5 vomiting episodes): 5% vs 7.5%, NS Major response (1-2 vomiting episodes): 22.5% vs 25%, NS Delayed vomiting: complete, major, minor responses, and failure Failure (>5 vomiting episodes): 12.5% vs 10%, NS Minor response (3-5 vomiting episodes): 15% vs 17.5%, NS Complete response (0 vomiting episodes): 55% vs 52.5%, NS Major response (1-2 vomiting episodes): 17.5% vs 20%, NS Acute nausea: no, mild, moderate, and severe nausea Severe nausea (bedridden because of nausea): 10% vs 10%, NS Moderate nausea (interferes with daily life): 10% vs 15%, NS Mild nausea (interferes with eating): 45% vs 37.5%, NS No nausea: 35% vs 37.5%, NS Acute nausea: Mean VAS score (range): 2.5(0-8) vs 2.2(0-9), NS Delayed nausea: no, mild, moderate, and severe nausea Moderate nausea (interferes with daily life): 15% vs 22.5%, NS Severe nausea (bedridden because of nausea): 7.5% vs 10%, NS Mild nausea (interferes with eating): 52.5% vs 40%, NS No nausea: 25% vs 27.5%, NS Delayed nausea: Mean VAS score (range): 2.8 (0-9) vs 2.9 (0-9), NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Poon **1997** Single Center 4	Ondansetron vs Granisetron Constipation: 30% vs 20%, NS Headache: 25% vs 20%,	The first two cycles of chemo for each pt were used for the trial. Pts were randomized to receive either Gran on Day 1 followed by Ond on Day 8 or Ond on Day 1 and Gran on Day 8. The order of the drugs were reversed in the second cycle. A total of 40 cycles were analyzed; and the data is given in terms of these cycles. Acute vomiting/nausea = in the first 24 h after chemo; delayed nausea vomiting = in the following 7 days after chemo. Chemo given after resection of breast cancer.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Raynov 2000 Single Center 5	Open RCT Parallel	none	MCL- day 1: 2mg/kg MCL- days 2-6: 1mg/kg Ondansetron: 8 mg all days Granisetron: 3mg all days Tropisetron: 5mg all days	yes, for some arms.	NR/NR	49 89%male NR
Ruff 1994 Multicenter 5	DB RCT Parallel	none	Ondanstron iv 8mg Ondansetron iv 32mg Granisetron iv 3mg once	No	No/NR	55 56%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Raynov 2000 Single Center 5	NR/NR/72	0/0/72	Primary Tumor- Lung: 54% Primary Tumor- Testis: 31% Primary Tumor- Ovary: 11% Primary Tumor- Head and Neck: 4% Chemo: Cisplatin monotherapy (120 mg/m2): 25% Chemo: Cisplatin (≥ 50) + Cyclophosphamide (≥500): 75% Chemo: Cisplatin (≥ 50) + Doxorubicin (≥ 50): 8% Chemo: Cisplatin (≥ 50) + Vinblastine (5): 31% Chemo: Cisplatin (≥ 50) + Bleomycin (30 flat dose): 31% Mean cisplatin dose = 75 mg/m2
Ruff 1994 Multicenter 5	NR/NR/NR	1/NR/Various	Age: 30-65: 75% Age: >66: 20% Alcohol use: current> 4units/day: 9% previous> 4units/day: 15% cisplatin dose: >100 mg/m2: 14% emetic potential: none: 25%; low: 42%; moderate: 32% Primary tumor: Gynecological: 30% Lung; 25%; Head and neck: 23%; Genitourinary: 9% Gastrointestinal: 8%; Bone/soft tissue: 2% Median cisplatin dose = 78 mg/m2 Mean body surface area = 1.73 m2

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Raynov **2000** Single Center 5	MCL vs MCL + CS vs OND vs Ond + CS vs Granisetron Need for Rescue Therapy: 29% vs 16% vs 6% vs 3% vs 22.2%, NR Ondansetron vs Ond + CS vs Gran vs Gran + CS vs Tropisetron Complete response for vomiting: No emetic episodes Acute: 63.9% vs 85.7% vs 22.2% vs 100% vs 45.4%, NR Delayed: Overall and major response for vomiting Major response for vomiting (1-2 emetic episodes): acute: 16.7 % vs 8.6% vs 33.3% vs 0% vs 27.3%, NR Overall response for vomiting (no episodes (CR) plus 1-2 emetic episodes): acute: 80.6% vs 94.3% vs 55.6% vs 100% vs 72.7%, NR No nausea: acute: 63.9% vs 85.7% vs 22.2% vs 84.7% vs 45.4%, NR Mild nausea and overall (mild+none) response for nausea Mild Nausea: acute: 22.1% vs 7.3% vs 33.3% vs 14.3% vs 40.9%, NR Overall response: no nausea + mild nausea: acute: 86% vs 93% vs 55.6% vs 100% vs 86.4%, NR
Ruff **1994** Multicenter 5	Ond 8 mg vs Ond 32 mg vs Gran 3 mg Complete response: no emetic episodes: 59% vs 51% vs 56%, NS Ondansetron 8 mg vs Ondansetron 32 m vs Gransetron 3 mg Moderate response: 1-2 emetic episodes: 17% vs 23% vs 22%, NS Nausea: none and/or mild Mild: 15% vs 21% vs 17%, NS Either none or mild combined: 71% vs 69% vs 73%, NS None: 56% vs 48% vs 56%, NS Gran 3 vs Ond 8 vs Ond 32 Pt satisfaction scores: 0= not at all satisfied to 100=completely satisfied: 89 vs 91 vs 85, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Raynov **2000** Single Center 5		Rescue medication was given to pts with ≥ 2 episodes of vomiting or severe chemo-induced nausea.
Ruff **1994** Multicenter 5	Ond 8 mg vs Ond 32 mg vs Gran 3 mg Overall Constipation: 0.61% vs 0% vs 2.4%, NS Diarrhea:1.2% vs 3.1% vs 0%, NS Headache: 12.1% vs 9.8% vs 6.5%, NS Total number of patients experiencing AEs: 14.5% vs 15.3% vs 14.7%, NS Dizziness: 0.61% vs 1.8% vs 0.59%, NS	

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Slaby **2000** Single Center 5	not specified RCT Parallel	ASCT	Ondansetron iv 16mg Granisetron iv 3mg Tropisetron iv 5mg 7 days	20 mg iv dexamethasone was added to antiemetics in case of its failure.	NR/NR	38.0 67%male NR
Spector **1998** Multicenter 5	DB RCT Parallel	none	Ondansetron po (tablet) 24mg Granisetron i.v. 0.10 mg/kg	No concurrent use of corticosteroids (including dexamethasone) allowed.	None/None	64.05 56%male Caucasian = 90%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Slaby **2000** Single Center 5	NR/NR/45	0/0/45	BEAM 200: 67% BEAM 400: 33% Lineages of previous therapy = 2%; range = 1%-5% Previous chemo-induced nausea: 91% Previous chemo-induced vomitus (emesis): 73%
Spector **1998** Multicenter 5	NR/NR/371	//371	Mean height = 169.4 cm: Mean weight = 72.55 kg Mean cisplatin dose = 65.4 mg/m2 Median cisplatin dose = 70 mg/m2 Range of cisplatin dosage = 31-100 mg/m2 Lung cancer: 59% Gynecological cancer: 10% Genitourinary cancer: 9% Gastrointestinal cancer: 8% Head/neck cancer: 7% Other cancer types: 7%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Slaby 2000 Single Center 5	Ondansetron vs Granisetron vs Tropisetron Nausea and/or emesis control failure (for 6 and 10 days) 10 days: 80% vs 46.7% vs 33.3%, Gran and Trop vs. ond: p=0.03 6 days: 26.7% vs 33.3% vs 13.3%, NS Emesis control failure (6 and 10 days) Emesis control failure (6 and 10 days) 10 days: 46.7% vs 26.7% vs 6.7%, Gran and trop vs. Ond; p=0.04 6 days: 6.7% vs 0% vs 0%, NS
Spector 1998 Multicenter 5	Ondansetron po vs Granisetron iv Therapeutic failures Withdrawal prior to failure: 1% vs 1%, >5 emetic episodes over 24 h: 27% vs 35%, Number with need for rescue therapy due to severity of nausea or vomiting: 50 vs 64, NS Complete response (CR): no emetic episodes and no use of rescue medications Males: 67% vs 59%, NS Females: 46% vs 41%, NS No emetic episodes and no use of rescue medication: 58% vs 51%, NS Major response MR (1-2 emetic episodes): 11% vs 10%, NS Minor response (3-5 emetic episodes): 3% vs 3%, NS Patient Assessments Of Nausea: no nausea over 24h (complete control: no nausea, rescue, or withdrawal): 43% vs 35%, NS Of Appetite: Worse than usual at 24h: 43% vs 44%, NS Of Appetite: As usual at 24h: 53% vs 52%, NS Of Appetite: Better than usual at 24h: 4% vs 4%, NS Patient Satisfaction with Antiemetic Therapy at 24h: very plus somewhat satisfied: 88% vs 83%, NS CR + MR CR + MR: 68% vs 61%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Slaby 2000 Single Center 5	Ondansetron vs Granisetron vs Tropisetron Headache: 53.3% vs 33.3% vs 20%, NS Total patients: Asthenia: 4.4%, NR	BEAM conditioning regimen consists of 4 cytotoxic drugs: Day 1 = carmustine 300 mg/m2; Day 2-5: etoposide 200 or 400 mg/m2/day; Day 2-5: cytosine arabinoside 400 mg/m2/day; Day 6: melphalan 140 mg/m2. Thus, two separate regimens: BEAM 200 (etoposide 200 mg/m2/day) and BEAM 400 (etoposide 400 mg/m2/day). The highest incidence of nausea and/or emesis control failures occurred on Day 3 (6 pts) and on Day 7 (7 pts). The maximum incidence of vomiting was observed from Days 7-10 (the post-chemo period). Constipation was not markedly pronounced in the pts.
Spector 1998 Multicenter 5	Ondansetron vs Granisetron Adverse events Fever: 3% vs 1%, NS Diarrhea: 3% vs 0.5%, NS Malaise/fatigue: 3% vs 4%, NS Constipation: 0.5% vs 2%, NS Any adverse event experienced: 24% vs 28%, NS Headache: 7% vs 12%, NS	Study protocol amended after the study initiation to allow use of carboplatin at a dose of >200 mg/m2 instead of cisplatin. P-values NS if no value specified. Chemo: cisplatin 50-75 mg/m2 administered as a single iv infusion over a period of ≤ 3 hrs (co-administration of other chemo agents was permitted at the discretion of the investigator, with the exception of cyclophosphamide at a dose of ≥500 mg/m2, nitrogen mustard, dacarbazine (DTIC), procarbazine, carmustine, and ifosfamide). No statistically significant differences existed between treatment groups for time to treatment failure. Of pts who failed treatment, few did so within the first 3h; most failed between 6-24h after the start of chemo. N of pts who finished appetite survey at 24h: Ond = 136/184 (73.9%) and Gran = 129/187 (69.0%). No explanation or reason given as to why drop in numbers occurred for this part of the study.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Stewart, A. **1995** Multicenter 4	DB RCT Parallel	women	Ondansetron iv+po 16mg Ondansetron po only 16mg Granisetron iv only 3mg 5 days	NR	NR/NR	50.3 0%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Stewart, A. **1995** Multicenter 4	NR/NR/514	16/10/488	Mean surface area = 1.70 m2: 95% Chemo: cyclophosphamide: 1% Chemo: CMF: 45% Chemo: AC combinations: 3% Chemo: EC combinations: 33% Other Cyclophosphamide combinations: 12%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
	Ondiv +po vs Ond po vs Gran iv Emesis control: Acute (day 1) Results No. of pts with no emetic episodes: Complete response: acute: 77.7% vs 78.1% vs 77.2%, NS No. of pts for whom data were missing: acute: 0.6% vs 6.4% vs 3.6%, NS No. of pts with 1-2 emetic episodes: acute: 10.8% vs 8.4% vs 9.6%, NS Rescued/withdrawn due to lack of response: acute: 1.8% vs 7.7% vs 4.2%, 0.014 Emesis control: Worst Day of Days 1-5 Results No emetic episodes days 1-5: Complete response: delayed: 58.1% vs 58.1% vs 52.4%, NS No. of pts for whom data were missing: 0.6% vs 0% vs 3.6%, NR Rescue/withdrawn due to lack of response days 1-5: 16.8% vs 20% vs 25.3%, P 1-2 emetic episodes days 1-5: 16.8% vs 10.9% vs 12.0%, NS
Stewart, A. **1995** Multicenter 4	Nausea control: Acute (day 1) Results No. of pts with moderate nausea episodes: acute: 12.6% vs 10.9% vs 15.1%, NS No. of pts with mild nausea episodes: acute: 28.1% vs 21.9% vs 18.7%, NS Severe nausea or rescued/withdrawn due to lack of response: acute: 8.4% vs 11.6% vs 9.6%, NS No. of pts for whom data was missing: acute: 0.6% vs 0.6% vs 4.8%, NR No. of pts with no nausea episodes: acute: 50.3% vs 54.8% vs 51.8%, NS Nausea control: worst day of Days 1-5 No. of pts experiencing no nausea days 1-5: 32.9% vs 33.5% vs 24.1%, see note No. of pts experiencing mild nausea: 29.3% vs 18.1% vs 23.5%, NS No. of pts experiencing moderate nausea: 18.0% vs 16.8% vs 18.7%, NS Severe nausea or rescued/withdrawn due to lack of response: 19.2% vs 31.0% vs 30.1%, NS No. of pts for whom data were missing: 0.6% vs 6.4% vs 3.6%, NR Gran iv vs Ond iv/po vs Ond po Global satisfaction with treatment Global satisfaction with treatment median score: 89% vs 91% vs 93%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Stewart, A. **1995** Multicenter 4	Ond iv+po vs Ond po only vs Gran Constipation: 11.1% vs 6.3% vs 7.8%, NS Headache: 7.8% vs 9.5% vs 8.4%, NS The most common AEs occurred in >1% of the study population according to treatment group.	Adverse events analyses were for all 514 patients randomized; ITT analysis (488 of 514) excluded 26 pts: 16 received incorrect antiemetics treatment prior to chemo and 10 received antiemetic treatment that was not clearly documented. CMF = cyclophosphamide + methotrexate + 5-fluorouracil; AC combinations = Adriamycin + cyclophosphamide + others (e.g., 5-fluorouracil, vincristine); EC combinations = epirubicin + cyclophosphamide + others (e.g., 5-fluorouracil, vincristine). For nausea control, the severity of nausea was significantly reduced with both Ond regimens compared to the Gran group (p=0.009) over the 5 day period.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Stewart L. **2000** Single Center 5	DB RCT Crossover	none	Ondansetron iv 8mg Granisetron iv 3mg	8-mg IV bolus of dexamethasone was given with the antiemetic on Day1; and 4 mg dex po was given tid on days 2-4 and/or metoclopramide 0 or 20 mg orally on days 2-4.	NR/NR	56 43%male NR
Yalcn **1999** Single Center 3	NR RCT Parallel	women	Granisetron iv 3mg Tropisetron iv 5mg Ondansetron iv 8mg	No	No/NR	44.0 2%male NR
Zeidman **1998** Single Center 3, 4, 5	NR RCT Parallel	none	ondansetron iv & po 16mg granisetron iv 3mg	No	none/none	55 71%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Stewart L. **2000** Single Center 5	NR/NR/21	5/NR/16	Cisplatin mean dose 74 mg/m2 (range: 59-100 mg/m2)
Yalcn **1999** Single Center 3	NR/NR/54	0/0/54	Breast Cancer: 100% Chemo: CMF: 31% Chemo: CAF: 33% Chemo: CEF: 35%
Zeidman **1998** Single Center 3, 4, 5	NR/NR/60	2/0/58	hematological neoplasms: 81% lymphoproliferative disorders: 53% multiple myeloma: 16% acute myeloid leukemia: 12% solid tumors: 19% Highly emetogenic chemo: adriamycin-cisplatin group: 55% Moderately emetogenic chemo regimens: 45%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Stewart L. **2000** Single Center 5	Ondansetron vs Granisetron Severity of nausea Day 1 mean nausea score (scale: 0-3): 0.65 vs 0.44, NS Day 2 mean nausea score (scale: 0-3): 1.0 vs 1.48, NR Day 7 mean nausea score (scale: 0-3): 0.7 vs 0.8, NR % of courses where pts had no nausea or mild nausea on day 1 Number(% of courses): 36 cycles(90%) vs 46 cycles(94%), NR Number of episodes of retching or vomiting Day 1 mean no. of vomiting episodes: 0.68 vs 0.43, NR Day 2 mean no. of vomiting episodes: 2.50 vs 0.8, NR Day 7 mean no. of vomiting episodes: 0.55 vs 0.60, % of course where pts suffered from no vomiting on day 1: 77.5% vs 88%, NR
Yalcn **1999** Single Center 3	
Zeidman **1998** Single Center 3, 4, 5	Adriamycin/cis. vs Moderate regimens Sensation of nausea Nausea, stratified by chemo type: 15.6% vs 11.5%, NR Sensation: 25% vs 7%, NR Ondansetron vs Granisetron Episodes of vomiting Episodes: 29% vs 13.3%, NR Vomiting, stratified by chemo type: 22% vs 8%, NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Stewart L. **2000** Single Center 5		The study was designed with a random allocation using a Latin square design in sets of four. First day was a head-to head of the study drugs; days 2-4 only corticosteroids (not the study drugs) were administered. No data on adverse events were given. Data on days 2-4, though given in study, are not reported here. Dex = dexamethasone; meto = metoclopramide. Emesis control info was collected for 16 pts (10 women, 6 men) who had received >1 treatment each of Ond and Gran. 40 course of Ond and 49 course of Gran were studied. Criterion for success would be that pts would suffer no more than mild nausea on Day 1.
Yalcn **1999** Single Center 3	No details on adverse events other than "the adverse events, including headaches, constipation, diarrhea, and insomnia, were rare and mild in all groups" given.	Chemo treatment: Cyclophosphamide, adriamycin, 5-fluorouracil (CAF); Cyclophosphamide, epirubicin, 5-fluorouracil (CEF); Cyclophosphamide, methotrexate, 5-fluorouracil (CMF); all were single day chemotherapy.
Zeidman **1998** Single Center 3, 4, 5	AE data: "There were no significant side effects in either antiemetic regimen".	2 pts who withdrew from the original 60 pts randomized were "withdrawn from the study because of refusal to continue". One came from each antiemetic group, and their genders were not specified. This left a group of 58 patients who were analyzed. There were 41 men and 17 women in these 58 patients.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Walsh **2004** Multicenter 5	DB RCT Parallel	HSCT	Granisetron iv 0.01mg/kg Ondansetron iv 0.45mg/kg 24hr	All received 10 mg dexamethasone (Dex) iv daily and lorazepam 1 mg iv every 8 hours.	No/NR	52 84%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Walsh **2004** Multicenter 5	NR/NR/110	14/0/96	Primary Cancer- Non-Hodgkin's lymphoma/Hodgkins: 35% Primary Cancer- Breast: 14% Primary Cancer- Other: 14% Primary Cancer- Myeloma: 28% Emesis w/ previous chemo: none-mild: 69% Emesis w/ previous chemo: mod-severe: 17% Emesis w/ previous chemo: unknown: 1% Alcohol intake: none-minimal: 57% Alcohol intake: mod-heavy: 27% Alcohol intake: unk: 3% Chemo: BuCy: 21% Chemo: CBV: 32% Chemo: Melphalan: 15% Chemo: Other: 19%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Walsh 2004 Multicenter 5	Granisetron vs Ondansetron Complete response: no emetic episodes and none-to-mild nausea Day 1: 83% vs 90%, NS; Day 2: 70% vs 84%, NS; Day 3: 69% vs 79%, NS; Day 4: 54% vs 56%, NS; Day 5: 48% vs 71%, NS; Day 6: 50% vs 46%, NS Major Response: 1-2 emetic episodes and none-to-moderate nausea; or no emetic episodes and moderate nausea Day 1: 13% vs 6%, NS Day 2: 18% vs 10%, NS Day 3: 17% vs 9%, NS Day 4: 23% vs 25%, NS Day 5: 35% vs 18%, NS Day 6: 14% vs 46%, NS Minor Response: 3-5 emetic episodes and any degree of nausea; or 0-2 emetic episodes and severe nausea Day 6: 36% vs 8%, NS; Day 5: 17% vs 12%, NS Day 4: 17% vs 17%, NS Day 3: 14% vs 9%, NS Day 2: 7% vs 4%, NS Day 1: 2% vs 2%, NS Failure: ≥6 emetic episodes and nay degree of nausea Day 1: 2% vs 2%, NS Day 2: 5% vs 2%, NS Day 3: 0% vs 2%, NS Day 4: 6% vs 3%, NS Day 5: 0% vs 0%, NS Day 6: 0% vs 0%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Walsh **2004** Multicenter 5	Granisetron vs Ondansetron Overall Diarrhea: 9% vs 12%, NS Hypersensitivity: 7% vs 2%, NS Sedation: 9% vs 4%, NS Tremors: 4% vs 2%, NS Other: 9% vs 12%, NS Constipation: 2% vs 4%, NS Hiccups: 26% vs 34%, NS Headache: 2% vs 10%, NS Total withdrawals __ Study drugs combined: 12.7%, Withdrawals due to AEs: 0% vs 0%,	Other meds allowed: antihistamines as premedication for blood transfusions; triazolam or diphenhydramine for insomnia. Chemo: Pts who received bisulfan + cyclophosphamide as regimen did not begin study drug until cycloph. administered since bisulfan has little emetogenic potential. The total days of study drug depended on type of chemo administered; so # of pts reporting data varied/day Rescue medication: prochlorperazine 10mg iv every 6 hrs as needed (if the pts had 3-5 emetic episodes in 24h or if the pt requested it). Pts were removed from study if they experienced a Southwestern Oncology group (SWOG) grade 3 or 4 toxicity, other than myelotoxicity, unless it was unrelated to the study medication. Reasons 14/110 pts withdrawn after randomization: 5 pts had baseline nausea or vomiting prior to first dose of study drug ; 5 pts received medication with antiemetic activity not permitted during the study period; 1 pt received wrong study drug; 1 pt developed severe opiate-induced confusion and hand tremors (unable to complete the VAS); 2 pts received the scheduled antiemetics incorrectly.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Dolasetron vs Ondansetron						
Hesketh 1996 Multicenter 5	DB RCT Parallel	prior chemo	Dolasetron iv 1.8mg/kg Dolasetron iv 2.4mg/kg Ondansetron iv 32mg once	Dex not allowed; for other drugs, see comment	No/NR	62 62%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Dolasetron vs Ondansetron			
Hesketh 1996 Multicenter 5	NR/NR/609	51/NR/558	previous chemotherapy: 8% history of heavy alcohol use: 16% Cancer Site- Lung: 55% Cancer Site- Gastrointestinal: 11% Cancer Site- Gynecologic: 10% Cancer Site- Head/Neck: 11% Cancer Site- Other: 14%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Dolasetron vs Ondansetron	
Hesketh **1996** Multicenter 5	Dolasetron 1.8 vs Dolasetron 2.4 vs Ondansetron Antiemetic Efficacy: complete response and other parameters Received rescue medication: 33.8% vs 42.0% vs 37.4%, NS Complete + major response: 63.1% vs 54.1% vs 59.2%, NS No emetic episodes and no rescue medication in 24h: 44.4% vs 40.0% vs 42.7%, NS Lower cisplatin dose stratum: 49.2% vs 45.6% vs 50.4%, NS Higher cisplatin dose stratum: 36.8% vs 31.3% vs 31.8%, NS Complete Response by Subgroup No previous chemotherapy: 46% vs 39% vs 42%, NR Narcotic analgesic use: 37.5% vs 34% vs 37%, NR Use of benzodiazepines: 50% vs 18% vs 43%, NR Previous chemotherapy: 27% vs 47% vs 50%, NR Patient ≥ 65 years age: 44% vs 46% vs 45%, NR History of heavy alcohol use: 66% vs 60% vs 56%, NR Female: 21% vs 25% vs 27%, NR Male: 58% vs 49% vs 54%, NR No use of benzodiazepines: 44% vs 42% vs 43%, NR No narcotic analgesic use: 48% vs 44% vs 46%, NR No history of heavy alcohol use: 40% vs 37% vs 40%, NR Median time to the first emetic episode or to rescue medication: 21.5 h vs 19.75 hvs 21.21 h, NS Patient VAS scores for nausea and general satisfaction (Nausea scale: 0=no nausea to 100=nausea as bad as can be) and (General satisfaction score: 0=not at all satisfied to 100=as satisfied as could be): 92 vs 85.5 vs 84, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Dolasetron vs Ondansetron		
Hesketh 1996 Multicenter 5	Dolasetron 1.8 vs Dolasetron 2.4 vs Ondansetron 32 <u>Overall</u> rales: 3% vs 1% vs 2%, NR diarrhea: 14% vs 13% vs 6%, NR fever: 7% vs 6% vs 7%, NR chills: 3% vs 1% vs 2%, NR loose stools: 1% vs 2% vs 2%, NR light-headed feeling: 1% vs 1% vs 2%, NR hypertension: 2% vs 2% vs 2%, NR fluid overload: 1% vs 2% vs 3%, NR AST increased: 2% vs 2% vs 2%, NR headache: 22% vs 22% vs 18%, NR ALT increased: 2% vs 2% vs 2%, NR	These benzodiazepine treatments were permitted: alprazolam if initiated 48h before study; midazolam during 24h before but not during study; temazepam or traizolam 24 h before and during the study. Lorazepam was not allowed during 24h before or during the study except as a rescue. Dexamethasone only allowed as a rescue medication. Pts were stratified into 2 groups: those receiving between 70-91 mg/m2 of cisplatin (mean dose for this group = 74.7 mg/m2) and those receiving cisplatin ≥ 90 mg/m2 (mean dose for this group = 100.6 mg/m2); all cisplatin doses were administered over ≤ 3 hours. Rescue medication was given if a pt requested it or if a pt experienced >2 emetic episodes during the 24h study period. Abstinence from narcotic analgesics, male gender, and a history of heavy alcohol use (present or past use of ≥ 5 drinks/day) were statistically significant predictors of a higher CR rate across all 3 treatment groups.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Fauser **1996** Multicenter 3, 4	DB RCT Parallel	women, prior chemo	Dolasetron po 25mg Dolasetron po 50mg Dolasetron po 100mg Dolasetron po 200mg Ondansetron po 32mg	No	NR/NR	53.2 39%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Fauser **1996** Multicenter 3, 4	NR/399/399	1/0/398	Mean height = 165.3 cm Mean weight = 70.7 kg Karnofsky Mean index = 89.0 Non-smoker: 69%; Ex-smoker: 12%; Smoker: 18% Alcohol use - no: 45%; rarely: 39%; occasionally: 12%; regularly: 5% Chemo-naïve: 42% Breast cancer: 57% Lung cancer: 8% Bladder cancer: 5% Colon cancer: 4% Rectal cancer: 3% Small-cell lung cancer: 3% Gastric cancer: 3% Mean Karnofsky status (+/- SD) = 91.4% (+/-10.9) Previous chemo: yes: 54% Chemo: cyclophosphamide: 28%; doxorubicin: 23%; carboplatin: 21%; platinum-based, alone or in combination: 28%; multiple moderately emetogenic non-platinum: 37% Primary neoplasm: breast cancer: 40%; lung cancer: 21%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Fauser **1996** Multicenter 3, 4	Dol po 25 vs Dol po 50 vs Dol po 100 vs Dol po 200 vs Ond po 32 Complete response (no emetic episodes and no need for rescue medication): All pts: 45.0% vs 49.4% vs 60.5% vs 76.3% vs 72.3%, p Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ond po 32 Complete + major response: 57.5% vs 59.5% vs 72.4% vs 85.0% vs 78.3%, p Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ondansetron No response: >2 emetic episodes; received escape antiemetic medication; or did not have data for ≥ 23.5h after chemo: 42.5% vs 40.5% vs 27.6% vs 15.0% vs 21.7%, NS Median time to first emetic episode (hours): 19.58 vs 21.75 vs >24.00 vs >24.00 vs >24.00, NS Patient VAS evaluation of nausea (median change from baseline at 24h) Score: 29.0 vs 31.0 vs 3.5 vs 0.0 vs 3.0, p=0.0061 for Dol 200 vs. ond Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ond po 32 Complete response: subgroup analyses Prior chemo = yes: 50.0% vs 39.0% vs 64.9% vs 72.3% vs 67.4%, NR Female: 38.8% vs 41.7% vs 51.2% vs 73.5% vs 67.4%, NR Prior chemo = no: 39.5% vs 60.5% vs 56.4% vs 81.8% vs 78.4%, NR Age ≥65 years: 50.0% vs 58.3% vs 80.0% vs 95.0% vs 78.9%, NR Male: 54.5% vs 61.3% vs 72.7% vs 80.6% vs 77.8%, NR Dolasetron groups' range vs Ondansetron Overall satisfaction (VAS) Median scores (0mm=not satisfied to 100mm=completely satisfied): 54mm to 99mm vs 98mm, NR Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ondansetron No nausea present By investigator report: 45.6% vs 36.7% vs 53.3% vs 69.9% vs 57.3%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Fauser **1996** Multicenter 3, 4	Doln 25 vs Dol 50 vs Dol 100 vs Dol 200 vs Ond All Adverse Events (AEs) Headache: 11.3% vs 8.8% vs 19.7% vs 18.8% vs 14.5%, NS Overall AEs experienced: 25.0% vs 37.5% vs 39.5% vs 33.8% vs 36.1%, NS Dizziness: 0% vs 2.5% vs 3.9% vs 1.3% vs 0%, NS Diarrhea: 0% vs 3.8% vs 2.6% vs 5.0% vs 1.2%, NS Death: .6% vs 1.2%, NR Fever: 1.3% vs 1.3% vs 0% vs 0% vs 4.8%, NS Fatigue: 0% vs 0% vs 2.6% vs 1.3% vs 3.6%, NS Weakness: 1.3% vs 3.8% vs 1.3% vs 0% vs 1.2%, NS Drowsiness: 0% vs 2.5% vs 3.9% vs 3.8% vs 2.4%, NS Constipation:0% vs 3.8% vs 1.3% vs 1.3% vs 0%, NS Withdrawals: 0% vs 1.3% vs 0% vs 0% vs 0%, NR Adverse events were reported if experienced by ≥3% of patients.	Note: 21 of the 83 Ondansetron patients received only 24 mg of the drug instead of the 32 mg. The one-post randomization withdrawal occurred when a pt received the study drug but not the chemo drugs they had been scheduled to receive. Patients were stratified by gender and prior chemo status and then randomized. The p-values for the complete response stratified by subgroup were as follows: males vs. females receiving dolasetron (p=0.0015); Chemo naïve vs non-naïve patients receiving dolasetron (p=0.0212); and pts <65 yrs. vs. pts ≥ 65 yrs receiving dolasetron (p=0.0078). P=NS for complete responders in the following variables: use of narcotics, use of steroids, use of benzodiazepines, or type of chemo regimen employed during study.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3	RCT Parallel	corticosteroids	Ondansetron iv 32mg Dolasetron iv 2.4mg/kg	Medication given along with dexamethasone 8 mg po, or dex alone for days 2-7	NR/NR	%male
Dolasetron vs Granisetron						
Audhuy **1996** Multicenter 5	DB RCT Parallel	women, prior chemo	dolasetron iv 1.8mg/kg dolasetron iv 2.4mg/kg granisetron iv 3mg	No	NR/NR	55 66%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3	NR/NR/407	//	NR
Dolasetron vs Granisetron			
Audhuy **1996** Multicenter 5	NR/NR/476	2/0/474	Previous chemo naïve: 60% Previous chemo non-naïve: 40% Chemo naïve: male: 45% Chemo naïve: female: 15% Chemo non-naïve: male: 22% Chemo non-naïve: female: 18%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3	Dex added vs No dex added Complete protection: no episodes of emesis, no rescue medication, no data missing Dexamethasone (dex) added vs. no dex added for 24h: 67% vs 55%, 0.001 Dexamethasone (dex) added vs. no dex added for 7 days: 48% vs 28%, <0.001 Dol (arms 1-3) vs. Ond (arms 4-6) for 7 days: 39% vs 36%, NS Dol (arms 1-3) vs. Ond (arms 4-6) for 24h: 67% vs 57%, 0.013
Dolasetron vs Granisetron	
Audhuy **1996** Multicenter 5	Dol iv 1.8 vs Dol iv 2.4 vs gran iv 3 Complete Response: overall population: no emetic episodes and no use of rescue antiemetics: 54% vs 47% vs 48%, NS Complete response: stratified by gender and/or chemo-naïve status Male naïve: 71% vs 57% vs 63%, NS Male non-naïve: 59% vs 58% vs 55%, NS Male: 67% vs 57% vs 60%, NS Female non-naïve: 20% vs 21% vs 30%, NS Female naïve: 43% vs 27% vs 17%, NS Female: 31% vs 24% vs 24%, NS Chemo-naïve: 63% vs 51% vs 51%, NS Chemo non-naïve: 42% vs 40% vs 43%, NS Patient Nausea score (VAS) Mean and median scores on scale 0 to 100 Mean score(Median score): 34(19) vs 38(26) vs 36(18), NS Number with no nausea: 41% vs 41% vs 41%, NS Investigators assessment of maximum nausea on scale 0 = none to 3 = severe mean score: 1.1 vs 1.2 vs 1.2, NS Patients with no nausea: 43% vs 44% vs 42%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3		
Dolasetron vs Granisetron		
Audhuy **1996** Multicenter 5	*data given as Dol 1.8 vs Dol 2.4 vs Gran 3* <u>AEs reported by ≥ 3% of all patients</u> headache: 28% vs 22% vs 23%, NS diarrhea:13% vs 11% vs 6%, NS abdominal pain: 6% vs 1% vs 3%, NS epigastric pain: 2% vs 1% vs 3%, NS hypertension: 2% vs 7% vs 4%, NS abnormal hepatic function: 9% vs 6% vs 3%, NS extrasystoles: 3% vs 1% vs 1%, NS asthenia: 3% vs 1% vs 1%, NS fever: 2% vs 3% vs 3%, NS Overall AEs: 58% vs 55% vs 45%, NS Severe AEs: 6% vs 7% vs 5%, NS Serious AEs considered to be possibly related to the study medication were angina/myocardial infarction/ acute pulmonary edema in 1 pt and fever/abdominal pain in 1 pt - both pts in Gran 3 group	2 pts assigned to treatment out of 476 did not receive study medication and were excluded. Pts stayed in the hospital for at least 8h after the start of chemo; most were hospitalized for the entire 24h study period. Mean cisplatin dose was significantly different among all groups (p= 0.0389) , the 2 mg/m2 magnitude of difference was not considered to be clinically significant.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Tan **2002** Single Center 4, 5	Open CT Parallel	none	Dolasetron po 100mg Granisetron po 2mg	All received 20 mg of iv dexamethasone with the antiemetic.	NA/NA	57.5 38%male NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Tan **2002** Single Center 4, 5	NR/NR/26	0/0/26	Lymphoma (primary cancer site): 46% Lungs (primary cancer site): 15% Larynx (primary cancer site): 15% Uterus (primary cancer site): 12% Other sites: 12% Patients receiving highly emetogenic chemo: 92%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Tan **2002** Single Center 4, 5	Dolasetron vs Granisetron Total control: no nausea, no emesis, no need for rescue antiemetic Within 24h following chemo: 69.2% vs 23.1%, Vomiting: no. of pts who had vomiting episodes: 53.8% vs 7.7%, Nausea: no. of pts who experienced nausea: 76.9% vs 30.8%, Nausea intensity: Score: ++ (3-5 episodes/d) vs + (Pts requiring rescue antiemetic: 76.9% vs 23.1%, Mean no. of doses of rescue antiemetic: 7.0 vs 1.0,

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Tan **2002** Single Center 4, 5		All chemo-naïve patients were 5-HT3 antagonist naïve, but this was not stated if it was an eligibility criterion. No specific data on adverse events given for the total population nor for either study group; a general statement that patients in both groups complained of occasional headaches but no statistically significant differences were found between groups was all that was stated pertaining tor AEs. nausea intensity scale: + : <2 episodes/d (mild); ++ : 3-5 episodes/d (moderate); +++ : >5 episodes/d (severe)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Palonsetron						
Aapro 2006 Multicenter 5	DB RCT Parallel	None	Palonosetron iv 0.25 mg Palonosetron iv 0.75 mg Ondansetron iv 32 mg	Low to moderately emetogenic chemotherapy agents were permitted Single dose of prophylactic corticosteroid was allowed at physician discretion	No/No	51.63 48.87% male 59.53% white 3.3% black 36.13% Hispanic 1.2% other
Gralla 2003 Multicenter 4	DB RCT Parallel	none	Palonosetron iv 0.25mg Palonosetron iv 0.75mg Ondansetron iv 32mg	No other medications allowed; no pt was allowed pretreatment with corticosteroids.	None/NA	55.4 28%male Caucasian = 557 (98.9%) Hispanic = 2 (0.36%) Asian = 2 (0.36%) Other = 2 (0.36%) Black = 0

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Palonsetron			
Aapro 2006 Multicenter 5	NR/NR/673	6/0/667	Chemotherapy naïve: 58% Tumor type Ovarian: 17%; Lung: 14%; Hodgkin's: <1%; Gastric: <1%; Breast: <1%;
Gralla 2003 Multicenter 4	NR/NR/570	12/0/563	Mean height = 165.3 cm Mean weight = 70.7 kg Karnofsky Mean index = 89.0 Non-smoker: 69% Ex-smoker: 12% Smoker: 18% Alcohol use - no: 45% Alcohol use - rarely: 39% Alcohol use - occasionally: 12% Alcohol use - regularly: 5% Chemo-naïve: 42% Chemo non-naïve: 58% Breast cancer: 57% Lung cancer: 8% Bladder cancer: 5% Colon cancer: 4% Rectal cancer: 3% Small-cell lung cancer: 3% Gastric cancer: 3%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Palonsetron	
Aapro 2006 Multicenter 5	Palon 0.25mg vs Palon 0.75mg vs Ondansetron 32mg Complete response rates Acute phase 0-24h following chemo: 59.2% vs 65.5% vs 57% (NS) Delayed phase 24-120h following chemo: 45.3% vs 48% vs 38.9% (NS0 Overall phase 0-120h following chemo: 40.8% vs 42.2% vs 33% (NS) Patients Emesis-Free Acute phase 0-24h following chemo: 75.3% vs 71.3% vs 59.2% (p<0.05 for both) Delayed phase 24-120h following chemo: 55.3% vs 50.7% vs 39.5% (p<0.05 for Palon 0.25mg ve Ondansetron 32mg) Overall phase 0-120h following chemo: 53.3% vs 46.7% vs 33.3% (p<0.05 for both)
Gralla 2003 Multicenter 4	Palon 0.25 vs Ondansetron Complete response; no emeit episodes and no rescue medication (all time periods) During 0-24h following chemo: 81.0% vs 68.6%, 0.0085 During 0-24h following chemo: 73.5% vs 68.6%, NS During 24-120h (delayed period) following chemo: 74.1% vs 55.1%, p<0.001 During 24-120h (delayed period) following chemo: 64.6% vs 55.1%, NS Overall (0-120h) following chemo: 69.3% vs 50.3%, p<0.001 Overall (0-120h) following chemo: 58.7% vs 50.3%, NS Palonosetron vs Ondansetron Complete control: study days 1-5 Delayed (24-120h): 66.7% vs 50.3%, 0.001 Overall (0-120h): 63.0% vs 44.9%, 0.001 Ondansetron vs Palon 0.25 vs Palon 0.75 No. of pts requiring rescue medication Overall (0-120h): 27.0% vs 18.5% vs 23.8%, NS Delayed (24-120h): 24.3% vs 15.9% vs 22.8%, NS

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Palonsetron		
Aapro 2006 Multicenter 5	Palon 0.25 vs Palon 0.75 vs Ond 32 Headache: 8% vs 12.4% vs 10.8% Constipation: 4.4% vs 7.6% vs 2.2% Diarrhea: 1.3% vs 0.4% vs 2.2%	
Gralla 2003 Multicenter 4	Palon 0.25 vs Palon 0.75 vs Ond 32 Headache: 4.8% vs 5.3% vs 5.3%), Dizziness: 0.5% vs 0% vs 3.2%, Constipation: 1.6% vs 3.2% vs 1.6%, Ondansetron vs Palon 0.25 vs Palon 0.75 Adverse reactions (i.e., AE;s considered to be treatment related): 16% vs 16% vs 13.9%, NR Serious AEs: 2.7% vs 2.6% vs 2.6%, NS Ondansetron vs Palon 0.75 Withdrawals due to AEs: 0.5% vs 0.5%, NS Deaths: all groups Total deaths in study: 0.7% Ondansetron vs Palon 0.25 vs Palon 0.75 All pts experiencing >1 AE: 64.2% vs 61.0% vs 66.5%, NS	Double-dummy technique used for study medications. Pts stratified at randomization by gender and prior chemotherapy experience. Complete control: Data given for delayed and overall intervals, with both Palonosetron groups combined. The rest of this data was given as: Palon. 0.25mg was superior to Ond on Study Days 2 (p=0.001), 3 (p=0.001), and 4 (p=0.003) with Palon 0.75mg superior to Ond on Days 3 (p=0.004) and 4 (p=0.006). On all ot6her days, both Palon. doses were as effective as Ond. Time to treatment failure: Palon 0.25 vs. Ond: p<0.001. Median time to treatment failure was >120h in all treatment groups. First quartile of Palon 0.25mg = 46.5h vs. Ond =19.5h. one pt who died during the study (in the Ond group) had a pulmonary embolism that resulted in death. The other 3 deaths were not specified.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Eisenberg 2003 Multicenter 3	DB RCT Parallel	none	Palonosetron iv 0.25mg Palonosetron iv 0.75mg Dolasetron iv 100mg 30 sec infusion	20mg dexamethasone iv or po, or 125 mg methylprednisolone iv allowed 15 min before chemo.	NR/NR	54.0 18%male White: 178 (31.3%) Black: 30 (5.3%) Hispanic: 344 (60.4%) Asian: 13 (2.3%) Other: 4 (0.70%)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Eisenberg 2003 Multicenter 3	NR/NR/592	23/0/569	Chemotherapy naïve: 67% Chemotherapy nonnaive: 33% Corticosteroid use: yes; 5% Corticosteroid use: no: 95% Alcohol use: none: 67% Alcohol use: rare: 14% Alcohol use: occasional: 13% Alcohol use: regular: 5% Breast carcinoma: 61% Lung carcinoma: 8% Non Hodgkins lymphoma: 4%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Eisenberg 2003 Multicenter 3	Pal 0.25 vs Pal 0.75 vs Dolasetron CR: during the first 24 h after chemo, delayed (24-120h), overall (0-120h), and by each 24h period Overall (97.5% CI =Pal minus Dol; Pal 0.25 vs. Dol; and Pal 0.75 vs. Dol): 46.0% vs 47.1% vs 34.0%, for Pal 0.25 and 0.75 vs Dol: p=0.021 and p=0.012 Delayed (97.5% CI =Pal minus Dol; Pal 0.25 vs. Dol; and Pal 0.75 vs. Dol): 54.0% vs 56.6% vs 38.7%, for Pal 0.25 and 0.75 vs Dol: 0.004 and p<0.001 First 24h after chemo (97.5 % CI = Pal minus Dol): 63.0% vs 57.1% vs 52.9%, NS Complete control: acute, delayed, overall, and by day Day 2: (p-value: P vs. Dol): 40.3%(NA) vs 55.0%(0.004) vs 57.7%(0.001), see table Day 3: (p-value: P vs. Dol): 48.2%(NA) vs 62.4%(0.005) vs 68.3%(0.001), see table Overall (0-120h): (p-value: P vs. Dol): 30.9%(NA) vs 41.8%(0.027) vs 42.9%(0.016), see table Delayed (24-120h): (p-value: P vs. Dol): 36.1%(NA) vs 48.1%(0.018) vs 51.9%(0.002), see table Median times to treatment failure and to first emetic episode Treatment failure: 24.6 h vs 51.1 h vs 52.8 h, p First emetic episode: 41.5 h vs >120 h vs >120 h, p Complete response rates for subpopulations: Chemo-naïve patients (0-24 h): 60.5% vs 46.4% vs 55.7%, NR Non-chemo-naïve patients(0-24 h): 67.7% vs 65.2% vs 60.3%, NR Corticosteroid-using patients (0-24 h): 62.5% vs 72.7% vs 50.0%, NR Non-corticosteroid-using patients(0-24 h): 52.5% vs 62.4% vs 57.6%, NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Eisenberg 2003 Multicenter 3	Palonosetron 0.25 vs Palonosetron 0.75 vs Dolasetron Headache (total: treatment and non-treatment related): 26.4% vs 24.1% vs 26.8%, NS Constipation (total: treatment and non-treatment related): 11.9% vs 14.9% vs 9.3%, NS Fatigue (total: treatment and non-treatment related): 21% vs 26% vs 24%, NS Death: 0.52% vs 1.03% vs 0%, NS Serious AEs (not specified as to what these are): 2.1% vs 6.7% vs 4.6%, NS Anxiety: treatment related: 2.1% vs 0% vs 0%, NS Diarrhea: treatment related: 1.6% vs 1.5% vs 2.1%, NS Dizziness: treatment related: 1.6% vs 1.0% vs 2.1%, NS Asthenia: treatment related: 0.5% vs 2.1% vs 0.5%, NS	569 patients analyzed for efficacy; 582 patients analyzed for adverse events. Of the original 592 who were randomized, 9 did not receive treatment, which leaves a group of 583, and one person in this group was excluded from ITT analysis because they had chemo with unacceptably low emetogenic potential. Of the remaining 582 patients, 13 were excluded post-randomization because they enrolled at a disqualified investigative site. Thus, the study reports its ITT cohort as 569 patients

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Granisetron iv vs Granisetron po						
1	DB RCT Parallel	BMT, PBPCT, women	granisetron iv 2mg granisetron po 2mg 10 days	Lorazepam iv or po 2 mg/day	nr/nr	49.2 35%male Caucasian: n=55 (92%) Non-Caucasian: n=5 (8%)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Granisetron iv vs Granisetron po			
1	NR/NR/60	9/0/51	Primary Tumor: Non-Hodgkin's disease: 25% Hodgkin's disease: 10% Breast: 47% Chronic myelogenous leukemia: 5% Multiple myeloma: 3% Lymphoma: 3%; Testicular: 2% Waldenstrom macroglobuliemia: 2% Chemo: Etoposide/carmustine/cyclophophamide: 41% Cyclophosphamide/carboplatin/etoposide: 49% Busulfan/cyclophosphamide: 12% Peripheral blood progenitor transplant: 83% Allogeneic bone marrow transplant: 15% Autologous bone marrow transplant: 2%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Granisetron iv vs Granisetron po	
1	Gran po vs Gran iv Complete response (CR): no emesis All patients: 9.1% vs 6.9%, NS Female: 8.3% vs 5%, NS Male: 10% vs 11.1%, NS Partial response (PR): 1-2 episodes of emesis Females only: 58.3% vs 35%, NS Males only: 30% vs 33.3%, NS All patients: 45.5% vs 34.5%, NS Failure: ≥ 3 episodes of emesis Males only: 60% vs 55.6%, NS Females only: 33.3% vs 60.0%, NS All patients: 45.5% vs 58.6%, NS No. of emetic episodes Day 10: 0 vs 1.3, Day 9: 3.0 vs 6.0, Day 8: 4.0 vs 8.0, Day 7: 5.3 vs 14.3, Day 6: 4.0 vs 15.3, NR Day 5: 6.0 vs 15.3, NR Day 4: 5.0 vs 13.0, NR Day 3: 10.0 vs 13.0, NR Day 2: 12.3 vs 15.3, NR Day 1: 1.0 vs 4.0, NR Total number, over 10 days: 50 vs 104, p=0.0008 Gran po vs Gran iv

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Granisetron iv vs Granisetron po		
1	Gran po 1 vs Gran iv 2 Headache: 8% vs 8%, NS Sedation: 4% vs %, NS Diarrhea: 4% vs 9%, NS Hypertension: 2% vs 2%, NS Hypotension: 3% vs 0%, NS Insomnia: 3% vs 3%, NS Jittery/EPS: 3% vs 6%, NS Hiccups: 1% vs 6%, NS Anxiety: 2% vs 4%, NS Sinus congestion: 2% vs 1%, NS Indigestion: 1% vs 3%, NS Mucositis: 1% vs 2%, NS Death: 0% vs 6.9%, NS Confusion: 0% vs 2%, NS Constipation: 0% vs 2%, NS Total withdrawals: 18.5% vs 9.1%, NS	Pts undergoing peripheral blood progenitory cell and bone marrow transplantation; chemo was administered for 10 days. Pts were stratified based on transplant type and conditioning regimen. Balance between the two groups was obtained through random blocks of two. Pts received Gran (+placebo) every 12h until either the day of marrow or stem cell infusion (day 0), or until the pt experienced 3 ≥ emetic episodes within any 24h period. Administration of prochloroperazine, lorazepam, and promethazine permitted during study. Withdrawals: 8 pts (Gran po= 5 pts and Gran iv = 3 pts had emesis prior to study medication and were excluded from analysis. One pt, initially randomized, received therapy for 9 days and then voluntarily withdrew [study did not say why] and was censored from the efficacy analysis.

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
L-758,298 vs Ondansetron						
Cocquyt 2001 Multicenter	DB RCT Parallel	None	L-758, 298 iv 60 or 100mg Ondansetron 32mg	Rescue therapy, determined by investigator, was allowed	NR/No use of antiemetic agent within 1 week of study day 1	56 53% male Ethnicity NR
Van Belle 2002 Multicenter	DB RCT Parallel	None	L-758, 298 iv 100mg day 1 and MK-869 days 2-5 (L 100) L-758,298 iv 100mg day 1 and placebo days 2-5 (L Plac) Ondansetron iv 32mg day 1 and placebo days 2-5 (Ond)	All received dexamethasone 20mg iv prior to cisplatin. Rescue medication was permitted	NR/No use of antiemetic agent within 72 hours of study day 1	58 63% male Ethnicity NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
L-758,298 vs Ondansetron			
Cocquyt 2001 Multicenter	NR/NR/53	NR/NR/53	Type of cancer Lung: 17% Gastrointestinal: 24.5% Head and neck: 15% Genitourinary: 34% Other: 9.5%
Van Belle 2002 Multicenter	NR/NR/177	2/NR/177	Type of cancer Lung: 40% Gastrointestinal: 19% Head and neck: 20.5% Genitourinary: 12% Other: 8.5%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
L-758,298 vs Ondansetron	
Cocquyt **2001** Multicenter	L-758,298 vs Ondansetron Proportion of patients without emesis: acute phase (day 1) 37% vs 52% Proportion of patients without emesis: delayed phase (day 2-7) 72% vs 30% (p=0.005) Proportion of patients with no use of rescue medications: acute phase (day 1) 37% vs 48% Proportion of patients with no use of rescue medications: delayed phase (day 2-7) 48% vs 17% (p<0.04) Median nausea scores: acute phase (day 1) 0.3 vs 0.0 Median nausea scores: delayed period (day 2) 0.0 vs 1.3 (p=0.043) Median nausea scores: delayed period (day 2-7) 0.4 vs 0.8
Van Belle **2002** Multicenter	L 100 vs L Plac vs Ond Proportion without emesis: acute phase (day 1) 49% vs 47% vs 84% (p<0.01 for L100 and L Plac vs Ond) Proportion without emesis: delayed phase (day 2-5) 65% vs 61% vs 41% (p<0.05 for L 100 and L Plac vs Ond) Proportion without emesis or use of rescue medication: acute phase (day 1) 44% vs 36% vs 83% (p<0.001 for L 100 and L Plac combined vs Ond) Proportion without emesis or use of rescue medication: delayed phase (day 2-5) 59% vs 46% vs 38% (p<0.05 for L 100 vs Ond)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
L-758,298 vs Ondansetron		
Cocquyt 2001 Multicenter	L-758,298 vs Ondansetron Constipation: 40% vs 39% Diarrhea: 60% vs 9% Anorexia: 40% vs 35% Headache: 47% vs 39% Abdominal pain: 17% vs 9% Asthenia: 40% vs 30% Haematological decrease Total white blood cells: 3% vs 0% Neutrophils: 3% vs 0% Transaminase elevations AST: 0% vs 0% ALT: 3% vs 0%	
Van Belle 2002 Multicenter	L 100 vs L Plac vs Ond Anorexia: 10% vs 12% vs 9% Constipation: 8% vs 7% vs 14% Diarrhea: 23% vs 23% vs 5% Nausea: 11% vs 19% vs 5% Dizziness: 8% vs 11% vs 5% Headache: 13% vs 19% vs 12% Hiccups: 8% vs 11% vs 4% Asthenia: 16%$ vs 19% vs 12% Abdominal pain: 8% vs 7% vs 11%	

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Ondansetron vs Ondansetron						
Pectasides 2007 Single Center	RCT Parallel	None	Ondansetron conventional tablet 8mg (OT) Ondansetron disintegrating table 8mg (ODT)	Rescue medication was allowed	NR/No medications with antiemetic activity or medications which could confound the efficacy evaluation in the 24 hours prior to inclusion	53 Gender NR Ethnicity NR

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Ondansetron vs Ondansetron			
Pectasides **2007** Single Center	NR/NR/134	NR/NR/NR/134	Disease stage Early: ODT=97% vs OT=96% Advanced: ODT=3% vs OT=4%

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Results
Ondansetron vs Ondansetron	
Pectasides 2007 Single Center	ODT vs OT Proportion with no emesis: 55% vs 65% (p=0.44) 1-2 emetic episodes: 15% vs 0% >2 emetic episodes: 6% vs 19% Rescue medication used: 24% vs 15% Complete or major control of emesis (0-2 emetic episodes, no rescue medication, no withdrawal): 70% vs 76% (p=0.28) Complete emesis control (no emesis, no rescue medication, no withdrawal): 52% vs 72% (p=0.020)

Evidence Table 1. Chemotherapy: Head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Ondansetron vs Ondansetron		
Pectasides **2007** Single Center	ODT vs OT AEs attributed to drug: 9% vs 10% (p>0.99)	

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Children								
Forni 2000 Not specified 5	children	NR/NR	NR/NR/90	NR/0/90	NR	NR	Inadequate data	Yes
Jaing 2004 Multicenter 3	children, females	4 wk run-in with antiemetics acc. to rand. scheme/NR	35/33/33	0/0/33	NR	NR	NR	Yes
Orchard 1999 Single Center 5	children, BMT, TBI	NR/NR	NR/NR/193	4/2/187	NR	NR	Yes	Yes
Corapcioglu 2005 5	children	No/no antiemetics 24 hours before surgery	NR/NR/22	NR/NR/unclear	Unclear	Unclear	Some differences - e.g. emetogenicity: ODT 76%, standard oral 58%	Yes
Sepulveda-Vildosola 2008 Single Center 2-5	none	NR/NR	NR/NR/100	NR/NR/100	Yes	Yes	Yes	Yes
White 2000 Multicenter 4, 5	children, kinetosis	No/NR	NR/438/428	0/0/428	Yes	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Children							
Forni 2000 Not specified 5	Yes, but not described	Yes, but not described	NR No No No	Unable to determine	Yes	No	Fair
Jaing 2004 Multicenter 3	No	No	Yes No No No	Unable to determine	No	Yes	Poor
Orchard 1999 Single Center 5	Yes, but not described	Yes, but not described	Yes No No No	Unable to determine	No	Yes	Fair
Corapcioglu 2005 5	Yes	Yes	Yes No No No	No	Unclear	No	Poor
Sepulveda-Vildosola 2008 Single Center 2-5	Yes	Yes	No No No No	No	NR	No	Fair
White 2000 Multicenter 4, 5	Yes	Yes	Yes No No No	Unable to determine	Yes	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Children		
Forni 2000 Not specified 5	Yes	NR
Jaing 2004 Multicenter 3	Yes	Supported in part by a grant from the Childhood Cancer Foundation of Taiwan.
Orchard 1999 Single Center 5	Yes	Children's Cancer Research Fund and the Bone Marrow Transplant Research Fund.
Corapcioglu 2005 5	No	No funding for this study.
Sepulveda-Vildosola 2008 Single Center 2-5	No	NR
White 2000 Multicenter 4, 5	Yes	Supported by a grant from Glaxo Wellcome Research & Development

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Adults								
Aprepitant vs ondansetron								
Schmoll 2006 NR ≥3	None	NR/No 5-HT_3 RAs within 48 hours of day 1	516/NR/489	29/3/484	Yes	Unclear	Yes	Yes
Granisetron vs Ondansetron								
Abali 2007 4,5	none	NR/NR	NR/NR158	NR/NR/158	No	No	Yes	No
Barrajon 2000 Single Center 5	women, alcoholics, prior chemo	NR/NR	NR/NR/136	16/0/120	Yes	Yes	Yes	Yes
Chiou 2000 Single Center 4, 5	none	No/NR	NR/NR/51	0/0/51	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Adults							
Aprepitant vs ondansetron							
Schmoll 2006 NR ≥3	Yes	Yes	Yes No Yes No	Yes, 2 in aprepitant group, 1 in control group	Yes - modified ITT = 5 patients excluded from analysis.	No	Good
Granisetron vs Ondansetron							
Abali 2007 4,5	No	No	NR NR NR NR	No	No	No	Poor
Barrajon 2000 Single Center 5	Yes	Yes	Yes No No No	No	No	Yes	Fair
Chiou 2000 Single Center 4, 5	No	No	Yes No No No	No	Yes	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Adults		
Aprepitant vs ondansetron		
Schmoll 2006 NR ≥3	Yes	Merck & Co, Inc
Granisetron vs Ondansetron		
Abali 2007 4,5	No	NR
Barrajon 2000 Single Center 5	Yes	NR
Chiou 2000 Single Center 4, 5	Yes	SmithKline Beecham Taiwan supplied granisetron for the study.

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Chua 2000 Single Center 5	none	NR/NR	94/89/89	0/0/89	Yes	NR	NR	Yes
Del Favero 1995 Multicenter 5	kinetosis	NR/NR	NR/NR/973	6/1/966	Yes	NR	Yes	Yes
deWit 2001 NR 5	none	No/NR	NR/45/40	0/0/40	NR	NR	Yes	Yes
Fox-Geiman 2001 Single Center 5	BMT; TBI	NR/NR	NR/NR/102	6/0/102	Yes	Yes	Yes	Yes
Gebbia 1994a Single Center 5	none	NR/NR	NR/NR/182	16/0/166	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Chua 2000 Single Center 5	No	No	Yes No No No	Unable to determine	No	Yes	Poor
Del Favero 1995 Multicenter 5	Yes	Yes	Yes No No No	No	No	Yes (7/973)	Fair
deWit 2001 NR 5	Yes	Yes	Yes No No Yes	No	No	Yes	Fair
Fox-Geiman 2001 Single Center 5	Yes	Yes	Yes No No No	No	Unable to determine	No	Fair
Gebbia 1994a Single Center 5	NR	NR	Yes No No No	No	No	Yes	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Chua 2000 Single Center 5	Yes	NR
Del Favero 1995 Multicenter 5	Yes	Supported in part by a grant from the Umbrian Cancer Association (A.U.C.C.)
deWit 2001 NR 5	Yes	NR
Fox-Geiman 2001 Single Center 5	Yes	Supported in part by an educational grant from Glaxo-Wellcome, Inc.
Gebbia 1994a Single Center 5	No	University of Palermo; Palermo, Italy

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Gebbia 1994b Single Center 3	none	NR/NR	NR/NR/164	8/0/158	NR	NR	Yes	Yes
Gralla 1998 Multicenter 5	corticosteroids	NR/NR	NR/NR/1054	13/0/1054	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Gebbia 1994b Single Center 3	NR	NR	Yes No No No	No	No	Yes	Fair
Gralla 1998 Multicenter 5	Yes, but not described	Yes, but not described	Yes No No No	No	Yes	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Gebbia 1994b Single Center 3	No	University of Palermo; Palermo, Italy
Gralla 1998 Multicenter 5	Yes	SmithKline Beecham Pharmaceuticals

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Herrington 2000 Multicenter 4	women	No/NR	65/61/61	0/0/61	NR	NR	unable to determine (reported for evaluated pts)	Yes
Kalaycio 1998 NR 5	ASCT, women	NR/NR	48/48/48	3/45/45	NR	NR	Yes	Yes
Jantunen 1993 Multicenter 3, 4	none	No/No	NR/NR/166	34/2/130	Yes	Yes	NR	Yes
Leonardi 1996 Multicenter 3, 4, 5	none	NR/NR	NR/NR/118	3/0/118	NR	NR	NR	Yes
Mantovani 1995 Single Center 5	none	NR/NR	NR/NR/117	0/0/117	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Herrington 2000 Multicenter 4	No	No	No No No No	No	No	Yes	Poor
Kalaycio 1998 NR 5	Yes	Yes	Yes No No No	Unable to determine	No	Yes	Poor
Jantunen 1993 Multicenter 3, 4	No	No	Yes No No No	Yes 36/166 not evaluated	No	Yes	Poor
Leonardi 1996 Multicenter 3, 4, 5	NR	NR	Yes No Yes No	Unable to determine	Yes	No	Poor
Mantovani 1995 Single Center 5	NR	Yes, but not described	No Yes No No	No	Yes	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Herrington 2000 Multicenter 4	Yes	Funded in part by SmithKline Beecham Pharmaceuticals
Kalaycio 1998 NR 5	Yes	NR
Jantunen 1993 Multicenter 3, 4	Yes	NR
Leonardi 1996 Multicenter 3, 4, 5	Yes	NR
Mantovani 1995 Single Center 5	Yes	The authors state that no support for this study came directly from a pharmaceutical company.

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Martoni 1995 Single Center 5	none	NR/NR	NR/NR/124	0/0/124	NR	NR	NR	Yes
Massidda 1996b NR 3	women	NR/NR	NR/NR/60	NR/NR/60	NR	NR	Yes	Yes
Navari 1995 Multicenter 5	women	NR/NR	NR/NR/994	7/0/987	NR	NR	Some differences (NS)	Yes
Noble 1994 Multicenter 3	none	None/NR	NR/NR/359	0/0/359	NR	NR	Yes	Yes
Oge 2000 NR 4, 5	none	NR/NR	NR/NR/106	0/0/106	NR	NR	NR	Yes
Park 1997 Single Center 5	none	No/NR	NR/NR/97	2/NR/95	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Martoni 1995 Single Center 5	No	No	Yes NR NR NR	No	Yes	No	Poor
Massidda 1996b NR 3	NR	NR	No No No No	Unable to determine Results appear to be based on 60 'evaluable' patients	NR	NR	Poor
Navari 1995 Multicenter 5	Yes	Yes, but not described	Yes Not relevant Not relevant No	Unable to determine	No	Yes	Fair
Noble 1994 Multicenter 3	Yes, but not described	Yes, but not described	Yes NA No No	No	No	No	Fair
Oge 2000 NR 4, 5	NR	NR	Yes No No No	No	Yes	No	Fair
Park 1997 Single Center 5	NR	NR	Yes No No No	No	No	Yes	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Martoni 1995 Single Center 5	Yes	NR
Massidda 1996b NR 3	Yes	Not stated
Navari 1995 Multicenter 5	Yes	Two authors are employees of SmithKline Beecham Pharmaceuticals
Noble 1994 Multicenter 3	Yes	One author is an employee at Smith Kline Beecham Pharmaceuticals, UK
Oge 2000 NR 4, 5	Yes	NR
Park 1997 Single Center 5	Yes	NR

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Perez 1998 Multicenter 4	women, corticosteroid use	Dexamethasone and methylprednisolone was permitted/NR	NR/NR/1085	16/1/1085	NR	NR	Yes	Yes
Perez 1998a Multicenter 3, 4	women, breast cancer	No/NR	NR/NR/623	//623	Yes	NR	Yes	Yes
Poon 1997 Single Center 4	women, breast cancer	NR/NR	NR/NR/20	0/0/20	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Perez 1998 Multicenter 4	Yes	Yes	Yes No No No	No	Yes	No	Fair
Perez 1998a Multicenter 3, 4	Yes	Yes	Yes No No No	Unable to determine	No	No	Poor
Poon 1997 Single Center 4	Yes	Yes	No No No No	No	Yes	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Perez 1998 Multicenter 4	Yes	SmithKline Beecham Pharmaceuticals
Perez 1998a Multicenter 3, 4	Yes	Funded by SmithKline Beecham Pharmaceuticals
Poon 1997 Single Center 4	Yes	NR

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Raynov 2000 Single Center 5	none	NR/NR	NR/NR/72	0/0/72	NR	NR	NR	Yes
Ruff 1994 Multicenter 5	none	No/NR	NR/NR/NR	1/NR/Various	NR	NR	NR	Yes
Slaby 2000 Single Center 5	ASCT	NR/NR	NR/NR/45	0/0/45	NR	NR	Yes	Yes
Spector 1998 Multicenter 5	none	None/None	NR/NR/371	//371	NR	NR	Yes	Yes
Stewart L. 2000 Single Center 5	none	NR/NR	NR/NR/21	5/NR/16	NR	NR	NR	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Raynov 2000 Single Center 5	No	No	No No No No	Unable to determine	Unable to determine	Unable to determine	Poor
Ruff 1994 Multicenter 5	Yes	Yes	No No No No	No	No	Unable to determine	Poor
Slaby 2000 Single Center 5	NR	NR	No No No No	No	Yes	No	Fair
Spector 1998 Multicenter 5	Yes	Yes	No No No No	NR	Yes	No	Fair
Stewart L. 2000 Single Center 5	Yes	Yes	Yes No No No	None	No	No	Poor

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Raynov 2000 Single Center 5	Yes	NR
Ruff 1994 Multicenter 5	Yes	NR, but 4 authors are employed by Glaxo.
Slaby 2000 Single Center 5	Yes	NR
Spector 1998 Multicenter 5	Yes	Supported by a grant from Glaxo Wellcome Inc.
Stewart L. 2000 Single Center 5	Yes	NR

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Stewart, A. 1995 Multicenter 4	women	NR/NR	NR/NR/514	16/10/488	NR	NR	Yes	Yes
Walsh 2004 Multicenter 5	HSCT	No/NR	NR/NR/110	14/0/96	Yes	NR	NR - excluded 12.7%	Yes
Yalcn 1999 Single Center 3	women	No/NR	NR/NR/54	0/0/54	NR	NR	Yes	Yes
Zeidman 1998 Single Center 3, 4, 5	none	none/none	NR/NR/60	2/0/58	NR	NR	Text specifies that groups were similar for "most"	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Stewart, A. 1995 Multicenter 4	Yes	Yes	Yes No No No	No LTFU	No	No	Fair
Walsh 2004 Multicenter 5	Yes	Yes	Yes No No No	None	No	No	Fair for acute Poor for delayed
Yalcn 1999 Single Center 3	Yes	Yes	No No No No	NR	Yes	No	Fair
Zeidman 1998 Single Center 3, 4, 5	NR	NR	Yes No No No	None	No	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Stewart, A. 1995 Multicenter 4	Yes	4 (of 13) authors employed by Glaxo
Walsh 2004 Multicenter 5	Yes	Study supported in part by unrestricted educational grant from SmithKline Beecham Pharmaceuticals.
Yalcn 1999 Single Center 3	Yes	NR
Zeidman 1998 Single Center 3, 4, 5	Yes	NR

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Dolasetron vs Ondansetron								
Fauser 1996 Multicenter 3, 4	women, prior chemo	NR/NR	NR/399/399	1/0/398	Yes	NR	Yes	Yes
Hesketh 1996 Multicenter 5	prior chemo	No/NR	NR/NR/609	51/NR/558	Yes	NR	Some differences (NS)	Yes
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	corticosteroids	NR/NR	NR/NR/407	//	NR	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Dolasetron vs Ondansetron							
Fauser 1996 Multicenter 3, 4	Yes	Yes	Yes No No No	No	Yes	No	Good
Hesketh 1996 Multicenter 5	Yes, but not described	Yes, but not described	Yes No No No	No	Yes	No	Good
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	Yes	Yes	Yes No No No	Unable to determine	No	Yes	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Dolasetron vs Ondansetron		
Fauser 1996 Multicenter 3, 4	Yes	Hoescht Marion Roussel, Inc.
Hesketh 1996 Multicenter 5	Yes	Supported by a grant from Hoescht Marion Roussel
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	Yes	Supported by the National Institute of Canada and Hoescht Marion Roussel.

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Dolasetron vs Granisetron								
Audhuy 1996 Multicenter 5	women, prior chemo	NR/NR	NR/NR/476	2/0/474	Yes	NR	Yes	Yes
Tan 2002 Single Center 4, 5	none	NA/NA	NR/NR/26	0/0/26	Not randomized	Not randomized	Inadequate Information	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Dolasetron vs Granisetron							
Audhuy 1996 Multicenter 5	Yes	Yes	Yes No No No	No	Yes, but 2 excluded because no drug received	No	Good
Tan 2002 Single Center 4, 5	NR	NR	No No No No	No	Yes	Unable to determine	Poor

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Dolasetron vs Granisetron		
Audhuy 1996 Multicenter 5	Yes	Supported by a grant from Hoescht Marion Roussel, Inc.
Tan 2002 Single Center 4, 5	Yes	Roche Laboratories

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Palonsetron								
Aapro 2006 Multicenter 5	none	No/No	NR/NR/673	6/0/667	Yes	Yes	Yes	Yes
Gralla 2003 Multicenter 4	none	None/NA	NR/NR/570	12/0/563	Yes	Yes	Unknown; excluded 7	Yes
Eisenberg 2003 Multicenter 3	none	NR/NR	NR/NR/592	23/0/569	Yes	Yes	Unknown, because only reported B/L for PPP	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Palonsetron							
Aapro 2006 Multicenter 5	Unclear	Yes	NR No Yes NR	None	Yes	No	Fair
Gralla 2003 Multicenter 4	Unclear	Unclear	Yes No No No	None	No	No	Fair
Eisenberg 2003 Multicenter 3	Yes	Yes	Yes No No No	None	No	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Palonsetron		
Aapro 2006 Multicenter 5	No	Helsinn Healthcare
Gralla 2003 Multicenter 4	Yes	Helsinn Healthcare
Eisenberg 2003 Multicenter 3	Yes	Helsinn Healthcare SA

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Granisetron iv vs Granisetron po								
Abang 2000 Multicenter 4	BMT, PBPCT, women	nr/nr	NR/NR/60	9/0/51	Yes	NR	Yes	Yes
L-758,298 vs Ondansetron								
Cocquyt 2001 Multicenter	None	NR/No use of antiemetic agent within 1 week of study day 1	NR/NR/53	NR/NR/53	Yes	Yes	Yes	Yes
Van Belle 2002 Multicenter	None	NR/No use of antiemetic agent within 72 hours of study day 1	NR/NR/177	2/NR/177	Yes	NR	Yes	Yes
Ondansetron vs Ondansetron								

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Granisetron iv vs Granisetron po							
Abang 2000 Multicenter 4	Yes	Yes	Yes No No No	None	No, only excluded 1	No	Fair
L-758,298 vs Ondansetron							
Cocquyt 2001 Multicenter	Yes	Yes	NR No NR NR	None	NR	No	Fair
Van Belle 2002 Multicenter	NR	NR	NR NR NR NR	None	NR	No	Fair
Ondansetron vs Ondansetron							

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Granisetron iv vs Granisetron po		
Abang 2000 Multicenter 4	Yes	Supported by a research grant from SmithKline Beecham Pharmaceuticals
L-758,298 vs Ondansetron		
Cocquyt 2001 Multicenter	No	NR
Van Belle 2002 Multicenter	No	Merck & Co, Inc
Ondansetron vs Ondansetron		

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified
Pectasides **2007** Single Center	None	NR/No medications with antiemetic activity or medications which could confound the efficacy evaluation in the 24 hours prior to inclusion	NR/NR/134	NR/NR/NR/134	Yes	NR	Yes	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis	Postrandomization exclusions	Quality rating
Pectasides **2007** Single Center	NR	NR	NR NR NR NR	None	NR	No	Fair

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Controlled group standard of care	Funding
Pectasides **2007** Single Center	Yes	NR

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Aprepitant				
Navari 1999 USA Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 400 mg po Days 2-5: Apr 300 mg po B: Day 1: Apr 400 mg po Days 2-5: placebo C: Days 1-5: placebo Pts received Gran + Dex 30 min before cisplatin on Day 1 *corticosteroids given concomitantly (see "Allowed other medications")*	Cisplatin-naïve patients ≥18 years who were scheduled to receive a first course of cisplatin at a dose of ≥70 mg/m2. Women of child-bearing age had to have a negative test for the beta subunit of human chorionic gonadotropin in serum.	Mean: 61.7 yrs Range: NR % Male: 62.9% Ethnicity: NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Aprepitant				
Navari 1999 USA Hesketh chemo level 5	Mean cisplatin dose: 79.3 mg/m2 Type of cancer: lung: 68.5 % gastrointestinal: 9.4% head and neck: 10.1% genitourinary: 7.5% other: 4.4% % receiving additional emetogenic chemo: 4% Alcohol intake - % of pts (drinks/wk): 0-4 drinks: 82.4% 5-10 drinks: 7.5% ≥11 drinks: 7.5%	NR/NR/159		Day 1: Gran 10 mcg/kg + Dex 20 mg po; Days 2-5: not allowed except as rescue

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	Primary measure: proportion of pts without emesis in the delayed emesis phase Numbers of episodes of vomiting Pts' nausea assessment (100 mm horizontal visual analogue scale [VAS]: 0mm= "no nausea" and 100mm="nausea as bad as it could be") Pts global satisfaction with antiemetic treatment (100 mm VAS): 0mm="not at all satisfied" and 100mm="completely satisfied"	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	***All comparisons: Group A vs. B vs. C*** ***Acute results (day 1)*** : No vomiting: 93% vs 94% vs 67% (p<0.001 for Groups A&B combined vs C) No emesis and no rescue therapy: 77% vs 83 % vs 57% (p=0.004 for Groups A&B combined vs C) Median nausea VAS scores: 0mm vs 0mm vs 1mm ***Delayed results (days 2-5):*** No vomiting: 82% vs 78% vs 33% (p<0.001 for Groups A&B combined vs C) No emesis and no rescue therapy: 52% vs 43% vs 16% (p<0.001 for A vs C; p=0.003 for B vs C) Pts with 0-2 emetic episodes: 98% vs 93% vs 59% (p<0.001 for Groups A& B combined vs C) No or minimal nausea: 51% vs 48% vs 24% (p=0.007 for A vs C; p=0.01 for B vs C) Median nausea VAS scores: 1mm vs 3mm vs 10mm Overall results (Days 1-5): No or minimal nausea: 49% vs 48% vs 25% (p=0.02 for A vs C; p=0.03 for B vs C) Global satisfaction median rating: 100 vs 98 vs 82 (p=0.001 for A vs C; p=0.03 for B vs C) Median nausea VAS scores: 1mm vs 2mm vs 5mm	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	*Comparisons are made between Groups A vs B vs C; and p=NS for all comparisons* *(Numbers reported are % of pts with the AE)* Clinical events: Constipation: 19 % vs 13% vs 18% Diarrhea: 17% vs 7% vs 10% Dehydration: 6% vs 6% vs 14% Headache: 22% vs 17% vs 20% Hiccups: 15% vs 17% vs 14% Asthenia: 26% vs 26% vs 25% Hematologic changes: Decrease in total white cell count: 2% vs 2% vs 2% Decrease in neutrophils: 0% vs 2% vs 2% Serum aminotransferase elevations (transient increase >2.5X ULN range in pts who had normal or below normal baseline values (NCI toxicity grade II, III, or IV): Aspartate aminotransferase: 0% vs 0% vs 8% Alanine aminotransferase: 9% vs 0% vs 14%	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Aprepitant	
Navari 1999 USA Hesketh chemo level 5	

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Chawla 2002 International Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 40 mg po Days 2-5: Apr 25 mg po B: Day 1: Apr 125 mg po Days 2-5: Apr 80 mg po C: Day 1: placebo Days 2-5: placebo D: (discontinued and not analyzed) Day 1: Apr 375 mg po Days 2-5: Apr 250 mg po Apr (or placebo) given one hour prior to cisplatin infusion; Ond and Dex given 30 min prior to cisplatin infusion on day 1. Days 2-5: pts took Apr or placebo between 8 AM and 10 AM *Corticosteroids given concomitantly; see "Allowed other medications"*	Cisplatin-naïve pts age ≥18 yrs who had histologically confirmed solid tumors, had a Karnofsky score ≥ 60, and were scheduled to receive a chemo regimen that included cisplatin ≥70 mg/m2. Female pts of childbearing potential were required to have a negative beta-human chorionic gonadotropin test result.	Mean: 56.0 yrs Range: NR % Male: 56.4% % White: 58.3% % Black: 6.3% % Other: 35.4%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Chawla 2002 International Hesketh chemo level 5	Mean cisplatin dose: 81.2 mg/m2 Primary cancer diagnosis: respiratory: 43.6% urogenital: 27.0% other: 28.9% Alcohol intake - % of pts (drinks/wk): 0 drinks: 74.5% 1-10 drinks: 19.4% >10 drinks: 5.8% % receiving concurrent emetogenic chemo (Hesketh level ≥3): 18.1%	663/NR/583		A: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po B: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po C: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po D: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Chawla 2002 International Hesketh chemo level 5	Primary response: Complete response (**CR**): no emetic episodes and no rescue therapy for Days 1-5 Total control (**TC**): no emetic episodes, no use of rescue therapy, and maximum nausea VAS< 5mm Complete protection (CP): no emesis, no rescue therapy, and no significant nausea (VAS<25 mm) No emesis No rescue therapy No nausea (maximum VAS <5 mm) No significant nausea (max. VAS <25 mm) Total number of emetic episodes (0, 1, 2, ≥3)	Pt diary for emetic episodes and use of rescue 100 mm Nausea visual analog scale (VAS): 0mm = no nausea 100mm = nausea as bad as it could be Pts marked this nausea VAS every morning (8 AM-10AM) for the nausea they experienced the previous day. Pts had a post-study visit between Day 1 and 3 days after last dose of study medication; and another visit between days 19-29 post cisplatin for FU and lab tests.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Chawla 2002 International Hesketh chemo level 5	*Comparisons are for groups A (Apr 40/25) vs. B (Apr 125/80) vs. C(placebo)* ***Acute (Day 1):*** CR: 75.6% vs 83.2% vs 71.4% (p=NR for A vs C; p=0.014 for B vs C) TC: 63.0% vs 67.9% vs. 58.7% (p=NR for both comparisons) CP: 72.3% vs 79.4% VS 66.7% (P<0.05 for A vs C; p=NR for B vs C) No emesis: 80.7% vs 87.0% vs 73.0% (p=NR for A vs C;p<0.01 for B vs C) No rescue: 87.4% vs 93.9% vs 93.7% (p=NR for both comparisons) No nausea:70.6% vs 71.8% vs 66.7% (p=NR for both comparisons) No significant nausea: 86.6% vs 90.8% vs 87.3% (p=NR for both comparisons) ***Delayed (Days 2-5):*** CR: 63.9% vs 72.7% vs 45.2% (p=0.002 for A vs C; p<0.001 for B vs C) TC: 51.3% vs 51.5% vs 32.5% (p<0.01 for A vs C and B vs C) CP: 58.0% vs 67.4% vs 41.3% (p<0.01 for A vs C and B vs C) No emesis: 69.7% vs 77.3% vs 50.0% (p<0.01 for A vs C and B vs C) No rescue: 75.6% vs 85.6% vs 63.5% (p<0.05 for A vs C; p<0.01 for B vs C) No nausea: 52.9% vs 58.3% vs 36.5% (p<0.01 for A vs C and B vs C) No significant nausea: 68.9% vs 83.3% vs 62.7% (p=NR for A vs C; p<0.01 for B vs C) ***Overall (Days 1-5):*** CR: 58.8% vs 71.0% vs 43.7% (p<0.05 for A vs C; p<0.01 for B vs C) TC: 44.5% vs 47.3% vs 31.0% (p<0.05 for A vs C; p<0.01 for B vs C) CP: 44.5 % vs 47.3% vs 31.0% (p<0.05 for A vs C; p<0.01 for B vs C) No emesis: 76.3% vs 65.5% vs 48.4% (p<0.01 for A vs C and B vs C) No rescue: 73.1% vs 83.2% vs 63.5% (p=NS for A vs C; p<0.01 for B vs C) No nausea: 48.7% vs 52.7% vs 34.1% (p=0.05 for A vs C; p<0.01 for B vs C) No significant nausea: 68.9% vs 81.7% vs 58.7% (p=NR for A vs C; p<0.01 for B vs C)	Tolerability was monitored by physical exams, including vital signs and weight measurements, lab studies, and electrocardiograms.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Chawla 2002 International Hesketh chemo level 5	*Comparisons: Groups A (40/25) vs B (125/80) vs C (placebo) vs D (375/250)* % with ≥ 1 adverse event (AEs)*: 71% vs 76% vs 72% vs 85%* % with drug-related AEs*: 27% vs 27% vs 26% vs 15%* % with serious AEs*: 17% vs 22% vs 12% vs 21%* % discontinued due to AEs*: 1% vs 2% vs 1% vs 9%* % with ≥ 1 laboratory AE*: 22% vs 23% vs 22% vs 27%* % with drug-related laboratory AE*: 6% vs 8% vs 9% vs 0%* With most common AEs (≥10% in at least 1 treatment group): Asthenia/fatigue: 13% vs 20% vs 17% vs 21% Constipation: 12% vs 14% vs 13% vs 15% Diarrhea: 11% vs 11% vs 12% vs 12% Nausea: 12% vs 13% vs 11% vs 21% Neutropenia: 2% vs 3% vs 6% vs 12% Anorexia: 6% vs 12% vs 11% vs 0% Headache: 8% vs 8% vs 10% vs 9% Hiccup: *16% vs 12% vs 9% vs 9%* % with febrile neutropenia: *9% vs 6% vs 4% vs 6%* *"No pt died or discontinued due to lab AEs"*	18/583= 3.1%; 13 withdrew due to AEs

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Chawla 2002 International Hesketh chemo level 5	The Apr 375/250 mg regimen (n=34) was replaced by the Apr 40/25mg regimen due to pharmacokinetic data and data showing an interaction between Apr and dexamethasone. No statistical comparisons were made for this group, and the results reported were for the complete response: Acute: 91%; Delayed: 73%; Overall: 70%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	Multicenter DB parallel	A: Day 1: Apr 375 mg Days 2-5: Apr 250 mg B: Day 1: Apr 125 mg Days 2-5: Apr 80 mg C: Days 1-5: placebo *corticosteroids given concomitantly (see "Allowed other medications")*	Cisplatin naïve patients ≥ 18 years, who had histologically confirmed solid malignancies, a Karnofsky score of ≥ 60, and who were scheduled to receive a chemo regiment with at least on cycle including cisplatin ≥70 mg/m2. If pts satisfactorily completed the preceding cycle and related study procedures including efficacy assessments and FU visits, and if their continued participation was considered appropriate by the investigator, pts could remain in the study for up to 5 additional cycles of chemo (if the minimum dose of cisplatin was >= 70 mg/m2 in any cycle)	Mean: 57.7 yrs Range: 20-82 yrs % Male: 63.9% % White: 73.8% % Black: 4.4% % Other: 21.8%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	Mean cisplatin dose: 80.3 mg/m2 % cisplatin ≥ 100 mg/m2: 5.9% Primary cancer diagnosis: respiratory: 45.0% urogenital: 19.8% other: 35.1% Alcohol intake - % of pts (drinks/wk): 0 drinks: 64.3% 1-10 drinks: 26.7% >10 drinks: 8.4% % receiving concurrent emetogenic chemo (Hesketh level ≥3): 17.3%	NR/NR/202	(#s changed from cycle to cycle)	Day 1: Ond 32 mg iv + Dex 20 mg po; Days 2-5: Dex 8 mg po Corticosteroid therapy equivalent to ≤10mg of prednisone was allowed provided it was not initiated within 72h of day 1 of cycle 1

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	Complete response: no emesis and no rescue therapy Partial response: 0-2 emetic episodes and no rescue therapy Failed response: >2 emetic episodes and/or use of rescue therapy	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	<u>Cycle 1 data: (Group B (n=80) vs. C(n=84))</u> % Complete response: 63.8% vs. 48.8%, p<0.05 % Partial response: 11.2% vs. 13.1%, p=NR % Failures: 25.0% vs. 38.1%, p=NR <u>Cycle 2 data: (Group B (n=46) vs. C(n=38))</u> % Complete response: 80% vs 71%, p=NR % Partial response: 10.9% vs15.8%, p=NR % Failures: 8.7% vs 13.1%, p=NR	

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	*Comparisons: Groups A (375/250, n=23) vs B (125/80, n=62) vs C (placebo, n=60)* **For AEs in cycles 2-6** % with ≥ 1 adverse event (AEs): 74 vs 76 vs 73 % with drug-related AEs: 26 vs 34 vs 25 % with serious AEs: 9 vs 26 vs 15 % discontinued due to AEs: 13 vs 10 vs 10 % with ≥1 laboratory AE: 22 vs 26 vs 27 % with drug-related laboratory AE: 0 vs 7 vs 5 With most common AEs (≥10% in at least 1 treatment group): Abdominal pain: 9 vs 10 vs 10 Fatigue: 26 vs 18 vs 17 Dehydration: 0 vs 13 vs 10 Dizziness: 9 vs 13 vs 10 Influenza-like disease: 13 vs 2 vs 2 Constipation: 22 vs 10 vs 13 Diarrhea: 9 vs 23 vs 13 Dysgeusia: 17 vs 5 vs 7 Nausea: 17 vs 18 vs 13 Anemia: 13 vs 7 vs 13 Febrile neutropenia: 0 vs 11 vs 2 Headache: 4 vs 11 vs 15 Hiccups: 9 vs 15 vs 8 Dyspnea: 13 vs 2 vs 5	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	Group A was discontinued early due to pharmacokinetic data suggesting the dose was too high; between treatment comparisons were made between Groups B and C only. 6 pts died between Cycles 2 and 6: 3 were in Group B (1 pt=cancer progression and respiratory insufficiency, 1 pt =cancer progression, 1 pt =hemoptysis) and 3 were in Group C (2 pts = cardiac arrest, 1 pt = metastasis)

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Herrington 2008 Texas Hesketh Level 5	Single-Center DB RCT Parallel	Arm A: Day 1 - Palonosetron 0.25 mg iv & dexamethasone 12 mg; Aprepitant 125 mg orally Day 2 & 3 - Aprepitant 80 mg orally Arm B: Day 1 - Palonosetron 0.25 mg iv & dexamethasone 12 mg; Aprepitant 125 mg orally Day 2 & 3 - Placebo Arm C: Day 1 - Palonosetron 0.25 mg iv & dexamethasone 18 mg; Placebo Day 2 & 3 - Placebo	Patients ≥ 18 years, histologically or cytologically confirmed malignant disease and an Eastern Cooperative Oncology Group performance status of 0-2. Chemotherapy naïve or chemotherapy non-naïve with the last chemotherapy separated by at least 3 weeks; however, study criteria demanded that they not have greater than grade 1 nausea.	58 Range: NR 26.6% male Ethnicity NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Herrington 2008 Texas Hesketh Level 5	Mean weight (kg): 87.5 Cancer diagnosis Breast: 54.6% Lung: 13.3% Head and neck: 18.6% Other: 13.5%	NR/82/75	NR/NR/75	All treatment arms received dexamethasone 8 mg orally on days 2-4 Rescue medication was allowed

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Herrington 2008 Texas Hesketh Level 5	Proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy	Patient diary for emetic episodes, breakthrough nausea medications, and nausea severity during the 120-hour observation period

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Herrington 2008 Texas Hesketh Level 5	Proportion of patients without emesis (Day 1) Arm A: 96.4% vs Arm B: 100% vs Arm C: 93.8% Proportion of patients without emesis (Day 2-5) Arm A: 92.9% vs Arm B: 92.6% vs Arm C: 50% Severity of Nausea Using Mean VAS (Day 1) Arm A: 12.6 vs Arm B: 8.7 vs Arm C: 15.6 Severity of Nausea Using Mean VAS (Day 2) Arm A: 15.2 vs Arm B: 11% vs Arm C: 28.4 Severity of Nausea Using Mean VAS (Day 3) Arm A: 15 vs Arm B: 12.3 vs Arm C: 30.3 Severity of Nausea Using Mean VAS (Day 4) Arm A: 10.5 vs Arm B: 16.6 vs Arm C: 19.6 Severity of Nausea Using Mean VAS (Day 5) Arm A: 12 vs Arm B: 18.3 vs Arm C: 20.6 Percentage with no rescue medication (Day 1) Arm A: 81.5% vs Arm B: 85.2% vs Arm C: 75% Percentage with no rescue medication (Day 2-5) Arm A: 55.6% vs Arm B: 70.4 vs Arm C: 43.8 Percentage with complete response (no emesis and no rescue medication: Day 1) Arm A: 66.7% vs Arm B: 70.4% vs Arm C: 56.2% Percentage with complete response (no emesis and no rescue medication: Day 2-5) Arm A: 63% vs Arm B: 59.3% vs Arm C: 31.2%	Patient report

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Herrington 2008 Texas Hesketh Level 5	NR	NR; NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Herrington 2008 Texas Hesketh Level 5	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Herrstedt 2005 Denmark Hesketh Level ≥3	Multicenter DB, Randomized, parallel	APR regimen Day 1: APR 125 mg, OND 8 mg and DEX 12 mg before chemotherapy and OND 8 mg 8 hrs later Day 2-3: APR 80 mg every day Control regimen Day 1: OND 8 mg and DEX 20 mg before chemotherapy and OND 8 mg 8 hours later Days 2-3: OND 8 mg 2x per day This was done for ≤ 3 more cycles of chemotherapy for a total of 4 cycles.	Patients ≥ 18 years, diagnosed with breast carcinoma and had received a single cycle of MEC (Hesketh Level ≥ 3) in the core protocol. Pts had a predicted life expectancy ≥ 4 months and a Karnofsky score ≥ 60. Pts required to successfully complete each previous chemotherapy cycle before continuing to the next cycle of treatment with the same hemotherapeutic regimen. Pts were treated with I.V.. cyclophosphamide 750-1500 mg/m2 (+/- 5%); i.v.. cyclophosphamide 500-`500 mg/m2 (+/-5%) and doxorubicin ≤ 60 mg/m2 (+/- 5%); i.v.. cyclophosphamide 500-1500 mg/m2 (+/- 5%) and i.v.. epirubicin ≤ 100mg/m2 (+/- 5%) or approved chemotherapeutic agents Hesketh level ≤ 2.	Mean: 52 yrs Range: NR % Male: 0.02% % white: 77.84%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Herrstedt 2005 Denmark Hesketh Level ≥3	Received a combination of cyclophosphamide plus an anthracycline as their chemotherapy regimen: 99%	866/NR/744	94/NR/650	Permitted rescue medications were 5-HT_3 antagonists, phenothiazines, butyrophenones, and benzodiazepines

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Herrstedt 2005 Denmark Hesketh Level ≥3	Proportion of patients with complete response (CR): no emesis and no use of rescue therapy, across multiple cycles of chemotherapy	Pts reported emesis or use or rescue medication over a 120 hour period after chemotherapy Completed a daily nausea visual analog scale (VAS: 0 mm is no nausea, 100 mm is nausea as bad as it could be)

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Herrstedt 2005 Denmark Hesketh Level ≥3	Complete Response Cycle 1: APR: 50.8% vs Control: 42.5% Cycle 2: APR: 40.9% vs Control: 30.7% Cycle 3: APR: 37.9% vs Control: 26.3% Cycle 4: APR: 34.5% vs Control: 23.9% (p=0.017, based on the log-rank test) No vomiting Cycle 1: APR: 75.7% vs Control: 58.7% Cycle 2: APR: 70.4% vs Control: 47.6% Cycle 3: APR: 66.8% vs Control: 42.3% Cycle 4: APR: 62.9% vs Control: 38.8% (p<0.001) No use of rescue medication Cycle 1: APR: 58.7% vs Control: 56.2% Cycle 2: APR: 49.9% vs Control: 44.8% Cycle 3: APR: 47.4% vs Control: 40.2% Cycle 4: APR: 44.6% vs Control: 37.3% (NS)	Patient report

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Herrstedt 2005 Denmark Hesketh Level ≥3	Cycles 2-4 Alopecia: APR: 12.7% vs Control: 14.8% Fatigue: APR: 20.8% vs Control: 17.5% Headache: APR: 9.4% vs Control: 9.2% Constipation: APR: 9.9 vs Control: 13.6% Neutropenia: APR: 9.1% vs Control: 5.8% Febrile Neutropenia: APR: 2.9% vs Control: 2.2% Infection: APR: 17.1% vs Control: 16.7% Dyspepsia: APR: 0.6% vs Control: 7.8% Nausea: APR: 11.9% vs Control: 11.4% Stomatitis: APR: 8.1% vs Control: 7.2% Diarrhea: APR: 8.6% vs Control: 5.3%	94 (none are due to AEs)

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Herrstedt 2005 Denmark Hesketh Level ≥3	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Hesketh 2003 International Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 125 mg po Days 2-3: Apr 80 mg po Day 4: placebo B: Day 1: placebo Days 2-4: placebo 1 hour before cisplatin on Day 1, pts received Apr or placebo *Corticosteroids given concomitantly; see "Allowed other medications"*	Cisplatin-naïve pts age ≥18 yrs who had histologically confirmed solid tumors, had a Karnofsky score ≥ 60, and were scheduled to receive a chemo regimen that included cisplatin ≥70 mg/m2. Female pts of childbearing potential were required to have a negative beta human chorionic gonadotropin test result.	Mean: 58.5 yrs Range: 18-84 yrs % Male: 62.5% % White: 3.0% % Black: 90.6% % Other: 6.4%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Hesketh 2003 International Hesketh chemo level 5	Mean cisplatin dose: 80.5 mg/m2 Primary cancer diagnosis: Respiratory: 42% Urogenital: 23% Other: 35% Alcohol intake - % of pts (drinks/wk): 0 drinks: 58% 1-10 drinks: 23.5% >10 drinks: 16% % receiving concurrent emetogenic chemo (Hesketh level ≥3): 15.5% % within US: 22% History of motion sickness: 6% History of morning sickness: 5.3% History of chemo: 14.5% History of CINV: 6%	562/536/530	/ /521	A: Day 1: Ond 32 mg iv + Dex 12 mg po Day 2-4: Dex 8 mg po once/day B: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-4: Dex 8 mg po twice/day given 30 min before cisplatin on Day 1

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Hesketh 2003 International Hesketh chemo level 5	Primary response: Complete response (CR): no emetic episodes and no rescue therapy for Days 1-5 Total control (TC): no emesis, no rescue therapy, and no nausea (nausea VAS< 5mm) Complete protection (CP): no emesis, no rescue therapy, no significant nausea (VAS <25mm) No emesis No rescue therapy No nausea (maximum VAS <5 mm) No significant nausea (max. VAS<25 mm) Impact of CINV on daily life, as measured by an FLIE total score of >108	Pt diary for # of emetic episodes and use of rescue therapy. 100 mm Nausea visual analog scale (VAS)

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Hesketh 2003 International Hesketh chemo level 5	*Comparisons are for groups A(Apr 125/80) vs. B(placebo)* **Acute (Day 1):** CR: 89.2% vs 78.1%; p<0.001 TC: 70.7% vs 64.2%, p=NR CP: 84.8% vs 74.6%, p<0.01 No emesis: 90.0% vs 79.3%, p<0.01 No rescue: 94.2% vs 88.8%, p<0.05 No nausea: 72.3% vs 69.1%, p=NR No significant nausea: 90.6% vs 86.5%, p=NR D**elayed (Days 2-5):** CR: 75.4% vs 55.8%; p<0.001 TC: 49.0% vs 42.7%, p=NR CP: 66.4% vs 51.5%, p<0.01 No emesis: 80.8% vs 58.8%, p<0.01 No rescue: 81.2% vs 73.5%, p<0.05 No nausea: 51.0% vs 47.7%, p=NR No significant nausea: 75.3% vs 68.5%, p=NR **Overall (Days 1-5):** CR: 72.7% vs 52.3%, p<0.001 TC: 45.5% vs 40.0%, p=NR CP: 63.4% vs 49.2%, p<0.01 No emesis: 77.7% vs 55.0%, p<0.01 No rescue: 80.8% vs 70.8%, p<0.01 No nausea: 47.5% vs 44.2%, p=NR No significant nausea: 73.2% vs 66.0%, p=NR FLIE: minimal or no impact of CINV on daily life: 74.0% vs 64.3% (p="significant" but not specified)	AE reported up to 14 days after treatment

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Hesketh 2003 International Hesketh chemo level 5	***Comparisons made between Groups A (n=261) and B (n=264)*** % with ≥ 1 clinical adverse event (AE): 65.1% vs 61.4% % with drug-related clinical AEs: 14.6% vs 11.0% % with serious clinical AEs: 16.1% vs 17.0% % with ≥ 1 laboratory AE: 14.0% vs 13.5% % with drug-related laboratory AE: 2.3% vs 1.2% With most common AEs (≥10% in at least 1 treatment group): Asthenia/fatigue: 17.2% vs 9.5% Constipation: 8.0% vs 12.1% Hiccups: 13.8% vs 6.8% Nausea (considered to be an AE if occurred after Day 5 or if determined at any time by the investigator to be serious, be drug-related, or to result in discontinuation): 10.7% vs 8.7% Dehydration: 1.9% vs 1.1% Febrile neutropenia: 2.3% vs 1.9% Neutropenia: 2.7% vs 0% Thrombocytopenia: 1.5% vs 0% Deaths (none considered drug-related): A: 2.7% vs B: 3.4% 3 serious AEs considered drug related: 1 in Group A = 1 pt with perforating duodenal ulcer, considered related to Dex 2 in group B = 1 pt with chills and leg pain; 1 pt with hyponatremia	

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Hesketh 2003 International Hesketh chemo level 5	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 125 mg po Days 2 & 3: Apr 80 mg po Day 4: no Apr given B: Day 1: placebo Days 2-4: placebo *corticosteroids given concomitantly*	Cisplatin-naïve pts >18 yrs who had histologically confirmed solid tumors, a Karnofsky score ≥60, and who were scheduled to receive a chemo regimen that included cisplatin ≥70 mg/m2 were eligible. Female pts of childbearing potential were required to have a negative beta-human chorionic gonadotropin test result.	Mean: 53.5 yrs Range: 18-82 yrs % Male: 51.5% Black: 5.4% White: 29.5% Other: 65.0%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Mean cisplatin dose: 81 mg/m2 % pts with a cisplatin dose ≥70-100 mg/m2: 82% Type of cancer: respiratory: 38.6% urogenital: 38.5% eyes/ears/nose/throat: 8.4% other: 16.5% % receiving additional emetogenic chemo: 17% Alcohol intake - % of pts (drinks/wk): 0 drinks: 85.5% 1-10 drinks: 13 % ≥11 drinks: 1.5% % pts with a history of morning sickness: 8.4% % pts with a history of motion sickness: 4% % pts with a history of chemotherapy: 8.6% % pts with a history of CINV: 5.5%	624/NR/569		A: Day 1: Ond 32 mg iv Days 2-4: Dex 8 mg po B: Day 1: Ond 32 mg iv Days 2-4: Dex 8 mg po

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Primary measure: Complete response (**CR**): no emetic episodes and no use of rescue therapy Complete protection (**CP**): no emesis, no rescue therapy, and nausea VAS <25mm Total control (**TC**): no emesis, no rescue therapy, nausea VAS <5mm No Emesis No use of rescue medication Impact of CINV on daily life (as measured by an FLIE score >108) No significant nausea (VAS <25mm) No nausea (VAS <5mm)	Acute results: Day 1 results only Delayed results: Days 2-5 Overall: Days 1-5

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	*for all results, comparisons are for Group A vs. Group B* ***Acute results (day 1):*** CR: 82.8% vs 68.4% (p<0.001) CP: 80.0% vs 64.6% (p<0.01) TC: 64% vs 57% (p=NS) No emesis: 84% vs 69% (p<0.01) No rescue: 96% vs 90% (p<0.01) ***Delayed results (Days 2-5):*** CR: 67.7% vs 46.8% (p<0.001) CP: 60.9% vs 44.1% (p<0.01) TC: 50% vs 34% (p<0.01) No emesis: 72% vs 48% (p<0.01) No rescue: 83% vs 74% (p<0.05) ***Overall results (Days 1-5):*** CR: 62.7% vs 43.3% (p<0.001) CP: 55.6% vs 40.7% (p<0.01) TC: 44% vs 32 % (p<0.01) No emesis: 66% vs 44% (p<0.01) No rescue: 82% vs 73% (p<0.01) *FLIE: minimal or no impact on daily life: 74.7% vs 63.5% (p=<0.05)*	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	*Comparisons made between Aprepitant (n=282) and Placebo (n=285)* % with ≥ 1 clinical adverse event (AE): 72.7% vs 72.6% % with drug-related clinical AEs: 19.5% vs 14.4% % with serious clinical AEs: 11.0% vs 9.8% % discontinued due to a clinical AE: 7.1% vs 5.3% % with ≥ 1 laboratory AE: 29.6% vs 25.2% % with drug-related laboratory AE: 5.7% vs 3.9% With most common clinical AEs (≥10% in at least 1 treatment group): Anorexia: 15.2% vs 14.0% Asthenia/fatigue: 18.4% vs 14.0% Constipation: 12.4% vs 12.3% Diarrhea: 12.1% vs 10.5% Headache: 9.9% vs 11.6% Nausea (nausea & vomiting considered AEs if they occurred >Day 5 or if determined at any time to be serious, drug-related, or to result in discontinuation): 14.5% vs 14.4% Vomiting: 8.9% vs 12.6% Dehydration: 1.8% vs 0.7% Febrile neutropenia: 0.4% vs 0.7% Neutropenia: 1.8% vs 2.1% Septic shock: 1.1% vs 0.7% Dyspnea: 1.1% vs 0.7% Respiratory insufficiency: 1.8% vs 0.4% Deaths (not considered to be drug-related): 4.6% vs 3.9% 3 serious AEs were thought to be drug related: 1 AE of worsening diabetes mellitus and 1 event of hyperglycemia in Group B; 1 event of disorientation in Group A	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Warr 2005 International (95 centers) Hesketh chemo level 4	Multicenter DB parallel	A: (N=438) Day 1: Apr 125 mg po 1 hr before chemo Day 2-3: Apr 80 mg po B: (N=428) Day 1: placebo po Day 2-3: placebo po	Patients ≥18 years with breast cancer being treated with moderately emetogenic chemo (hesketh level ≥ 3) and scheduled to receive their first course of moderately emetogenic chemotherapy. Patients had to have a predicted life expectancy of ≥4 months and a Karnofsky score of ≥60 to be eligible.	Age: 52.6 yrs Female: 99.8% White: 78.6%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Warr 2005 International (95 centers) Hesketh chemo level 4	Motion sickness: 18.9% History of vomiting during pregnancy: 30.5%	910 / unclear / 866	122 / NR / 857	Antiemetic treatments were not allowed within 48 hour before treatment, except for single daily doses of lorazepam. A: Day 1: Ond 8 mg po 30-60 min before chemo + dex 12 mg po 30 min before chemo Ond 8 mg po 8 hrs after first dose Day 2-3: placebo po bid B: Day 1: Ond 8 mg po 30-60 min before chemo + dex 20 mg po 30 min before chemo Ond 8 mg po 8 hrs after first dose Day 2-3: 8 mg po bid

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Warr 2005 International (95 centers) Hesketh chemo level 4	Complete response: no vomiting and no rescue therapy throughout the acute and delayed phases (120 hrs)	Patient diary for emetic episodes, use of rescue medication, and daily nausea ratings (on a VAS where 0="n from Day 1 to day 6. FLIE questionnaire (9 items on vomiting and 9 items on nausea) administered on day 1 and day 6; "minimal or no impact of CINV on daily life" is defined for this study as average score of >6 on the 7-point scale for each item.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Warr 2005 International (95 centers) Hesketh chemo level 4	Aprepitant vs placebo Complete response for 0-120 hours: 51% vs 42%, p=0.015 Complete response for acute (0-24 h) phase: 76% vs 69%, p=0.34 Complete response for delayed (24-120h) phase: 55% vs 49%, p=0.64 % of patients reporting no vomiting: 76% vs 59%, p<0.001 No significant difference between groups in use of rescue therapy FLIE: Patients reporting minimal or no impact on daily living overall: 63.5% vs 55.6%, p=0.019 Minimal impact or no impact of vomiting on daily living: 85.7% vs 71.8%, p<0.001 Minimal impact or no impact of nausea on daily living: 53.5% vs 50.5%, p=NS	Safety and tolerability assessed by clinical and statistical review of AEs, vital signs, and laboratory values.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Warr 2005 International (95 centers) Hesketh chemo level 4	Aprepitant vs placebo AE's thought to be drug-related: 21.5% vs 19.6% Serious AEs: 3.4% vs 4.2% Febrile neutropenia: 2.1% vs 2.1% Constipation: 12.3% vs 18.0% Dyspepsia: 8.4% vs 4.9%	Total withdrawals Total withdrawals due to AEs: 1.4% (12/866 patients) By drug: apr 1.6% vs placebo 2.1%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Warr 2005 International (95 centers) Hesketh chemo level 4	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Other outcomes				
Barrenetxea 1996 Spain	Single-center DB parallel	A: Day 1: Ond 8 mg iv Day 2-4: Ond 8 mg po X3 B: Day 1: Ong 8 mg iv Days 2-4: metoclopramide 10 mg po X3 C: Day 1: Ond 8 mg iv Days 2-4: placebo X3	Breast cancer pts who were eligible if they had received no previous chemo, were ≥ 18 yrs, and had a Karnofsky status of ≥ 60%. Pts were receiving either a regimen of CMF [cyclophosphamide 500 mg day 1, methotrexate 50 mg on days 1 & 8, and 5-fluouracil 600 mg days 1 & 8] every 28 days or of FEC [cyclophosphamide 500 mg day 1, epirubicin 75 mg day 1, and 5-fluorouracil on day 1] every 21days. All pts selected were available for follow-up.	Age: NR Gender: NR Ethnicity: NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Other outcomes				
Barrenetxea 1996 Spain	Cancer: 100% breast cancer	NR/NR/NR	NR/NR/NR	No

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Other outcomes		
Barrenetxea 1996 Spain	Primary efficacy measure: Number of emetic episodes: Complete response: no emetic episode Major response: 1-2 emetic episodes Minor response: 3-5 emetic episodes Failure: >5 emetic episodes C+M response = Complete + major responses Failure rate = Minor + failure responses Quality of Life: Functional Living Index (FLIC): 7 pts scale, with 7=good and 1=poor	FLIC questionnaire complete during a 5 day period following chemo; the degree of nausea and disability were recorded each day on a 7-point scale.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Other outcomes		
Barrenetxea 1996 Spain	*(Data given for number of emetic episodes, but not reported here)* *FLIC scores are approximates because they are read from a graph* **CMF Pts FLIC scores by day, A vs B vs C:** Day 1: 5.1 vs 5 vs 1; p<0.0001 for A & B vs C Day 2: 5 vs 5 vs 2.7; p<0.0001 for A & B vs C Day 3: 5 vs. 5.1 vs 3.5; p<0.0001 for A & B vs C Day 4: 5.2 vs 5.6 vs 3.9; p<0.0001 for A & B vs C Day 5: 5.5 vs 6 vs 4.8; p<0.0001 for A & B vs C **FEC pts FLIC scores by day, A vs B vs C:** Day 1: 4.6 vs 3.7 vs 0.7; p<0.0001 for C vs A; p=0.0440 for C vs B Day 2: 3.9 vs 3.3 vs 2.2; p=NS Day 3: 4.6 vs 4.1 vs 2.2; p=0.032 *(note: p-value given but comparison to which it belongs is not stated)* Day 4: 5.3 vs 5.2 vs 3.3; p=NS Day 5: 5.7 vs 6.1 vs 3.7; p=NS	NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Other outcomes		
Barrenetxea 1996 Spain	"No severe or unexpected event was reported by the pts. Constipation and hot flushes tended to be more frequent among pts receiving Ond for 3 days (group A) than in pts assigned to Groups B or C. However, there was no significant differences between the groups (p=0.1421 and p=0.1001 for constipation and hot flushes respectively.)"	NR; NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Comments
Other outcomes	
Barrenetxea 1996 Spain	

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Aprepitant							
Navari 1999 USA Hesketh chemo level 5	Yes	NR	Yes	Yes	NR	Yes	Yes
Chawla 2002 International Hesketh chemo level 5	Yes	NR	Yes	Yes	NR	Yes	Yes

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Aprepitant					
Navari 1999 USA Hesketh chemo level 5	Yes, No, No, No	None	No, but only excluded 2 (1.2%)	No	Fair
Chawla 2002 International Hesketh chemo level 5	Yes, No, No, No	None	No, but only excluded 5 (1.3%)	No	Fair

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	NR/159/159	Primary exclusion criteria included a Karnofsky score<60; allergy to or intolerance of metoclopramide, dexamethasone, or granisetron; therapy with another antiemetic drug (serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, metoclopramide, or glucocorticoids) within 72h before day 1; an episode of vomiting or retching within 24h before the start of the cisplatin infusion; treatment for or history of a seizure within previous two years; severe concurrent illness other than cancer; gastrointestinal obstruction or active peptic ulcer; radiation therapy to the abdomen or pelvis within 1 week before or after day 1; or any of the following laboratory levels: hemoglobin < 8.5 g/dL, white-cell count <3500/mm3, platelet count <100,000/mm3, serum aspartate aminotransferase level ≥2X upper limit of normal (ULN), serum alanine aminotransferase ≥2X ULN, serum bilirubin ≥2X ULN, serum alkaline phosphatase ≥2X ULN, serum albumin <3 g/dL, and serum creatinine level >2 mg/dL (180 micro-mol/L). Five pts scheduled to receive paclitaxel plus cisplatin were permitted to receive additional glucocoricoids before day 1.
Chawla 2002 International Hesketh chemo level 5	NR/381/381	Exclusion criteria: concomitant treatment with nonapproved drug within 4 wks of study entry; significantly abnormal lab values (including white blood cell count < 3000/mm3, absolute neutrophil count <1500/mm3, platelet count <100,000/mm3, aspartate aminotransferase >2.5X ULN; alanine aminotransferase >2.5X ULN, bilirubin >1.5X ULN, or creatinine >1.5X ULN); known CNS malignancy, active infection or uncontrolled disease that should exclude the patient for safety reasons; a planned regimen of multiple-day, cisplatin-based chemotherapy in a single cycle; moderately or highly emetogenic chemo on the days prior to and/or after cisplatin; or radiation therapy to the abdomen or pelvis within 1 wk prior to day 1. Aside from study drug, additional antiemetics including benzodiazepines, opiates, or other agents (such as 5-HT3 antagonists, phenothiazines, butyrophenones, benzamides, domperidone, or cannabinoids) were not permitted within 72h of day 1, except as rescue therapy for established nausea or emesis after cisplatin. Corticosteroid therapy equivalent to ≤10 mg of prednisone was permitted provided it was not initiated within 72h of day 1.

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

Author Year Country Chemo Level	Funding
Aprepitant	
Navari 1999 USA Hesketh chemo level 5	NR, but 1st author is with Merck
Chawla 2002 International Hesketh chemo level 5	Merck

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	NR	NR	Yes	Yes	NR	NR	NR
Herrington 2008 Texas Hesketh Level 5	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	Yes, No, No, No	No, No	No, but only excluded 3 (1.7%)	Unclear; 22% were excluded after receiving treatment due to the reason of "ineligible", which was not explained	Fair
Herrington 2008 Texas Hesketh Level 5	Yes, No, No, No	No, No	Implied, but not specifically described	None	Fair

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	NR/NR/202	see Chawla 2005
Herrington 2008 Texas Hesketh Level 5	NR/82/75	Patients who experienced an episode of emesis within 24 hours before the start of chemotherapy or who had documented primary or secondary brain neoplasm, and any patient who was receiving radiation to abdomen or pelvis, medications with known antiemetic activity, or medications known to induce the cytochrome P450 enzymes.

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

Author Year Country Chemo Level	Funding
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	Merck; 1st author is consultant for Merck
Herrington 2008 Texas Hesketh Level 5	MGI Pharma and Scott & White grant #R3429

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Herrstedt 2005 Denmark Hesketh Level ≥3	Yes	Yes	Yes	Yes	NR	Yes	Yes
Hesketh 2003 International Hesketh chemo level 5	Yes	Yes	Yes	Yes	NR	Yes	Yes
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Yes	NR	Several statistically insignificant differences	Yes	NR	Yes	Yes

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Herrstedt 2005 Denmark Hesketh Level ≥3	Yes, No, Yes, No	No loss to follow-up, but withdrawals are different (20.1% for APR and 27.1% for control)	Yes	No	Fair
Hesketh 2003 International Hesketh chemo level 5	Yes, No, No, No	No loss to follow-up	No, but only excluded 6 (1.1%)	Unclear; 7.4% excluded due to reason "other"	Fair
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Yes, No, No, No	No, No (1 patient in each group)	No; excluded 9.2% (40 patients excluded from 1 site whose efficacy data were considered unreliable)	Yes	Fair

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Herrstedt 2005 Denmark Hesketh Level ≥3	866/NR/744	NR
Hesketh 2003 International Hesketh chemo level 5	562/530/530	Primary exclusion criteria included: a current user of illicit drugs or had signs of current alcohol abuse; abnormal laboratory values (including WBC< 3,000/mm3 and absolute neutrophil count< 1,500/mm3, platelet count < 100,000/mm3, AST > 2.5X upper limit of normal [ULN], ALT > 2.5X ULN, bilirubin >1.5X ULN, or creatinine >1.5X ULN); uncontrolled disease for which, in the opinion of the investigator, the patient should be excluded for safety reasons; multiple-day cisplatin-based chemotherapy in a single cycle; or radiation therapy to the abdomen or pelvis within 1 wk before study day 1 or between days 1- 6. Additional chemotherapeutic agents of high emetogenicity (Hesketh level ≥3) were permitted only on day 1; pts could not have received such agents within 6 days before or after day 1. Pts could not receive additional antiemetics within 2 days before day 1 or between days 1 and 6 of the study, unless such medications were given as rescue therapy for established nausea or vomiting.
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	624/569/569	Primary exclusion criteria included: abnormal lab values (including white blood count < 3000/mm3 and absolute neutrophil count < 1500/mm3, platelet count < 100,000/mm3, aspartate aminotransferase >2.5X ULN, alanine aminotransferase >2.5X ULN, bilirubin > 1.5X ULN, or creatinine >1.5X ULN); active infection or uncontrolled disease that excluded the pt for safety reasons; a planned regimen of multiple-day cisplatin-based chemotherapy in a single cycle; radiation therapy to the abdomen or pelvis within 1 week prior to day 1 of study or between day 1 and day 6; or moderately or highly emetogenic chemotherapy on the 6 days prior to and/or after the day the cisplatin infusion. Additional chemo agents of high emetogenicity (Hesketh level ≥3) were permitted only on day 1, and additional antiemetics were prohibited within 2 days prior to day 1 or between day 1 and day 6 of study, unless such medications were given as rescue therapy for established nausea and vomiting.

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

Author Year Country Chemo Level	Funding
Herrstedt 2005 Denmark Hesketh Level ≥3	Merck and Co, Inc
Hesketh 2003 International Hesketh chemo level 5	Merck
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Merck

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Warr 2005 International Hesketh chemo level 4	Yes	NR	Yes	Yes	NR	Yes	Yes

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Warr 2005 International Hesketh chemo level 4	Yes, No, No, No	No loss to follow-up	No for efficacy (excluded 1%); yes for safety	No	Fair

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Warr 2005 International Hesketh chemo level 4	910/866/866	Patients were excluded if they had a symptomatic CNS malignancy; received radiation therapy to the abdomen or pelvis in the week before treatment; had vomited in the 24 hours before treatment day 1; had an active infection, an active systemic fungal infection, or any severe concurrent illness except for malignancy; or had abnormal laboratory values (including absolute neutrophil count < 1,500/mm3, WBC count < 3,000/mm3, platelet count < 100,000/mm3, AST > 2.5x the upper limit of normal, ALT > 2.5x the upper limit of normal, bilirubin > 1.5x the upper limit of normal, creatinine > 1.5x the upper limit of normal). Patients taking systemic corticosteroid therapy at any dose were excluded. Antiemetic agents could not be administered within 48 hours before treatment, except for single daily doses of lorazepam.

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

Author Year Country Chemo Level	Funding
Warr 2005 International Hesketh chemo level 4	Merck

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Other outcomes							
Barrenetxea 1996 Spain	NR	NR	Unclear; comments (no table) made about "evaluable" PATIENTS; whereas it was CYCLES that were evaluated; unclear how number of patients corresponds to number of cycles	Yes	NR	Yes	Yes

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Other outcomes					
Barrenetxea 1996 Spain	No, No, No, No	Unclear	Unclear	Unclear	Poor

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Other outcomes		
Barrenetxea 1996 Spain	NR/NR/NR	Pts with severe concurrent illness, had jaundice or showed laboratory evidence of hepatic dysfunction not attributable to metastatic involvement; required rescue medication

Evidence Table 4. Quality assessments of chemotherapy placebo-controlled trials

Author Year Country Chemo Level	Funding
Other outcomes	
Barrenetxea 1996 Spain	NR

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Design	Subpopulation	Exclusion criteria
Bhatia 2004 Single Center 5 Rotterdam	RCT Observer blind Parallel	NR	Pts excluded if any applied: severe concurrent illness, vomiting due to some other cause, antiemetic therapy administered concurrently or in the 24 preceding chemo, administration of benzodiazepines except when given for night sedation, vomiting in 24h before chemo, pregnant or lactating women, concurrent radiation therapy, impaired renal function (serum creatinine >2.0 mg/dL) jaundice (serum bilirubin >2.0 mg/dL) or an elevated aminotranserase level (SGOT/SGPT> 2X ULN).
Lachaine 1999 Single Center 4 EORTC, QLC-3	Not Randomized Not blinded Parallel	women, breast cancer	NR
Clavel 1995 Multicenter 4 FLIE; FLIC	DB RCT Parallel	women, breast cancer	Pts not eligible if any of the following applied: serious disease other than the cancer being treated, another cause of nausea or vomiting other than the chemo, a clinical hepatic disorder, a persistent chronic alcoholism, emesis or anti-emetic treatment during 24h preceding study entry.

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Intervention	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled
Bhatia 2004 Single Center 5 Rotterdam	There were 6 groups: I, II, IIIa, IIIb IVa, IVb Ond: 8 mg iv (30 min prior to each cisplatin administration); 8 mg ond po tid for 5 days this Ond regimen given to II, IVa, IVb Meto: 20 mg iv (30 min prior to cisplatin); 20 mg po tid for 5 days this meto regiment given to I, IIIa, IIIb	Dex 8 mg iv given to groups IIIb and IVb along with study meds	No run-in; washout-no antiemetics within 24h of study entry	Mean Age: 45.7y 0% male	NR/NR/80
Lachaine 1999 Single Center 4 EORTC, QLC-3	A: Ond 21mg (avg dose for Day 1) B: Metoclopramide 306mg	A: for 91% of these pts, Dex ~19 mg on day 1 and 53% received 1 mg lorazepam;		Mean age: 55.4y 0% male Ethnicity: NR	NR/NR/58
Clavel 1995 Multicenter 4 FLIE; FLIC	A: Ond po (tablet) 16mg (8 mg bid) B: Alizapride iv 150mg	No	No run-in; washout-no antiemetics within 24h of study entry	Mean Age: 51.5y 0%male NR	NR/259/259

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Bhatia 2004 Single Center 5 Rotterdam	NR/NR/80	Malignancy: Head and Neck 54% Cervix 41% Others 5% Tumour surgery: Yes: 14% vs No: 86% Alcohol intake: none 80% <7 units/wk 14% >7 units/wk 6% % smokers: 49% Karnofsky Performance mean score: 96.9 (+/- 4.7) % with history of motion sickness: 0%
Lachaine 1999 Single Center 4 EORTC, QLC-3	5/NR/52	Average Body Surface: 1.68 m2 (+/- 8.5 m2) Average dose cyclophosphamide: 990 mg (+/- 157mg) Language: French Speaking: 41%; English Speaking: 50% Chemo types: Cyclo + dox: 57%; CMF: 24%; FAC: 3%; Cyclo + carboplatin: 3%; Cyclo + epir 2%
Clavel 1995 Multicenter 4 FLIE; FLIC	5/NR/254	Mean body surface area: 1.66 (+/- 0.01) m2 Alcohol consumption >4 units/day: 0% Histological type: Ductal: 87% Lobular: 7% Colloid: 0% Other: 4% Chemotherapy regimens: FEC: 79%, FAC: 20%

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Results
Bhatia 2004 Single Center 5 Rotterdam	*Comparisons are for* ***I*** *(M+C-20) vs* ***II*** *(O+C-20) vs* ***IIIa*** *(M+C-60) vs* ***IVa*** *(O+C-60) vs* ***IIIb*** *(M+D+C-60)* Quality of Life scores Psychological subscale (QoL): (0="not at all", 1="a little", 2="somewhat", 3="very much") Day 0 score(Day 5 score): 1.1(1.0) vs 2.1(1.8) vs 2.3(1.6) vs 2.9(2.9) vs 2.7(1.8), NS Physical subscale (QoL): (0="not at all", 1="a little", 2="somewhat", 3="very much") Day 0 score(Day 5 score): 1.2(1.0) vs 1.2(1.2) vs 1.7(2.2) vs 1.9(2.2) vs 1.9(1.5), NS Functional subscale (QoL): (0="without help", 1="w/o help with difficulty", 2="only with help", 3="unable") Day 0 score(Day 5 score): 1.5(1.5) vs 2.4(2.4) vs 1.9(1.9) vs 1.0(1.0) vs 2.8(2.8), NS Patient satisfaction mean scores: (0="not at all satisfied" to 100="totally satisfied") 75.7 vs 86 vs 45 vs 65 vs 68; IIIb vs IVb, p<0.02
Lachaine 1999 Single Center 4 EORTC, QLC-3	Mean change in ETORCG scores between baseline and Day 3 Physical: -19 vs. -35, p=NS Role Functioning: -2 vs. -13, p=0.002 Emotional: +8 vs. +5, p=NS Cognitive: -5 vs. -13, p=NS Social: -9 vs. -2, p=NS Global health/QoL: -21 vs. -22, p=0.28 Nausea/vomiting: 13 vs. 11, p=NS
Clavel 1995 Multicenter 4 FLIE; FLIC	*all data given as Ond vs Aliz* Pt nausea grade (0= none, 100= nausea as bad as it could be) : 25.8 vs 44.5 (p<0.0001) Pt satisfaction: pts wished to receive same treatment during next chemo regimen: 83% vs 54%, p<0.001 *For FLIC and FLIE, a lower score means a better QoL for the pt* Mean differences in FLIC scores (change from baseline to post-chemo): -0.55 vs 0-.73, p=NS Mean differences in FLIE scores (change from baseline to post-chemo): -1.45 vs -1.93, p=0.04

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Adverse events
Bhatia 2004 Single Center 5 Rotterdam	AEs reported (a total of 39 AEs were reported by 20 pts; incidence =25%) *Results given as all Ond groups (n=40) vs all Met groups (n=40), p = NR* Dystonia/akathisia: 0% vs 0% Constipation: 17.5% vs 2.5% Headache: 15% vs 12.5% Heartburn: 10% vs 5% Weakness: 5% vs 12.5% Epigastric pain: 5% vs 7.5% Nervousness: 2.5% vs 2.5%
Lachaine 1999 Single Center 4 EORTC, QLC-3	In meto group, 4 pts had serious AEs which caused them to stop the antiemetic (no other data on these AEs given) 0 pts had serious AEs requiring treatment cessation in Ond group
Clavel 1995 Multicenter 4 FLIE; FLIC	AEs were minor in both groups, data only given for headache Headache: ond - 1.6% vs aliz - 2.3% , p = NR

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Comments
Bhatia 2004 Single Center 5 Rotterdam	Chemo: All pts received a regimen consisting of cisplatin, bleomycin and 5-flurouracil, making the chemo uniform in all the patients. Pts were randomized according to a table of random numbers to receive either low dose cisplatin regimen (I and II) or high dose cisplatin (III and IV). In high dose cisplatin, pts given 60 mg/m2 cisplatin iv as a single dose on 1st day; in low dose cisplatin, cisplatin was split into 3 iv doses of 20 mg/m2 each on 3 consecutive days. Cisplatin was administered as continuous iv infusion over 1h. All pts also received bleomycin 15 mg iv on 1st and 5th day, and 5-fluorouracil 500 mg iv for 5 days.
Lachaine 1999 Single Center 4 EORTC, QLC-3	The most frequent chemotherapies were the combination of cyclophosphamide and doxorubicin (64%), and the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (27%). Two patients received cyclophosphamide. Doxorubicin and 5-fluorouracil (FAC).; two received cyclophosphamide and carboplatin; and one received cyclophosphamide and epirubicin. The type of chemotherapy was not significantly different between the two groups.
Clavel 1995 Multicenter 4 FLIE; FLIC	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author	Year	Setting	Chemo Level	Type of Test
Bhatia	2004	Single Center	5	Rotterdam
Lachaine	1999	Single Center	4	EORTC, QLC-3
Clavel	1995	Multicenter	4	FLIE; FLIC

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Design	Subpopulation	Exclusion criteria
Soukop 1992 Multicenter 4 Rotterdam	DB RCT Parallel	women, breast cancer	Pts excluded if any of the following applied: severe concurrent illness, gastrintestinal obstruction, central nervous system metastases, anti-emetic therapy administered concurrently or in 24 h before chemo, administration of benzodiazepines except when given for night sedation, vomiting in th 24h before chemo, cisplatin-containing regimens, and pregnancy.
Crucitt 1996 Multicenter 4 FLIE	DB RCT Parallel	women, breast cancer	Pts who had received chemo or ond at any time during the past as well as pts who had received any medication with potential antiemetic activity (phenothiazines, butyrophenones, hydroxyzine, lorazepam, cannabinoids, metoclopramide, corticosteroids, or trimethobenzamide) within 24h before the first dose of the study drug or during 3 days after initiation of chemo were excluded.

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Intervention	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled
Soukop 1992 Multicenter 4 Rotterdam	O: Ond 8mg M: metoclopramide 60mg	Dex 16 mg iv one time only	No run-in; washout-no antiemetics within 24h of study entry	Mean Age: 48.58y 0% male	NR / 187/ 187
Crucitt 1996 Multicenter 4 FLIE	O: Ond po 16mg (8 mg bid) for up to 3 days P: Prochlorperazine po 20mg (10 mg bid) for up to 3 days	No	No run-in; washout-no drugs with antiemetic activity within 24h of study entry	Mean Age: 57.8y 10% male White: 87% Black: 9% Other: 4%	NR / NR/ 133

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Soukop 1992 Multicenter 4 Rotterdam	4/ NR / 183	Height mean: 161.0 (+/- 6.71) cm range: 140-181 cm Mean weight: 65.14 (+/- 12.85) kg range: 40.5-135.0 kg Surface area (SA) mean: 1.66(+/- 0.17) m2 SA range: 1.2 - 2.4 m2
Crucitt 1996 Multicenter 4 FLIE	20/ NR/ 113 (133 for safety)	Mean body weight = 72 kg (range: 43-149 kg) Chemotherapy regimen: CYC/DOX :10% CYC/DOX/FU 24:18% CYC/DOX/FU/VCR : 1%; CYC/DOX/VCR: 4% CYC/DOX/VCR/prednisone: 8% CYC/DOX/VP16: 1%; DOX/FU:1% CYC/methotrexate/FU: 58%; Data Not Available:1% Alcohol consumption: < 5 drinks/y 66%; < 7 drinks/wk 30% 1-4 drinks/d 3%; > 5 drinks/d 0% Prior heavy use: > 5 drinks/d: 1%

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Results
Soukop 1992 Multicenter 4 Rotterdam	Quality of Life: Rotterdam subscales *Differences in scores between baseline and Day 5, O vs M* Psychological: +25% vs +12%, p=0.002 Physical: -24% vs –24%, p=NS Change in functional activity: 0 vs 0
Crucitt 1996 Multicenter 4 FLIE	*Ondansetron vs Prochlorperazine* FLIE scores (100 is highest possible score) decrease in nausea subscore, baseline to final score: -25.3 vs -33.5, p=NS decrease in vomiting subscore, baseline to final score: -7.9 vs -26.3, p=0.01 for O vs P

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Adverse events
Soukop 1992 Multicenter 4 Rotterdam	Met: 15% withdrawn due to extrapyramidal symptoms (EPS). 4% reported EPS (restlessness, agitation) of a less severe nature that did not lead to withdrawal Ond: 0% reported EPS Skin rashes : Ond - 4% vs Met - 0% Allergy: Ond - 1% vs Met - 0% (likely caused by methotrexate, not Ond) 1 pts showed elevated liver enzymes in 2nd course but no further abnormalities in courses 3-6 <u>Most common AEs, O vs M</u> EPS: 0% vs 19% Diarrhea: 0% vs 14% Constipation: 19% vs 5% Headache: 13% vs 9%
Crucitt 1996 Multicenter 4 FLIE	*Data given as O vs P* Headache: 16% vs 3%, p<0.05 No other AE occurred in ≥3% in either group 3 pts were withdrawn from study due to AEs: 2 pts (1 in O and 1 in P) were withdrawn due to injection site reaction (iv infiltration due to chemo; considered not to be related to administration of study drug); 1 P pt had persistent vomiting that required hospitalization (considered unlikely to be related to the study drug)

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Comments
Soukop 1992 Multicenter 4 Rotterdam	
Crucitt 1996 Multicenter 4 FLIE	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author	Year	Setting	Chemo Level	Type of Test
Soukop	1992	Multicenter	4	Rotterdam
Crucitt	1996	Multicenter	4	FLIE

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Design	Subpopulation	Exclusion criteria
Luisi 2006			Pts excluded if had renal or hepatic abnormalities, or chronic vomiting, or were given oral antiemetics on the day chemotherapy was administered.

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Intervention	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled
Luisi 2006	G: Granisetron: 50µg/kg in a single dose over 5 minute period M: 2 mg/kg metoclopramide plus an 8-hour infusion of 5 mg/kg dimenhydrinate			Mean age: 14 yrs Range: 7-19 yrs % male: NR	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Luisi 2006		

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Results
Luisi 2006	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Adverse events
Luisi 2006	

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test	Comments
Luisi 2006	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-control trials

Author Year Setting Chemo Level Type of Test
Luisi 2006

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 6. Quality assessment for chemotherapy active-control trials

Author Year Setting Chemo Level	Subpopulation	Exclusion criteria	Run-in/ Washout	Screened/ Eligible/ Enrolled
Bhatia 2004 Single Center 5	NR	Patients were excluded if any of the following applied: severe concurrent illness, vomiting due to some other cause, antiemetic therapy administered concurrently or in the 24 preceding chemotherapy, administration of benzodiazepines except when given for night sedation, vomiting the 24 h before chemotherapy, pregnant or lactating women, concurrent radiation therapy, impaired renal function (serum creatinine > 2.0 mg/dl), jaundice (serum bilirubin > 2.0 mg/dl) or an elevated aminotransferase level (SGOT/SGPT > twice the upper normal limit).	No/No	NR/NR/NR
Lachaine 1999 Single Center 3-4	women, breast cancer	NR	No/No	NR/NR/58
Clavel 1995 Multicenter 4 FLIE; FLIC	women, breast cancer	Patients not eligible if any of the following applied: serious disease other than the cancer being treated, another cause of nausea or vomiting other than the chemo, a clinical hepatic disorder, a persistent chronic alcoholism, emesis or anti-emetic treatment during 24h preceding study entry.	No/No	NR/NR/259
Soukop 1992 Multicenter 4 Rotterdam	women, breast cancer	Patients were excluded if any of the following applied: severe concurrent illness, gastrointestinal obstruction, central nervous system metastases, anti-emetic therapy administered concurrently or in the 24 h before chemotherapy, administration of benzodia	No/No	NR/NR/187
Crucitt 1996 Multicenter 4	women, breast cancer	Patients who had received chemotherapy or ondansetron at any time during the past as well as patients who had received any medication with potential antiemetic activity (phenothiazines, butyrophenones, hydroxyzine, lorazepam, cannabinoids, metoclopramide, corticosteroids, or trimethobenzamide) within 24 hours before the first dose of the study drug or during the 3 days after initiation of chemotherapy were excluded.	No/No	NR/NR/133

Evidence Table 6. Quality assessment for chemotherapy active-control trials

Author Year Setting Chemo Level	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination
Bhatia 2004 Single Center 5	NR/NR/80	NR	NR	Yes	Yes	No	No	No, No, No, No
Lachaine 1999 Single Center 3-4	6/0/52	NR	NR	No, more patients in O group were English-speakers (70% vs 36%)	Yes	Yes	Yes	Yes, No, No, No
Clavel 1995 Multicenter 4 FLIE; FLIC	5/0/254	NR	NR	Yes	Yes	Yes	Yes	Yes, No, No, No
Soukop 1992 Multicenter 4 Rotterdam	4 didn't return diaries/NR/187	NR	NR	Yes	Yes	Yes	Yes	Yes, No, No, No
Crucitt 1996 Multicenter 4	20/0/113 (57 for QOL)	NR	NR	Yes	Yes	Yes	Yes	Yes, No, No, No

Evidence Table 6. Quality assessment for chemotherapy active-control trials

Author Year Setting Chemo Level	Loss to follow up	Intention-to-treat analysis	Post-randomization exclusions	Quality rating	Controlled group standard of care	Funding
Bhatia 2004 Single Center 5	Unclear	Unclear	Unclear	**Fair**	Yes	NR
Lachaine 1999 Single Center 3-4	None	No	No	**Fair**	Yes	NR
Clavel 1995 Multicenter 4 FLIE; FLIC	None	No	No	**Fair**	Yes	NR
Soukop 1992 Multicenter 4 Rotterdam	None	Yes	Unclear	**Fair**	Yes	NR
Crucitt 1996 Multicenter 4	None	No	No	**Fair**	Yes	Glaxo Research Institute funded this study

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
Direct comparison trials			
Spitzer 2000 Multicenter	RCT, DB Parallel	Pts with a diagnosis of either malignant disease or aplastic anemia and who were hospitalized to receive 11 fractions of 120 cGy over 4 days prior to BMT and initiation of any conditioning chemo. Females of childbearing potential were required to have a negative serum or urine hCG pregnancy test and had to continue using adequate contraception during the study. Males had to be either surgically sterilized or practicing adequate contraception throughout the study.	11 fractions each of 120cGy of radiation over 4 days for a total radiation exposure of 1320 cGy prior to BMT and chemo. On day 0 to 1, the chest wall was blocked during radiation to protect the lungs. The block was removed for fractions given on days 2 and 3 to allow for radiation of the ribs and soft tissue underlying the lungs.

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
Direct comparison trials		
Spitzer 2000 Multicenter	Excluded were pts with a Karnofsky Performance Status score <60, those who had received an investigational new drug within 30 days or 5 half lives of the medication, received conditioning or intrathecal chemo within 24h of first dose of TBI, received emetogenic systemic or intrathecal chemo during the study, or who had an unstable medical disorder or primary or secondary brain neoplasm with increased intracranial pressure. Other reasons for exclusion included known hypersensitivity to any 5HT3 receptor antagonist, unwillingness or inability to comply with the study protocol, or any medication with antiemetic activity taken within 24h of receiving study medication on Day 0. Those who experienced nausea within 1 hr or any emesis (vomiting or retching) within 24h of receiving study mediations on Day 0 were excluded from the protocol defined population but were included in the intent to treat population.	G: Granisetron 2mg O: Ondansetron 24mg

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
Direct comparison trials				
Spitzer 2000 Multicenter	No	No/ NR	41.3 32% female White = 31 (91.2%) African American = 2 (5.9%) Other = 1 (2.9%)	Mean weight = 178.4 pounds Range of weights = 117.5 to 323.0 pounds Mean height = 67.7 inches Range of heights = 60.0-75.0 in

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
Direct comparison trials			
Spitzer 2000 Multicenter	36/ 34/ 34	2/ 0/ 34	*Data given as Gran po 2 vs Ond po 8* Complete emetic control: no emetic episodes and no rescue antiemetic medication use overall: 27.8% vs 26.7% Day 0: 61.1% vs 46.7% Day 1: 50% vs 54.5% Day 2: 87.5% vs 87.5% Day 3: 62.5% vs 66.7% Complete nausea control: no nausea and no rescue medications by day overall: 11.1 % vs 13.3% Day 0: 44.4% vs 26.7% Day 1: 20% vs 36.4% Day 2: 28.6% vs 50% Day 3: 37.5% vs 66.7% Emetic episodes on day 0 and overall (over 4 days) 0 episodes: Day 0: 61.1% vs 46.7% overall : 33.3% vs 26.7% 1-2 Episodes: overall: 22.2% vs 20% Day 0: 5.6% vs 26.7% 3-5 Episodes: overall: 44.4% vs 33.3% Day 0: 33.3% vs 26.7% >5 Episodes (failure): overall: 0% vs 20% Day 0: 0% vs 0% Median time to first emesis: 36 h vs 15.8 h

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Adverse events	Comments
Direct comparison trials		
Spitzer 2000 Multicenter	*Data given as Gran po 2 vs Ond po 8* All adverse events Rash: 0% vs 12.5% Back pain: 0% vs 12.5% Peripheral edema: 5.6% vs 12.5% Insomnia: 5.6% vs 12.5% Asthenia: 11.1% vs 0% Diarrhea: 22.2% vs 6.3% Headache: 27.8% vs18.8% Serious AEs (Ond only) Nonfatal irregular pulse: 6%	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
Placebo-controlled trials			
Bey 1996	RCT, DB multicenter parallel	Cancer pts ≥ 18 y of either gender undergoing radiotherapy to the upper abdominal field, incl. the epigastrium, in single, high-dose exposure; pts had riven malignant disease and had a Karnofsky performance score of ≥50%. Pts did not have to be chemo-naive.	Single fraction radiotherapy of ≥6 Gy over fields of either 80-100 cm2 centered between T10 and L2 inclusive or fields of 100-150 cm2 centered between T8 and L3 inclusive.
Lanciano 2001	RCT, DB multicenter parallel	Cancer pts ≥ 18 y of either gender undergoing radiotherapy; males were surgically sterilized or agreed to practice adequate contraception during the study. Females were of nonchildbearing potential or were of childbearing potential, had negative pregnancy tests, and agreed to practice adequate contraception during the study.	Abdominal radiotherapy to fields encompassing T11-L3 with a field size ≥ 100 cm2; pts had to receive between 10 and 30 fractions of radiotherapy with a radiation dose of ≥ 1.8 Gy/fraction (9.0Gy weekly for ≥ 2 weeks) at the midplane of the treated volume, not to exceed 3.0 Gy/fraction. Seminoma pts could receive a lower dose of <1.5 Gy/fraction and pts undergoing total abdominal irradiation could receive <1.8 Gy/fraction.

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
Placebo-controlled trials		
Bey 1996	If pts had chemo within 2 weeks of the study; also excluded were pts who had radiotherapy <7 days before study entry, had a history of significant neurological, cardiac, or psychiatric illness (except alcoholism), showed abnormal prestudy serum potassium and/or sodium, were receiving antiarrhythmic therapy, or showed evidence of clinical significant liver disease (i.e., serum aspartate aminotransferase / alanine aminotransferase ≥ 2 the upper limit of normal (ULN), serum bilirubin ≥2.0 IU/dL or known liver metastases). Also excluded were pts who were pregnant or female of childbearing potential not using contraception measures, had been administered any drug with antiemetic efficacy within 24h of study initiation, had received previous therapy with Dol, had vomited as a result of any organic etiology or had vomited in the 24h preceding radiotherapy, had experienced SWOG grade 2-4 nausea in the 24h preceding radiotherapy, or had used any investigational drug within 21 days of the study.	D1: Dolasetron (Dol) 0.3 mg/kg iv D2: Dol 0.6 mg/kg iv D3: Dol 1.2 mg/kg iv Pl: placebo 30 min before radiation start
Lanciano 2001	Pts were not eligible if they had participated in any drug trial using an investigational drug within 30 d or 5-half lives (whichever was longer) prior to screening, had an unstable medical disorder, or a Karnofsky performance status score of <60. They could not receive chronic (≥1 month) or concurrent (day 0 and through end of assessment treatment with agents known to have significant effect on emesis, including ondansetron, sedating antihistamines, antipsychotics, cannabinoids, corticosteroids, metoclopramide, narcotic analgesics and benzodiazepines. Pts could not have primary or secondary brain tumors with signs or symptoms of increased intracranial pressure. Pts were excluded if they had known hypersensitivity to 5-HT3 receptor antagonist or were unwilling/unable to comply with study protocol or experienced nausea within 1 h and/or emesis within 24h before administration of study medication on Day 0. Emetogenic chemo could not be administered within 72h of study medication or during study assessment period. Previous abdominal radiotherapy (T11-L3), wedge-field radiation therapy to the spine, and prophylactic radiotherapy to the CNS were also reasons for exclusion. No radiation therapy could be administered 24h pı	G: Gran 2 mg (n=134) po qd Pl: Placebo

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
Placebo-controlled trials				
Bey 1996	No	Washout: 2 wks for chemo, 7 d for radiotherapy, 24 h for any drugs with antiemetic properties No run-in	Median age: 63y 34% female Ethnicity: NR	Median dose of radiotherapy: 6.76 Gy Median duration of radiotherapy: 0.17 h % of pts receiving previous chemo or radiotherapy: 66% % experiencing nausea and/or vomiting after prior treatment: 36%
Lanciano 2001	No (only nonemetogenic chemotherapy was allowed concomitantly)	Washout: 30 d for investigational drug, 72 for emetogenic chemotherapy, 24 h for radiation No run-in	Mean age: 55.3y Range: 19-88y 34.8% female White: 78.4% African American: 10.6% Asian: 1.5% Other: 9.5%	Mean weight: 170 lbs (Range: 76.5-348 lbs) Mean height: 68 in (Range: 57-77.2 in) Mean alcohol units/week: 4.45 units/wk Range: 0-79.4 units/week Primary disease sites: Genitourinary system: 45.5% Lymphatic/hematologic system: 19.7% Gastrointestinal system: 22% Mean total dose of radiation: 24.4 Gy Mean daily dose: 1.85 Gy Mean days of treatment: 19.1 days

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
Placebo-controlled trials			
Bey 1996	NR/50/50	NR/ NR 50	*All data are given as D1; D2; D3; Pl (if not noted; p=NS and p given only for each D group vs. placebo and not for D groups vs one another)* % pts having emesis or use of rescue medication per group: 9.1% (p=0.05); 28.6%; 41.7%, 46.1% Time range for first emesis or use of rescue medication: (3.4); (2.0 - 22.5); (3.0 - 15.8); (0.5 - 8.0) % with complete response: 91% (p=0.05 vs Pl); 71%, 58%, 54% Complete + Major response: 100% (p=0.011); 93% (p=0.019); 83%, 54% Pt max nausea VAS score over 24h: 1.3 (p=0.014); 9.9; 13.8; 22.4 % with no nausea (<= 5 mm nausea VAS): 54%; 62;%; 70%; 54% Investigator assessment of no nausea (% of pts): 91%; 86%; 67%; 54% Mean pt satisfaction score (0-100, with 100="completely satisfied"): 98; 100; 78; 93
Lanciano 2001	NR/ 264/ 264	121/ NR/ 260	*All data are G vs Pl* Median time to first emesis: 35 days vs 9 days, p<0.001 Median time to first nausea: 11 days vs 1 day, p<0.001 Emesis-free pts (overall endpoint analysis): 57.7% (77 of 134) vs 42.1% (53 of 126), p=0.0047 % of pts nausea free on all days of study: 31.3% vs 16.7%, p<0.001 *Data below is estimated from graphs:* % pts emesis-free at 24h: 91% vs 61%, p<0.0001 % pts emesis-free at 10 fractions: 85% vs 68%, p=0.0012 % pts emesis-free at 20 fractions: 75% vs 64%, NS (p=0.0636) % of pts with 0 episodes of emesis at 24 h; 10 fractions; and 20 fractions: 98% vs 71%; 86% vs 71%; 76% vs 63%, p = NR % of pts experiencing severe nausea at 24 h: 1.5% vs 15.15, p=NR

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Adverse events	Comments
Placebo-controlled trials		
Bey 1996	1 serious AE in D2 group (a pt who presented with a suspected colon cancer and was hospitalized for mild melena 48h after study medication administration) was not considered to be related to study medication; 9 events across the four groups (8 events in 6 Dol pts and 1 event in 1 Pl pt) were considered treatment-related. Most commonly reported AEs: *(data given as D1; D2; D3; Pl)* Overall rate: 27.3%; 42.9%; 58.3%; 7.7% Headache: 0%; 7.1%; 0%, 0% Abdominal pain: 0%; 14%; 8.3%; 0% Fever: 18%; 0%; 8.3%; 7.7% Tachycardia: 0%; 0%; 17%; 7.7% Back pain: 0%; 7.1%; 8.3%; 0%	
Lanciano 2001	Pts reporting ≥ 1 AE: 75.8% (G: 82.1% vs Pl: 69.2%) AEs probably unrelated to treatment drug: G: 50.4% vs Pl: 50.4% Commonly-reported AEs, G vs. Pl: Diarrhea: 27.6% vs 33.8% Asthenia: 25.4% vs 19.2% Constipation: 19.4% vs NR Headache: NR vs 11.5% 2 G pts had 3 AEs (constipation, abnormal thinking, and rash) deemed treatment related 3 Pl pts had 3 AEs (abdominal pain, moniliasis, and nausea) deemed treatment related Deaths: G: 4 pts vs Pl 7 pts deemed not related to study medication	PTs withdrawal counted as a pt needing rescue medication.

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
LeBourgeois 1999	RCT, DB multicenter parallel	Male and female pts ≥ 18 y with a diagnosis of cancer who were to receive a course of ≥5 daily fractions of radiotherapy to sites between the thorax and pelvis.	≥ 5 daily fractions of radiotherapy to sites between the thorax and pelvis median total dose: 8 Gy *% and numbers below are out of total of 416 ITT pts* reason for fractionated RT: radical: 76%; pallative: 24% RT site: thorax - 18% abdomen - 42% pelvis - 23% spine - 4% other - 13%
Tiley and Powles 1992 UK	Consecutive pts ≥18 y undergoing conditioning with melphalan (110 mg/m2) and TBI prior to autologous or allogeneic BMT		Radiation delivered as a single fraction from opposed 60 Co sources as at rate of 4cGy/min to a total lung dose of 10.5 Gy

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
LeBourgeois 1999	Pts with severe concurrent illness (other than neoplasia) or with other potential causes of emesis and nausea (.e.g.. gastrointestinal obstruction, raised intracranial pressure, hypercalcemia, brain metastases); pts who had experienced emesis and/or moderate/severe nausea in the preceding 24h, had received chemo in the preceding 5 days, had in the last 30 days received or were about to receive an investigational drug, or who were receiving conditioning for bone marrow transplantation were excluded. Other exclusion criteria were: concurrent or past medical conditions that might interfere with the study, impaired hepatic function, pregnancy, or lactation.	O1: Ond 8 mg ODT O2: Ond 16 mg ODT Pl: placebo Pts were instructed to take study drug only if emesis or moderate or severe nausea occurred
Tiley and Powles 1992 UK	Pts undergoing autologous transplantation for acute myeloid leukemia were excluded because they are conditioned with melphalan at 140 mg/m2	O: Ond 8 mg iv Pl: placebo iv single dose given at commencement of TBI

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
LeBourgeois 1999	No	Washout: 5 d for chemo, 30 d for investigational drugs	Mean age: 48y 46% Female Caucasian: 95% African American: 3% Asian: <1% Other: 2%	Mean weight: 70.6 kg Mean height: 170 cm Previous motion sickness: 15% Previous sickness during pregnancy: 39.6% (76 of 192 women) Current alcohol use: none: 58% <7 units/wk: 26% 7-28 units/week: 13% >28% units/wk: 2%
Tiley and Powles 1992 UK	Yes: metoclopramide 20 mg iv, dexamethasone 4 mg iv, and lorazepam 1-2 mg po given to all pts prior to melphalan All pts given phenobarbitone 60 mg/m2 iv and dexamethasone 8 mg iv at 10 pm on day prior to TBI and at 6 am on day of TBI	No, No	Median age: O - 23y; PI - 32.5y Age range: 19-53 y 30% female Ethnicity: NR	Diagnosis: AML CR1: 40% ALL CR1: 40% CR2: 15% REL1: 5% Mean irradiation time: 316 min Total time to deliver TBI: 369 min % pts anxious at randomization: 75% % pts vomiting at randomization: 5%

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
LeBourgeois 1999	NR/1492/1489	unclear /unclear / 461	*Data given as O1 vs O2 vs Pl* treatment success (ts): 0-1 emetic episodes in 0-2h after study medication; 0 emetic episodes after 2 h until the end of assessment pd; no worse than mild nausea during assessment period; no rescue; no withdrawal Complete control (no emesis, nausea, rescue, or premature withdrawal): 53% vs 58% vs 405 (p = NS for O1 vs O2) % of pts with treatment success (ts) in 12h after administration of study meds: 53% vs 56% vs 41% (p=NS for O1 vs O2) % of pts with ts in 2 h period immediately after administration of study meds: 69% vs 70% vs 52% (p = NS for O1 vs O2)
Tiley and Powles 1992 UK	NR/20/20		*Data given as O vs Pl* Vomiting during TBI: 10 % vs 50%, p=0.07 Nausea or retching during TBI: 10% vs 50%, p = 0.07 Any emetic event during TBI: 10% vs 60%, p= 0.029 Any emetic event 6 h after TBI: 10% vs 50%, p= 0.07 Any emetic event 12 h after TBI: 20% vs 10%, p = NS Time in TBI lost for nausea and vomiting: 0.5 min vs 12.5 min, p=0.01

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Adverse events	Comments
LeBourgeois 1999	Serious AE in O1 group: 2 pts experienced nausea and vomiting and 1 pt a variety of events related to breathing disorders and bone/skeletal pain *data given as O1 [n=150] vs O2 [n=139] vs Pl [n=127]* Most common AEs during treatment: Any AE: 8% vs 4% vs 3% (total = 5%) Nausea and vomiting: 3% vs 0.8% vs 0% (total: 2%) Headache: 2% vs 0% vs 3% (total: 2%) Diarrhea: 0% vs 2% vs 0% (total: 0.5%) Most common AEs during treatment (*O1 vs O2 vs Pl*): Any AE: 5% vs 6% vs 3% (total: 4%) Diarrhea: 1% vs 0.8% vs 0.7% (total: 1%) Gastrointestinal discomfort and pain: 1% vs 0% vs 0% (total: 0.5%)	1492 was # of pts entering study; but study only evaluated those who had nausea or emesis after radiation treatment, so the number of pts analyzed was 416.
Tiley and Powles 1992 UK	No AEs noted in either pt group nor were any biochemical abnormalities seen	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
Active-controlled trials			
Sykes 1997 UK	RCT Single center parallel	>18 pts who were to receive pallative single fraction radiotherapy	60 pts received a single fraction to the lower half- body of 8 Gy; 6 pts received a single fraction of 12.5 Gy to the upper lumbar spine
Priestman 1990 **Priestman** 1989	RCT, DB parallel	Males or females 18-80y who were to be treated with single anterior or single posterior fields to the upper abdomen giving incident doses of 8-10 Gy or those treated with opposed fields to this region giving 8-10 Gy as a mid-point dose. Field sizes of 80-100 cm2 had to be centered between T10-L2 inclusive; fields of >100cm1 were centered between T8-L3 inclusive.	8-10 Gy radiation

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
Active-controlled trials		
Sykes 1997 UK	Pts not allowed if any of the following applied: concurrent chemo; concurrent antiemetic therapy, including prednisolone and dexamethasone with the exception of the study drugs; severe concurrent illness; gastrointestinal obstruction; CNS metastases; vomiting in the 24h prior to study entry; administration of concurrent benzodiazepines except for night sedation	O: Ond 8 mg po 1-2 h before radiotherapy + 8 mg 12 h later. Days 1-3, Ond given 8 mg po bd (n=33) C: Chloropromazine (chlor) 25 mg po +dexamethasone (dex) 6 mg po 1 h before radiotherapy + Chlor 25 mg po 12 h later. Days 1-3, Chlor 24 mg tds (n=33)
Priestman 1990 **Priestman** 1989	Pts excluded if clinically jaundiced, had vomited in the previous 24h, had received antiemetics within the previous 24h or were suffering severe concurrent illness unrelated to their neoplasia.	Pts fasted for 2 hours and then given drugs 1-2 h prior to radiation O: Ond 8 mg po (Days 1-3 or Days 1-5, 8 mg po tid) (n=46) M: metoclopramide 10 mg po (Days 1-3 or Days 1-5, 10 mg po tid) (n=51)

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
Active-controlled trials				
Sykes 1997 UK	No	No, No	NR NR NR	NR
Priestman 1990 **Priestman** 1989	No - 13 of 15 withdrawals (exclusions) were due to pts taking concurrent medication with antiemetic properties	Washout: 24 h for antiemetics No run-in	mean age: 64.0y Range: 18-83y 50.5% Female Ethnicity: NR	Primary tumor sites: Lung: 11.3% Breast: 25.8% Gastrointestinal: 28.9% Genitourinary: 17.5% Other: 16.5%

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
Active-controlled trials			
Sykes 1997 UK	NR/66/66	NR	Complete or major control of emesis (0-2 emetic episodes) on day 1, O vs C : 93.9% vs 34.4%, p<0.001 Complete or major control of emesis (0-2 episodes) delayed, O vs C: Day 2: 96.2% vs 42.9%, p<0.001 Day 3: 96.2% vs 39.3%, p<0.001 Day 4: 96% vs 37%, p<0.001 Pts rating of antiemetic effectiveness, O vs C: 90% vs <60% Pts and investigators willing to use antiemetic again, O vs C: 98% vs 75% FLIC: no significant differences for decline in scores post-treatment for O vs C FLIE: declines were greater for Ond-treated pts, p=0.02
Priestman 1990 **Priestman** 1989	NR/97/97 (at time of interim analysis; 160 planned)	15/ NR/ 82	*All data given is for O vs M* % pts with complete, major, minor responses, failure/rescued: Day 1: 97%, 3%, 0%, 0% vs. 45%, 25%, 11%, 18%, p<0.001 Days 1-3 inclusive: 68%, 24%, 0%, 8% vs 39%, 27%, 11%, 23%, p=NR Day 4 Complete or major control: 97% vs 88%, p = NS Day 5 Complete or major control: 96.9% vs 95.2%, p = NS Grading of nausea: None, mild, moderate, severe: Day 1: 73%, 22%, 5%, 0% vs. 41%, 20%, 18%, 20%, p =<0.001

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: Controlled-clinical trials

Author, Year	Adverse events	Comments
Active-controlled trials		
Sykes 1997 UK	No deaths occurred during study period and no significant difference in levels of AEs between O and C. Less drowsiness for O than C, but p= NS	
Priestman 1990 **Priestman** 1989	*All data given as O vs M* deaths: 6 pts vs 4 pts, p = NR (none thought to be related to antiemetic therapy) severe headache and vertigo: 1 pt vs 0 pt, p = NR Fevers and night sweats: 0 pt vs 1 pt, p = NR No changes in clinical chemistry, renal function of hematological parameters that were considered treatment related for either drug.	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Comparative trials							
Spitzer 2000	Yes	NR	Yes	Yes			
Placebo-controlled trials							
Bey 1996	NR	NR	Yes	Yes	Not reported	Yes	Yes
Franzen 1996	Yes	NR	Yes for radiotherapy regimens; unknown for other demographic/ prognostic factors because they were NR	Yes	Not reported	Yes	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity				
Author, Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**	**Quality Rating**
Comparative trials					
Spitzer 2000	Yes, NR, NR, NR				
Placebo-controlled trials					
Bey 1996	Yes, NR, NR, NR	None	Yes	No	Fair
Franzen 1996	Yes, NR, NR, NR	None	No; 98.2%	No	Fair

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

Author, Year	Funding
Comparative trials	
Spitzer 2000	
Placebo-controlled trials	
Bey 1996	Hoechst Marion Roussel
Franzen 1996	Glaxo Wellcome

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Placebo-controlled trials, cont.							
Lanciano 2001	NR	NR	No; various differences in radiation treatment	Yes	Not reported	Yes	Yes
LeBourgeois 1999	Unclear; "block balanced"	NR	Unclear; only provided baseline characteristics for 415 (27.8%) patients that received study medication	Yes	Not reported	Yes	Yes
Spitzer 1994	NR	Yes	Yes	Yes	Not reported	Yes	Yes
Tiley and Powles 1992	NR	Yes	No, placebo group older (32.5 vs 23)	Yes	Not reported	Yes	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity				
Author, Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**	**Quality Rating**
Placebo-controlled trials, cont.					
Lanciano 2001	Yes, NR, NR, NR	None	No; 97.6%	No	Fair
LeBourgeois 1999	Yes, NR, NR, NR	None	No; 99%	No	Fair
Spitzer 1994	Yes, NR, NR, NR	None	Yes	No	Fair
Tiley and Powles 1992	NR, NR, NR, NR	NR	Yes	NR	Fair

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

Author, Year	Funding
Placebo-controlled trials, cont.	
Lanciano 2001	NR, 4th author from SmithKline Beecham
LeBourgeois 1999	Glaxo Wellcome
Spitzer 1994	Glaxo, Inc.
Tiley and Powles 1992	NR

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Active-controlled trials							
Prentice 1995	NR	NR	Yes	Yes	Not reported	Yes	Yes
Sykes 1997	NR	NR	NR; baseline characteristics were not presented or discussed	Yes	Not reported	Yes	Yes
Priestman 1990 Priestman 1989	NR	NR	Yes	Yes	Not reported	Yes	Yes
Priestman 1993	NR	NR	Yes	Yes	Not reported	Yes	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity				
Author, Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**	**Quality Rating**
Active-controlled trials					
Prentice 1995	NR, NR, NR, NR	NR	Yes	No	Fair
Sykes 1997	NR, NR, NR, NR	NR	Unknown, no information about number of patients analyzed	Unknown	Poor
Priestman 1990 Priestman 1989	Yes, NR, NR, NR	None	No, 84.5%	No	Fair
Priestman 1993	Yes, NR, NR, NR	None	Yes	No	Fair

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

Author, Year	Funding
Active-controlled trials	
Prentice 1995	SmithKline Beecham
Sykes 1997	Glaxo Laboratories, Inc.
Priestman 1990 Priestman 1989	NR, 5th author from Glaxo Group Research Limited
Priestman 1993	NR, 3rd author from Glaxo Group Research Limited

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Adults					
Dolasetron vs. Ondansetron					
Birmingham 2006	DB RCT Parallel	Under the care of a mental health-care provider, physical status ASA class III or higher, pregnant, taking medications with antiemetic properties within 48 hours before surgery, presenting for inpatient surgery, requiring admission to the hospital for surgical reasons, not receiving general anesthesia	Dolasetron 12 mg iv Ondansetron 4mg iv	Rescue medication was allowed (determined by anesthesia provider)	No/No
Browning 2004 Single Center	DB RCT Parallel	Pts excluded if they were <18, pregnant, received and ASA physical classification of ≥ III, experienced emesis 24 h prior to procedure, or received antiemetic medication or investigational research drug 24 h prior to surgery.	Dolasetron iv 12.5mg Ondansetron iv 4mg	No	NR/NR
Erhan 2008 Single Center	DB, RCT Parallel	ASA class III-IV; aged >70 years; BMI >30; Prenancy; smoking; signs of gastrointestinal, endocrine, renal, hepatic or immunological disease; use of opioids or tranquillizers less than 1 week before the operation; treatment with steroids; history of alocohol or drug abuse; history of motion sickness; preoperative diagnosis of gallbladder empyema and previous endoscopic sphincterotomy for common bile duct stones; and conversion to open cholecystectomy.	Group 1: 0.9% NaCl Group 2: ondansetron 4mg iv Group 3: granisetron 3mg iv Group 4: dexamethasone 8mg iv	Diclofenac sodium 75mg iv diven for postoperative pain Metoclopramide 10mg iv was used as rescue medication	NR/no opioids or tranquillizers within 1 week of surgery

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Adults				
Dolasetron vs. Ondansetron				
Birmingham 2006	35.1 (Dolasetron) 32.7 (Ondansetron) 18% male NR	NR/NR/100	NR/NR/100	Surgical Service Urology: 2% Gynecology: 22% Orthopedics: 7% Plastic surgery: 22% Ophthalmology: 1% General surgery: 15% Ear/nose/throat: 29% Oral surgery: 29%
Browning 2004 Single Center	NR 0%male NR	NR/NR/212	NR/NR/212	NR
Erhan 2008 Single Center	51.5 years 23.7% male Ethnicity NR	NR/NR/80	NR/NR/80	Mean weight (kg): 62.5 Mean height (cm): 162 Time of surgery (min): 73.15 Time of anesthesia (min): 88.45

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Adults		
Dolasetron vs. Ondansetron		
Birmingham 2006	Dolasetron vs Ondansetron Satisfaction with medication (VAS Score, 0-100 mm): 70.9 vs 67.9 (NS) Overall satisfaction (VAS Score, 0-100 mm): 87.9 vs 85.3 (NS) Complete response: 40% vs 50% (NS) Emetic episodes: 44% vs 34% (NS) Postdischarge emesis: 30% vs 26% (NS) Delay in PACU discharge attributable to PONV (minutes): 41.11 vs 21.13 (NS)	NR
Browning 2004 Single Center	Emetic episodes - no data given, only that difference was NS	headache dizziness dysrhythmia allergic reaction
Erhan 2008 Single Center	Control vs Ondansetron vs Granisetron vs Dexamethasone Patients with nausea 0-6h after surgery: 40% vs 25% vs 10% vs 5% (p<0.05 for Granisetron vs Control and Dexamethasone vs Control) Patients with nausea 6-12h after surgery: 10% vs 0% vs 10% vs 5% Patients with nausea 12-24h after surgery: 5% vs 0% vs 0% vs 0% Patients with vomiting 0-6h after surgery: 30% vs 5% vs 10% vs 10% (p<0.05 for Ondansetron vs Control) Patients with vomiting 6-12h after surgery: 10% vs 5% vs 0% vs 10% Patients with vomiting 12-24h after surgery: 5% vs 0% vs 0% vs 0% Patients who used rescue meds 0-6h after surgery: 55% vs 15% vs 10% vs 10% (p<0.05 for each vs Control) Patients who used rescue meds 6-12h after surgery: 15% vs 5% vs 0% vs 10% Patients who used rescue meds 12-14h after surgery: 10% vs 0% vs 0% vs 0%	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Adults	
Dolasetron vs. Ondansetron	
Birmingham 2006	
Browning 2004 Single Center	PACU nurses allowed to administer rescue antiemetics according to postoperative anesthesia orders, if they determined it was needed, if the pt experienced persistent nausea for ≥15 minutes, had ≥1 emetic episode, or if the pts requested medication. Study results were in narrative form only, with the exception of how many patients were in the study, and how many per group received spinal narcotics. No other numbers were given, though the results were all "not significant statistically". Analyses of emetic episodes both in the PACU or in 24h postsurgery were found not to differ significantly between groups. The same results were found for mean numeric nausea intensity scores at any time, pt satisfaction scores, and side effects. S Norris 9/13/05: There was no run in or wash out. Pts who got antiemetic in last 24 h were excluded . No data tables or information on attrition. No data provided on number screened or eligible.
Erhan 2008 Single Center	

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Kushwaha 2007 Single Center	Comparative Study	Gastrointestinal disorders, pregnancy or menstruation, history of motion sickness or previous history of PONV, aged <10 years or >60 years.	A) Placebo B) Granisetron 40mcg/kg C) Granisetron 40mcg/kg + dexamethasone 8mg D) Ondansetron 0.1mg/kg E) Ondansetron 0.1mg/kg + dexamethasone 8mg	Premedicated with oral alprazolam 0.25mg and ranitide 150mg	NR/NR
Meyer 2005 Single Center	RCT, DB, Parallel	Pts were excluded for any of the following reasons: 1) the patient declined participation, 2) the physician responsible for patient care considered the study not to be in the best interest of the patient for any reason, 3) the patient was allergic to either primary study drug, or 4) the patient was unable to understand the study.	Ondansetron iv 4mg Dolasetron iv 12.5mg	Rescue medication was permitted	NR/NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Kushwaha 2007 Single Center	26.28 years 49.6% male Ethnicity NR	NR/NR/125	NR/NR/125	Mean weight (kg): 49 Mean duration of anesthesia (min): 128.17
Meyer 2005 Single Center	NR 76% female NR	559/351/92	NR/NR/92	History of PONV: 20.6% Prior surgery: 87% Prophylactic antiemetic: 25%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Kushwaha 2007 Single Center	Patients without nausea and vomiting A: 24% vs B: 84% vs C: 92% vs D: 72% vs E: 88% Male patients without nausea and vomiting A: 40% vs B: 22.5% vs C: 0% vs D: 22% vs E: 9% Female patients without nausea and vomiting A: 96% vs B: 12.5% vs C: 33% vs D: 33% vs E: 14.2% (P<0.05 for B vs A)	NR
Meyer 2005 Single Center	Use of Rescue Medication Ond: 70% vs Dol: 40% (p=0.004) Postoperative vomiting before discharge Ond: 23% vs Dol: 16% (p=0.34) Time in day surgery recovery (min) Ond: 158 vs Dol: 131 (p=0.17)	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Kushwaha 2007 Single Center	
Meyer 2005 Single Center	

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Paech 2003 Single Center	DB RCT Parallel	Pts experiencing preoperative nausea, receiving medication with antiemetic activity or with contraindication to nonsteroidal anti-inflammatory medication or epidural anesthesia were excluded from this study. Women in whom an open procedures was not performed or who underwent unplanned bowel surgery were excluded.	Dolasetron iv 12.5mg Ondansetron iv 4mg Tropisetron iv 2mg	All premedicated with 20 mg temazepam 1-2 h before transfer to the theatre.	No/NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Paech 2003 Single Center	48.8 years 0%male NR	NR/NR/120	2 /0/ 118	Mean weight = 76.2 kg History of PONV 33% History of motion sickness 18% Pts in 0-8 days of menstrual period 21% Gynecological procedures 55% Gynecological oncological procedures 43% Median surgical duration: 92.2 min Median vol. of post-op epidural soln:142.3ml Range of surgical durations: 65-152 minutes

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Paech 2003 Single Center	*Dol iv 12.5 vs Ond iv 4 vs Trop iv 2* Complete response: no vomiting and no rescue drugs required during the study period 20% vs 16.7% vs 23.8%, p: NS Incidence of vomiting: overall and by time period recovery-2h : 17.5% vs 25.0% vs 22.0%, p: NS 2-6h: 17.5% vs 11.1% vs 11.9%, p: NS 6-12h: 15.4% vs 13.9% vs 14.3%, p: NS 12-18h: 27.5% vs 22.2% vs 4.3%, p: NS 18-24h: 35.0% vs 47.2% vs 28.6%, p: NS overall: 60% vs 75% vs 69%, p: NS Median no. of antiemetic treatment doses and % receiving rescue drugs No. of treatment doses: 1 dose vs 1 dose vs 1 dose, p: NS % receiving 1 rescue drug : 30% vs 42% vs 31%, p: NS % receiving 2 rescue drugs : 25% vs 33% vs 24%, p: NS Nausea scores: no nausea (score=0), overall, and worst score by time period: score No nausea: 25% vs 33.3% vs 129.3%; p=NS 2h; 2-6h; 6-12h: 0 vs 0 vs 0, p: NS 12-18h: 0 vs 0 vs 8.5, Trop iv 2 vs. Dol and Ond, p=0.02 18-24h: 18 vs 24.5 vs 10, p: NS Overall nausea score (0-24h): scale of 0-100: 14.5 vs 20 vs 20, p: NS Postoperative characteristics (median time in hours) Time to drink: 12 vs 7.25 vs 5.5; p=NS Time to eat: 64.5 vs 66 vs 48; p=NS Time to ambulation: 20 vs 20 vs 19; p=NS Pt satisfaction score with recovery (scale 0-100): 96.5 vs 100 vs 95; p=NS Patient satisfaction score with PONV control (0= not satisfied to 100=completely satisfied): 99.5 vs 97.5 vs 100; p=NS	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Paech 2003 Single Center	A low thoracic (T9-T12) epidural was inserted prior to induction of anesthesia and 6 to 10 ml of epidural ropivacaine 7.5 mg/ml with fentanyl 50 micrograms was administered. Muscle relaxation was reversed with iv neostigmine (2.5 mg) and atropin (1.2 mg). Postoperative pain relief was provided by epidural infusion of ropivacaine 2 mg/ml with fentanyl 4 microgram/ml at 6 to 12 ml/h and rectal diclofenac 100 mg was administered twice daily.

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Tang 2003 Single Center	DB RCT Parallel	Exclusion criteria included pregnancy; active menstruation; body weight more that 50% above the ideal body weight; vomiting or retching within 24h before the operation; administration of antiemetic or psychoactive medication within 24h before surgery; a previous history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine, or neurologic disease; alcohol or drug abuse; and impaired renal or hepatic function.	Dolasetron iv 12.5mg Ondansetron iv 4mg Saline iv (placebo) mg	Droperidol 0.625 mg iv, and dexamethasone, 4 mg iv, were administered to all patients after induction of anesthesia.	No/No

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Tang 2003 Single Center	54.7 years 37%male NR	NR/NR/135	0/0/135	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Tang 2003 Single Center	*Data given as Dol iv 12.5 vs Ond iv 4 vs Placebo* Complete response (no emetic episodes and no rescue medication) to PONV prior to discharge: 98% vs 98% vs 98%, p: NS after discharge: 98% vs 98% vs 98%, p: NS Post-operative nausea score (SD) at 30 min: 5(10) vs 3(9) vs 5(12), p: NS at discharge: 3(4) vs 2(3) vs 3(3), p: NS Nausea, vomiting, and rescue rates Need for rescue medication after discharge: 0% vs 0% vs 0%; p=NS Nausea prior to discharge: 9% vs 4% vs 11%; p=NS Nausea after discharge: 6.7% vs 9% vs 11%; p=NS Vomiting prior to discharge: 0% vs 0% vs 0%; p=NS Vomiting after discharge: 2% vs 2% vs 0%; p=NS Need for rescue medication prior to discharge: 2% vs 2% vs4%; p=NS Overall PONV incidence:11% vs 13% vs 18%; p=NS Patients very satisfied: 96% vs 98% vs 93%; p=NS Patients satisfied: 2pts vs 1pts vs 3pts; p=NS Patients dissatisfied: 0 vs 0 vs 0; p=NS Recovery times after the end of anesthesia Time until pt tolerates oral fluids: 21min vs 22min vs 23min Time to actual discharge: 51min vs 46min vs 48min Time to eye opening: 4min vs 4min vs 4min, p: NS Time to response to commands: 4min vs 4min vs 4min, p: NS Time to orientation: 5min vs 5min vs 5min, p: NS Time to sitting up: 14min vs 12min vs 14min, p: NS Time to pt ambulates: 16min vs 16min vs 17min Time until pt has "fitness" for discharge: 23min vs 22min vs 24min Time of recovery room stay: 37min vs 32min vs 33min Time to standing up: 16min vs 14min vs 15min; p=NS	Only information given on AEs: "Th

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Tang 2003 Single Center	Ketorolack, 30mg iv, administered during surgery to minimize postoperative pain. Study medications were prepared by the local pharmacy in identical-appearing 5-ml syringes. The maintenance anesthetics were discontinued at the start of skin closure. On awakening from anesthesia, the patients' abilities to meet specific fast-track discharge criteria were assessed at 2-min intervals. After applying the surgical dressing, the patients were asked to sit up on the operating room table. After standing up, they were allowed to walk to the recovery area with assistance. Rescue medications for PONV (e.g., 10 mg metoclopramide iv) and pain management (i.e., 500 mg acetaminophen with 5 mg hydrocodone) were administered upon pt. request. Snorris 9/13/05: "double blind" but unclear who blinded. Drugs prepared "identical". Telephone interviewer (some outcomes) blinded. No antiemetic during last 24 hours, but no information on whether ever had an antiemetic.

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Zarate 2000 Single Center	DB RCT Parallel	Patients were excluded if they had received an antiemetic medication within 24h before their operation, were pregnant, had clinically significant cardiovascular , neurologic, renal , hepatic, gastrointestinal, or endocrinological diseases, had a history of drug abuse, or were >100% above their ideal body weight	Dolasetron iv 12.5mg Dolasetron iv 25mg Ondansetron iv 4mg Ondansetron iv 8mg	All received midazolam 0.02 mg/kg IV for premedication.	No/No

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Zarate 2000 Single Center	45 years 56%male NR	NR/NR/200	0/0/200	Mean weight = 80.04 kg Previous motion sickness 18% Previous PONV 31% Palate/tonsil surgery 12% Endolymphatic sac procedures 10% Nastoidectomy/tympanoplasty 32% Nasal septal surgery 24% Endosinus surgery 21% Mean duration of surgery = 73.2 min Mean duration of anesth. admin. = 94.2 min

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Zarate 2000 Single Center	*data given as Dol iv 12.5 vs Dol iv 25 vs Ond iv 4 vs Ond iv 8* Nausea and vomiting rates experienced Nausea while in-hospital: 26% vs 24% vs 23% vs 30% Nausea post-discharge: 18% vs 12% vs 13% vs 14% Nausea 24h symptoms overall: 38% vs 24% vs 27% vs 28% Vomiting while in-hospital: 8% vs 4% vs 4% vs 0% Vomiting post-discharge: 6% vs 4% vs 2% vs 2% Vomiting at 24h overall: 12% vs 8% vs 6% vs 2% Lack of complete response In-hospital: 26% vs 20% vs 21% vs 30%; p=NS Post-discharge: 20% vs 12% vs 10% vs 14%; p=NS 24h period overall: 26% vs 27% vs 25% vs 30%; p=NS Rescue antiemetics needed promethazine only: 26% vs 23% vs 21% vs 28% promethazine + droperidol: 2% vs 2% vs 2% vs 2% promethazine + droperidol + ondansetron: 2% vs 2% vs 0% vs 0% Pts experiencing frequent (≥ 2) PONV episodes: 6% vs 4% vs 2% vs 2% Maximum nausea VAS in PACU (0=none to 100=maximum) Score: 14mm vs 9mm vs 8mm vs 10mm; p=NS Complete response: no emesis, no nausea, no rescue medication for 24h : 74% vs 73% vs 76% vs 70%; p=NS	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Zarate 2000 Single Center	Anesthesia induced with propofol 1.5 mg/kg IV and reminfentanil 1 microgram/kg IV. Snorris 9,13,05: "double blind", and assessor blinded. But unclear whether patient or provider blinded. Crossover, adherence, contamination NR explicitly. One group was 51, olne 49, could have been due to cross/over?

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Korttilla 1997 Multicenter	DB RCT Parallel	Pts scheduled for post-operative gastric suctioning or pts who had ingested any drug with antiemetic efficacy within 24h before surgery. Other exclusion criteria included clinically significant cardiac or liver disease, abnormal prestudy serum potassium levels, obesity (.40% above ideal body weight), nausea and vomiting within 24h prior to surgery, previous treatment with dolasetron mesilate, use of any investigational drug within 30 days of dolasetron administration, or known alcohol abuse.	Dolasetron iv 25mg Dolasetron iv 50mg Ondansetron iv 4mg	Pts may have received a benziodiazepine before general anesthesia.	NR/NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Korttilla 1997 Multicenter	42.0 years 5%male Caucasian: 365/389 = 93.8% African American: 9/389 = 2.3% Asian: 9/389 = 2.3% Other: 6/389 = 1.5%	NR/NR/518	1/3/514	Previous surgery: yes: 83% Previous surgery: no: 17% Mean weight, kg: 64.6 kg Mean height, cm: 164.0 cm ASA physical status I: 80% ASA physical status II: 19% ASA physical status III: 1% History of PONV: yes: 29% History of PONV: no: 71% History of motion sickness: yes: 15% History of motion sickness: no: 85% Laproscopic surgery: 50% Non-laproscopic surgery: 50% Gynecological surgery: 77% Non-gynecological surgery: 23%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Korttilla 1997 Multicenter	*Dol iv 25 vs Dol iv 50 vs Ond iv 4 (p=NS if not specified)* Complete response: 0 emetic episodes and no rescue medication during 24h study period CR, for all pts: 51% vs 71% vs 64% fentanyl equivalent analgesic requirement: >250 mcg : 48% vs 63% vs 57% ≤250 mcg : 55% vs 76% vs 69% Non-gynecological surgery: 55% vs 66% vs 75% Surgical technique: laproscopy: 42% vs 63% vs 60% Anesthesia duration ≤ 1.66h: 60% vs 78% vs 73% History of motion sickness (yes vs. no) Yes(No): 56%(50%) vs 79%(69%) vs 75%(61%) Gynecological surgery: 50% vs 72% vs 61% History of PONV- yes: 33% vs 65% vs 54% ASA physical status (ASA=I vs. ASA=II & III) ASA=I(ASA=II or III): 52%(48%) vs 74%(57%) vs 61%(78%) Age (≤ 43 years vs.> 43 years) ≤ 43 years(> 43 years): 54 %(47%) vs 81%(58%) vs 69%(59%) Males: 75% vs 86% vs 50% Female: 50% vs 70% vs 64% Anesthesia duration >1.66h : 44% vs 63% vs 55% Surgical technique: non-laproscopy: 62% vs 77% vs 67% Total response: complete response plus no nausea (i.e., VAS ≤5 at t=2,4, & 6h post-recovery) All pts: 43% vs 60% vs 54% Dol 50 vs. Dol 25: p=0.005 Failure: receipt of rescue medication: all patients: 29% vs 19% vs 24% % with no nausea (max VAS rating ≤ 5) 57% vs 71% vs 62% , Dol 50 vs. Dol 25: p=0.008 Maximum nausea VAS (0= no nausea to 100= as bad as can be) Mean max VAS score : 19 vs 11 vs 18 Dol 50 vs. Dol 25: p=0.013, Dol 50 vs. Ond; p=0.062 Patient satisfaction VAS (0= not at all satisfied to 100= as satisfied as can be) mean score: 83 vs 89 v D50 vs D25: p=0.016	*Dol 50 vs Dol 100 vs Ond 4* Overall AEs : 27% vs 24% vs 27% Bradycardia: 6% vs 5% vs 7% Headache : 6% vs 5% vs 4% Hypertension: 2% vs 5% vs 3% Hypotension: 2% vs 2% vs 3% AV block first degree: 0% vs 2% vs 2% Drowsiness: 2% vs 0% vs 0% Abnormal hepatic function: 1% vs 2% vs 0% Bronchospasm: 1% vs 0% vs 1% Rash: 0% vs 1% vs 2%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Korttilla 1997 Multicenter	The placebo arm (n=128) was not included in this abstraction, which gives a total of 389 pts entering this study. 518 pts were enrolled, and 1 pt withdrew from the study after randomization but before receiving study drug (n= 517); 3 pts were withdrawn from study before cessation of anesthesia: 2 had serious AEs, and 1 pt required nasogastric suctioning during and after surgery). Investigators could administer rescue medication according to institutional practice if they determined alternative therapy was needed, or if the pt experienced ≥ 15 min persistent nausea, had >1 emetic episode, or requested rescue medication. Recovery was defined as the first response to the spoken command, "Open your eyes." Pta may have received a benzodiazepine before general anesthesia.

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Granisetron vs. Ondansetron					
Bhatnagar 2007	DB RCT Parallel	Pts with gastrointestinal disease, those who were menstruating, or those who had received any antiemetic medication within 24 hours of the surgery	Granisetron 2mg Ondansetron 4mg	Pts received diazepam 5mg the night before and morning of surgery	No/No
Dua 2004 Single Center	DB RCT Parallel	Pts with known stomach disorders, history of heartburn, motion sickness, pervious PONV, lower esophageal sphincter disorders, menstruation, uncontrolled hypertension, poorly controlled diabetes, or pre-operative emesis less than 12h prior to surgery were excluded.	Granisetron 1mg Ondansetron 4mg	Glycopyrrolate	None/No

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Granisetron vs. Ondansetron				
Bhatnagar 2007	NR 0% male NR	NR/NR/90	0/0/90	Mean weight:58KW
Dua 2004 Single Center	48.5 years 0%male NR	NR/NR/60	NR/NR/NR	Mean weight in kg = 60.2 kg mean total intraoperative dose of fentanyl=100.7g ASA status 1: 57% ASA status 2: 42% Mean duration of anesthesia = 114.2 min Preoperative PONV: 2% Post-op anesth.:diclofenac Na 75/150 mg: 10%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Granisetron vs. Ondansetron		
Bhatnagar 2007	Granisetron vs Ondansetron vs Placebo Complete Response during 0-2 hour after anesthesia 63% vs 90% vs 43% Required Rescue Antiemetics 17% vs 7% vs 40% Absent nausea/vomiting during 0-2 hour after anesthesia 63% vs 90% vs 43%	Granisetron vs Ondansetron vs Placebo 0-2 hours after anesthesia Incidence: 16% vs 20% vs 20% Headache: 3% vs 6% vs 6% Dizziness: 6% vs 3% vs 6% Drowsiness: 3% vs 6% vs 3%
Dua 2004 Single Center	Gran iv 1 vs Ond iv 4 Patients PONV scores Complete response: no vomiting and no nausea: 75% vs 60%, p: NR PONV = 3 (vomiting ≥2 within 30m): acute: 20% vs 25%, p: NR PONV = 1 (only nausea, no vomiting): 5% vs 10%, p: NS PONV = 2 (1 episode of vomiting): acute: 0% vs 5%, p: NS Pts needing rescue medication in 24 h :15% vs 20%; p=NR	*Gran iv 1mg vs Ond iv 4mg* Headache: 5% vs 10% Dizziness: 0% vs 5% Drowsiness: 5% vs 0% Anxiety, insomnia: 5% vs 0% Others: 5% vs 5% Total number of AEs: 20% vs 20%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Granisetron vs. Ondansetron	
Bhatnagar 2007	Many meds given for the purpose of surgery and anesthesia
Dua 2004 Single Center	Before tracheal extubation, a nasogastric tube was inserted and suction was applied to empty the contents of the stomach. At the cessation of the surgical procedure, nitrous oxide and isoflurane administration were ceased. The trachea was extubated when the patient was awake. All patients received intramuscular injection of diclofenac sodium 75 mg for postoperative pain relief. Snorris 9/13/05: No run-in for treatment drugs. Patients did receive diazepam evening prior as part of pre-med. Attrition not reported.

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Gan 2005 Multicenter	RCT, DB, Parallel	Pts were excluded if they 1) had known hypersensitivity of contraindication to study medications, 2) had chronic nausea and vomiting or experienced retching, vomiting, or moderate or severe nausea in the 24 h before anesthesia, 3) had received an antiemetic drug or a drug with antiemetic properties during the 24 h before anesthesia, 4) had a body mass index ≥ 36, 5) were pregnant or breast feeding, or 6) had a condition requiring chronic opioid use.	Granisetron 0.1mg + dexamethasone 8mg Ondansetron 4mg + dexamethasone 8mg	Premedication, if desired Morphine or fentanyl was permitted for pain management Rescue medication was permitted	No/NR
Janicki 2006 Hershey Medical Center	RCT, DB, Parallel	Pts were excluded for: pregnancy or breast feeding, use of propofol for maintenance of anesthesia, allergy to study medication, neuroaxial anesthesia, history of vomiting within 24 hours before anesthesia, history of cardia arrhythmia and/or history of antiarrhythmic therapy, and history of vomiting from any organic etiology.	Dolasetron 12.5 mg iv Granisetron 1 mg iv	All received dexamethasone 4mg IV before anesthesia induction Promethazine (12.5-25mg) used for rescue medication	NR/NR
Khan 2005 General hospital	RCT, parallel	Pts with severe systemic or endocrine disease whom had predisposing factors for delayed gastric emptying, such as diabetes, chronic cholecystitis or neuromuscular disorders	Granisetron (40 ug/kg) Ondansetron (40-60 ug/kg) Propofol (2-3mg/kg) Placebo saline	all premedicated with midazolam 0.1mg/kg	NR/NR
Naguib 1996 NR	DB RCT Parallel	Patients who were receiving drugs known to have antiemetic effects (such as tricyclic antidepressants, scopolamine, phenothiazines, lorazepam, corticosteroids, and trimethobenzamides. Pts were also excluded if they had experienced nausea or vomiting of it they had taken antiemetic treatment in the 48h before surgery. No premedication was given.	Granisetron iv 3mg Ondansetron iv 4mg Tropisetron iv 5mg	No	No/NA

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Gan 2005 Multicenter	48 years 100% female 62.5% White 20% Black 14.5% Hispanic 2.5% other	NR/NR/210	34/0/176	Mean weight (kg): 72 Smokers: 18.8% Alcohol consumers: 39.2% History of motion sickness: 26% History of PONV: 27%
Janicki 2006 Hershey Medical Center	46.25 yrs 84% female 97.4% White	NR/NR/159	6/3/150	Mean weight (kg): 90.8 Current smoker: 23.3% Type of surgery Head & neck: 14% Orthopedic: 34.7% Laparoscopic: 10.7% Open abdominal: 31.3% Mastectomy: 9.3%
Khan 2005 General hospital		NR/NR/120	NR/NR/120	
Naguib 1996 NR	37.4 years 22%male NR	NR/NR/132	0/0/132	Mean weight = 73.7 kg (range: 40-98kg) Mean duration of anesthesia = 118.5 minutes (range: 60-260 min) Mean micrograms of intraoperative fentanyl =182.0 (range: 100-400 mcg)

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Gan 2005 Multicenter	Gran vs Ond No vomiting 0-2h after surgery: 94% vs 97% 0-6h after surgery: 87% vs 93% 0-24h after surgery: 83% vs 87% Complete response 0-2h after surgery: 75% vs 75% 0-6h after surgery: 59% vs 66% 0-24h after surgery: 46% vs 49% Required rescue medication 0-2h after surgery: 24% vs 21% 0-6h after surgery: 40% vs 30% 0-24h after surgery: 55% vs 46%	Incidence of AEs Gran: 37% vs Ond: 41%
Janicki 2006 Hershey Medical Center	Dol vs Gran While in PACU Incidence of vomiting or retching: 10.7% vs 13.3% Incidence of nausea episodes: 24% vs 26.7% Use of rescue therapy: 28% vs 21.3% Complete response: 69.3% vs 73.3% 0-24h after PACU discharge Incidence of vomiting or retching: 50.7% vs 46.7% Incidence of nausea episodes: 40% vs 42.7% Use of rescue therapy: 42.7% vs 29.3% (p=0.43) Complete response: 38.7% vs 54.7% (p=0.049)	None reported by subjects in either group
Khan 2005 General hospital	Incidence of vomiting Gran: 15% vs Ond: 25% vs Prop (1): 50% vs Prop (2): 40% vs Prop: (3): 35% vs Pla: 55% Intensity of Nausea Gran:	Headache Dizziness
Naguib 1996 NR	Gran iv 3 vs Ond iv 4 vs Trop iv 5 vs 12 Patients with PONV (treatment failures) Patients with PONV (treatment failures): over 24h: 48% vs 34.5% vs 52%, p: NS PONV-free patients (complete response) Complete response: Pts without any PONV in 24h: 52% vs 65.5% vs 48%, p: NS	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Gan 2005 Multicenter	
Janicki 2006 Hershey Medical Center	Also has information on genotyping information for CYP2D6
Khan 2005 General hospital	NEED Tables and Figures
Naguib 1996 NR	No premedication was given and pts fasted from midnight before surgery. After tracheal intubation, all pts had an orogastric tube placed to ensure baseline emptying of the stomach of air and gastric contents. All orogastric tubes were removed at the end of surgery and before tracheal extubation. Retching was not assessed separately from vomiting and nausea. If nausea or vomiting occurred, rescue antiemetic treatment of metoclopramide iv 10 mg was administered. For post-operative analgesia, meperidine im 50 mg was administered if pain score was ≥ 5. Study also included a metoclopramide arm (n=24) and a placebo arm (n=29), but these results are not included in this data abstraction. After intubation the concentrations of the nitrous oxide, oxygen, carbon dioxide, and isoflurane were determined continuously by a multiple-gas anaesthesia monitor .Abdominal insufflation for the laparoscopic procedure was accomplished with carbon dioxide. No major adverse effects were observed per the authors.

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Oksuz 2007 NR	RCT, DB, Parallel	Those with cardiovascular, pulmonary, renal, hepatic or neurologic diseases were excluded. As well as those receiving drugs know to have antiemetic effects, such as tricyclic antidepressants, scopolamine, phenothiazines, larazepam, corticosteroids, and trimethobenzamides; had experienced nausea or vomiting, or who had received antiemetic treatment in the 48 hours before surgery.	Metoclopramide 10mg Granisetron 40mcg/kg Ondansetron 15mcg/kg iv	Rescue medication was permitted	NR/No antiemetic within 48 hours of surgery
White 2006 Multicenter USA	RCT, ACT, DB	Pts with history of allergy to any of the potential study medications, pregnancy, breastfeeding, active menstruation, vomiting or retching within 24 h before the operation, administration of antiemetic or psychoactive medication within 24 h before surgery, a history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine or neurologic disease, active alcohol or drug abuse, as well as impaired renal or hepatic function.	Granisteron (1mg) Ondansetron IV (4mg)	Dexamethasone 4mg IV given to all after induction Cisatracurium 0.025-0.05mg/kg IV for maintenance period Metocloparmide 10mg IV was used as rescue therapy	NR/No antiemetic or psychoactive medication within 24 hours of surgery
Ondansetron: ODT vs IV					

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Oksuz 2007 NR	39.5 years 65.3% female Ethnicity: NR	NR/NR/75	NR/NR/75	History of PONV: 9.3%
White 2006 Multicenter USA	38.5 yrs 11.7% males NR	NR/NR/220	15/NR/205	Mean weight (kg: 102 Mean height (cm): 163 Mean BMI: 37.5 Smoking history: 13.2% History of PONV: 16.6% History of motion sickness: 11.2% Type of surgery Cholecystectomy: 40.5% Tubal ligation: 15.6% Gastric bypass: 43.6%
Ondansetron: ODT vs IV				

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Oksuz 2007 NR	Incidence of PONV (0-3h after surgery) Met: 12% vs Gran: 0% vs Ond: 12% Incidence of PONV (4-24h after surgery) Met: 44% vs Gran: 4% vs Ond: 12% (p<0.001) Rescue medication needed (0-3h after surgery) Met: 12% vs Gran: 0% vs Ond: 12% (p<0.05) Rescue medication needed (4-24h after surgery) Met: 44% vs Gran: 4% vs Ond: 12% (p<0.001) Nausea-vomiting score (0-3h after surgery) Met: 0.4 vs Gran: 0.2 vs Ond: 0.44 (p<0.05) Nausea-vomiting score (4-24h after surgery) Met: 1.68 vs Gran: 0.12 vs Ond: 0.36 (p<0.001)	NR
White 2006 Multicenter USA	Ond vs Gran Time to awakening (min): 9 vs 10 Duration of PACU stay (min): 67 vs 71 Complete response rates: 53% vs 48% Normal sleep at 48 hours: 68% vs 76% Willingness to have same treatment in future: 85% vs 90% Use of rescue therapy 0-4h after surgery: 34% vs 39% Use of rescue therapy 4-24h after surgery: 25% vs 24% Use of rescue therapy 24-48h after surgery: 8% vs 8% Use of rescue therapy 0-48h after surgery: 28% vs 29%	NR
Ondansetron: ODT vs IV		

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Oksuz 2007 NR	
White 2006 Multicenter USA	Subanalysis of outpatient vs inpatient.
Ondansetron: ODT vs IV	

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Demiraran 2005 Single Site Turkey	RCT, DB	Those who had experienced nausea or vomiting 24 hours before the study or who were taking antiemetic medication	ODT ondansetron 8mg and 5 mL normal saline IV IV ondansetron 4mg in 5 mL saline and oral placebo Placebo: 5 ml normal saline IV and oral placebo	Metoclopramide 10mg IV was used as rescue medication	NR/NR
Pirat 2005 NR	RCT, DB	Pts with history of motion sickness or PONV, preoperative pruritus, treatment with opioids or antiemetics within 48 hours of surgery, hypersensitivity to ondansetron, morphine, or bupivacaine, and contraindication for or refusal or spinal anesthesia. Cases in which dural puncture could not be performed or opioids were required to control intraoperative or postoperative pain were also excluded. No pts were premedicated.	ODT ondansetron 8mg and 5 mL normal saline IV IV ondansetron 4mg in 5 mL saline and oral placebo Placebo: 5 ml normal saline IV and oral placebo	IM injection of diclofenac sodium 100mg was used for postoperative pain Rescue medication was permitted	NR/No antiemetic within 48 hours of surgery
Aprepitant vs ondansetron					

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Demiraran 2005 Single Site Turkey	47.3 years 100% female Ethnicity: NR	NR/NR/90	NR/NR/90	Mean weight (kg): 71.2 Mean height (cm): 159 Duration of anesthesia (min): 149 Bleeding (ml): 950
Pirat 2005 NR	24 yrs 100% males NR	NR/NR/150	NR/NR/150	Mean weight (kg): 73 Mean height (cm): 174 Smokers: 62.6% Type of surgery Inguinal hernia: 54% Cord hydrocele: 31.3% Pilonidal sinus: 14.7%
Aprepitant vs ondansetron				

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Demiraran 2005 Single Site Turkey	ODT vs IV vs Pla Incidence of nausea or vomiting (1st min) Nausea: 28% vs 25% vs 55% (p<0.05 for both ODT vs Pla and IV vs Pla) Vomiting: 4% vs 4% vs 10% (p<0.05 for both ODT vs Pla and IV vs Pla) Incidence of nausea or vomiting (10th min) Nausea: 25% vs 20% vs 60% (p<0.05 for both ODT vs Pla and IV vs Pla) Vomiting: 0% vs 4% vs 10 % (p<0.05 for both ODT vs Pla and IV vs Pla) Incidence of nausea or vomiting (30th min) Nausea: 18% vs 15% vs 35% (p<0.05 for both ODT vs Pla and IV vs Pla) Vomiting: 0% vs 0% vs 7% (p<0.05 for both ODT vs Pla and IV vs Pla) Incidence of nausea or vomiting (60th min) Nausea: 5% vs 5% vs 12% (p<0.05 for both ODT vs Pla and IV vs Pla) Vomiting: 0% vs 0% vs 4% (p<0.05 for both ODT vs Pla and IV vs Pla) Incidence of nausea or vomiting (120th min) Nausea: 8% vs 8% vs 11% (p<0.05 for both ODT vs Pla and IV vs Pla) Vomiting: 4% vs 4% vs 7% (p<0.05 for both ODT vs Pla and IV vs Pla) Incidence of nausea or vomiting (6th h) Nausea: 5% vs 5% vs 12% (p<0.05 for both ODT vs Pla and IV vs Pla) Vomiting: 0% vs 0% vs 4% (p<0.05 for both ODT vs Pla and IV vs Pla)	ODT vs IV vs Pla Headache: 13% vs 17% vs 15% Cough: 21% vs 30% vs 23% Dizziness: 25% vs 30% vs 25% Tremor: 10% vs 9% vs 7% Pruritus: 8% vs 8%vs 5% Visual disturbances: 8% vs 5% vs 8%
Pirat 2005 NR	Overall 24-h frequency of Pruritus ODT: 56% vs IV: 66% vs Pla: 86% (p=0.001 for ODT vs Pla and p=0.017 for IV vs Pla) Overall 24-h frequency of Rescue antipruritic ODT: 18% vs IV: 34% vs Pla: 40% (p=0.013 for ODT vs Pla) Overall 24-h frequency of PONV ODT: 44% vs IV: 40% vs Pla: 50% Overall 24-h frequency of Vomiting episodes ODT: 24% vs IV: 12% vs Pla: 18% Overall 24-h frequency of Rescue antiemetic ODT: 16% vs IV: 24% vs Pla: 22%	NR
Aprepitant vs ondansetron		

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Demiraran 2005 Single Site Turkey	Data presented in graphs, numbers are estimates of the graphs.
Pirat 2005 NR	
Aprepitant vs ondansetron	

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Diemunsch 2007 Multicenter	RCT, DB	Exclusion criteria included pregnancy/breastfeeding status, need for a nasogastric or oral-gastric tube, use of neuroaxial- or propofol-maintained anaesthesia, vomiting within 24 h before surgery or of any organic aetiology, allergy to any medications to be used before operation or intra-operatively, pre-established need for intensive care or step-down unit care after operation, evidence of disease or history of illness which according to the investigator rendered the patient inappropriate for the study, abnormal preoperative laboratory values (aspartate aminotransferase >2.5 x upper limit of normal, alanine aminotransferase >2.5xupper limit of normal, bilirubin >1.5 x upper limit of normal, or creatinine >1.5 x upper limit of normal), or need for opioid antagonists or benzodiazepine antagonists. Medications known to induce CYP3A4 were prohibited within 30 days of the study start and CYP3A4 inhibitors were prohibited 7 days before start of study.	Aprepitant 40mg, orally Aprepitant 125mg, orally Ondansetron 4mg iv	Premedication, as needed rescue medication (chosen by investigator)	No/ no prophylactic antiemetics within 24h before surgery
Gan 2007 Multicenter	RCT, DB	Patients who were pregnant or breast-feeding, undergoing surgery requiring routine placement of a nasogastric or oral-gastric tube, or receiving spinal regional or propofol-maintained anesthesia. Pts whom were vomiting of any organic etiology, had vomited for any reason within 24 hours of surgery, or had abnormal laboratory values as specified by the protocol (alanine aminotransferase of aspartate aminotransferase >2.5 x upper limit of normal, bilirubin >1.5 x upper limit of normal, or creatinine >1.5 x upper limit of normal) were also excluded. Those taking medications metabolized by CYP3A4 were excluded.	Aprepitant 40mg orally Aprepitant 125mg orally Ondansetron 4mg iv	Rescue medication was permitted	No/no prophylactic antiemetics within 24 hours before surgery
Dolasetron vs Granisetron vs Ondansetron					

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Diemunsch 2007 Multicenter	45.68 yrs 91% female 11% Black 48.67% White 10.33% Asian 13.3% Other	1004/NR/922	54/2/866	Type of surgery Gynaecological: 81.6% Non-gynaecological: 18.4% History of PONV: 16% History of motion sickness: 14.4%
Gan 2007 Multicenter	45 yrs 94.3 % female 67% White 20.33% Black 1.67% Asian 11% Other	903/NR805	72/NR/733	Type of surgery Gynecologic: 88.12% Other 7.5% History of PONV: 31.7% History of motion sickness: 26.3%
Dolasetron vs Granisetron vs Ondansetron				

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Diemunsch 2007 Multicenter	Aprepitant 40mg vs Aprepitant 125mg vs Ondansetron 4mg Complete Response 64% vs 63% vs 55% No vomiting 0-24h after surgery 84% vs 86% vs 71% (p<0.001 for both A40 vs O4 and A125 vs O4) No vomiting 0-48h after surgery 82% vs 85% vs 66% (p<0.001 for both A40 vs O4 and A125 vs O4) No use of rescue therapy (0-24h after surgery) 67% vs 65% vs 63% (NS) Peak median nausea VRS score (0-24h after surgery) 2 vs 2 vs 4 (p<0.05 for A40 vs O4 and A125 vs O4) No significant nausea (peak VRS score 0-4) 62% vs 60% vs 53% (p<0.05 for A40 vs O4)	Most common AEs reported: Pyrexia: 8.3% Constipation: 5.6% Headache: 5.3% Bradycardia: 5%
Gan 2007 Multicenter	Aprepitant 40mg vs Aprepitant 125mg vs Ondansetron 4mg Complete Response 45% vs 43% vs 42% No use of rescue therapy (0-24h after surgery) 45% vs 44% vs 46% No vomiting (0-24h after surgery) 90% vs 95% vs 75% (p<0.001 for both A40 vs O4 and A125 vs O4) No vomiting (0-48h after surgery) 87% vs 92% vs 68% (p<0.001 for both A40 vs O4 and A125 vs O4)	Most common AEs reported: Pyrexia: 7.3%% Constipation: 9.2% Nausea: 13.3% Pruritus: 14.5%
Dolasetron vs Granisetron vs Ondansetron		

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Diemunsch 2007 Multicenter	
Gan 2007 Multicenter	
Dolasetron vs Granisetron vs Ondansetron	

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Bridges 2006 Women's hospital	DB, RCT	Allergy to 5-HT_3RA drugs or previous intolerance, pregnant or ≤18 years	Dolasetron 12.5mg Ondansetron 4mg Granisetron 0.1mg	Rescue medication was allowed (determined by investigator)	NR/NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Bridges 2006 Women's hospital	44 years 100% female NR	NR/NR194	NR/NR/194	Type of surgery Breast: 11% Lap: 19% TAH: 28% Other: 41%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Bridges 2006 Women's hospital	Dolasetron vs Granisetron vs Ondansetron Incidence of PONV 48% vs 39% vs 39% (p=0.45) Early failure (0-6h postoperatively) 33% vs 23% 26% (p=0.37) Late failure (6-24h postoperatively) 26% vs 24% vs 28% (p=0.9) Administration of multimodal therapy 26% vs 34% vs 30%	5 AEs reported in dolasetron group compared to 0 in granisetron and ondansetron (p<0.05) Events: postoperative crying and dysphoria sustained coughing and possible bronchospasm

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Bridges 2006 Women's hospital	

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Children					
Dolasetron vs. Ondansetron					
Karamanlioglu 2003	DB RCT Parallel	Children who received antiemetics or antihistamines in the 24h before surgery were excluded, as were children with diabetes mellitus or gastro-esophageal reflux. Any child unable to swallow the methylene blue capsule or the study drugs or who vomited them before the induction of anesthesia was excluded from the study.	Dolasetron po 1.8mg/kg Ondansetron po 0.15mg/kg	no	None/NA

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Children				
Dolasetron vs. Ondansetron				
Karamanlioglu 2003	9.85 years 49%male NR	NR/NR/150	0/0/150	ASA I - 78% ASA II - 22% Mean weight = 29.45 kg Strabismus surgery --46% Adenotonsillectomy - 29% Orchiopexy - 13% Middle ear surgery - 12% Mean duration of anesthesia = 79.9 min Mean duration of surgery = 76.25 min No. of pts with methylene blue contamination - 12% Median metoclopramide consumption/pt = 0 (range: 0-4.0) Number of pts taking metoclopramide -20%

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Children		
Dolasetron vs. Ondansetron		
Karamanlioglu 2003	*data given as Dol po 1.8 vs Ond po 0.15* PONV scores for 0-1h post-surgery, Score = 3 (vomiting): 4% vs 6%, p: NS Score = 0 (complete response: no nausea): 84% vs 80%, p: NS Score = 1 (nausea): 8% vs 10%, p: NS Score = 2 (retching): 4% vs 4%, p: NS PONV scores for 0-24h post-surgery, Score = 0 (complete response: no nausea): 68% vs 52%, p: NS Score = 1 (nausea): 16% vs 26%, p: NS Score = 2 (retching): 8% vs 6%, p: NS Score = 3 (vomiting): 8% vs 16%, p: NS Median VAS scores (scale 1-10) for post-operative pain, median (range) t=4h : 4 vs 4, p: NS t=8h : 3 vs 3.5, p: NS t=1h : 5 vs 5, p: NS t=0h : 7 vs 7, p: NS Median sedation scores (0=awake to 2=asleep) at post-surgery times: t=0h, 1h, 4h, 8h post-surgery : 0 vs 0, p = NS for all 4 times Median acetaminophen consumption/patient: 240 vs 240, p: NS % pts receiving acetaminophen: 64% vs 68%, p: NS	Sedation - see efficacy Pain - see efficacy

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Children	
Dolasetron vs. Ondansetron	
Karamanlioglu 2003	Study also contained a placebo arm (n=50); giving a total of 150 patients entered into the study; but this arm was not included in this abstraction, giving an N=100. Metoclopramide was given to any pt with a score of ≥2, or if the child requested an antiemetic. Postoperative analgesia (acetaminophen 10-25 mg/kg) was given to the older children when they complained of pain and to the younger children when they were restless and crying. Oral intake was not allowed until 4h after recovery from anesthesia. Each child received fentanyl 1 microgram kg-1 iv before surgery. Patients breathed spontaneously towards the end of operation. Residual muscular relaxation was not antagonized pharmacologically. During extubation, there was as little stimulation and suction of the airway as possible to avoid disturbing the child and stimulating gagging. Contamination of the mouth and endotracheal tube by methylene blue was assessed. SNorris 9/12/05: For 'class naïve' question, this information is not reported; only that patients hadn't taken drug in last 24 hours.

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Olutoye 2003 Single Center	DB RCT Parallel	Pts with ASA physical status of ≥ III, a previous history of gastroesophageal reflux, vomiting from organic causes, obesity (>95th percentile of weight for age), emergency surgery, antiemetic therapy within 24h before surgery or the use of neuraxial anesthesia or drugs known to have antiemetic effects (e.g., steroids, propofol). Children undergoing tonsillectomy and adenoidectomy procedures were excluded because they routinely receive steroids at this institution. A history of POV or motion sickness was noted during the preanaesthetic evaluation but did not preclude enrollment.	Dolasetron iv 45micrograms/kg Dolasetron iv 175micrograms/kg Dolasetron iv 350micrograms/kg Dolasetron iv 700micrograms/kg Ondansetron iv 100micrograms/kg	All subjects received midazolam 0.5 mg/kg per os 15-30 min before anesthesia induction.	No/No
Sukhani 2002 Single Center	DB RCT Parallel	Children who received antiemetics, antihistaminics, or psychoactive drugs within 24h before surgery were excluded. Also excluded were children who had a history of diabetes and those who required an iv induction, i.e., those with gastroesophageal reflux, obese children (>150% of ideal body weight), and children with a known history of allergy to any of the drugs used in the study.	Dolasetron iv 0.5mg/kg Ondansetron iv 0.15mg/kg	All received midazolam 0.5-0.6 mg/kg (maximum 20 mg) po 20-30 min before anticipated induction... Each received acetaminophen 30 mg/kg suppository, fentanyl 1 microgram/kg iv, and dexamethasone 1 mg/kg (max. 25 mg) iv before the start of surgery.	No/NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Olutoye 2003 Single Center	6.0 years 73%male NR	NR/225/216	9/3/204	Mean weight = 22.1 kg Herniorrhaphy 44% Orchidopexy 18% Penile surgery 7% Superficial plastic surgery 11% Umbilical hernia surgery 21% Previous history of motion sickness 18% Previous history of POV 2% Mean anesthesia time = 76.0 min Mean surgical time = 39.5 min End of Surgery (EOS) to PACU arrival = 15.0 min EOS to phase 1 PACU discharge = 62.7 min EOS to phase 2 PACU discharge = 150.2 min
Sukhani 2002 Single Center	5.7 years 47%male NR	NR/NR/150	1/2/147	Weight = 24.8 kg ASA physical status = I: 80% ASA physical status = II: 20% Mean anesthesia duration = 54.0 min Mean surgery duration = 38.1 min

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Olutoye 2003 Single Center	*data given as Dol 45 vs Dol 175 vs Dol 350 vs Dol 700 vs Ond 100* Freedom from postoperative emetic symptoms; complete response: no emesis, no rescue for 0-6h: 54.3% vs 71.9% vs 87.1% vs 78.4% vs 79.7%, p: NS for 24h: 45.7% vs 62.5% vs 74.2% vs 73.0% vs 78.3%, p: NS Rescue antiemetics needed, 2.9% vs 0% vs 3.2% vs 5.4% vs 4.3% ≥ 2 episodes of POV (failure), 25.7% vs 21.9% vs 3.2% vs 0% vs 8.7% Parental satisfaction scores (score (SD)) 8.1(3.3) vs 9.0(1.8) vs 9.2(2.0) vs 9.4(1.9) vs 9.6(0.9) Dol 175 vs. Dol 45, p<0.05; Dol 350 vs. Dol 45, p<0.05; Dol 700 vs. Dol 45, p<0.05; Ond 100 vs. Dol 45, p<0.05 Complete satisfaction with POV control, 65.7% vs 62.5% vs 74.2% vs 73.0% vs 75.4%	NR
Sukhani 2002 Single Center	Dol 0.5 vs Ond 0.15 Complete response (no emesis and no antiemetics given during 48h post-surgery) : 74% vs 76%, p: NS Need for rescue antiemetics: overall and by time period: overall: 8% vs 4%, p: NS 24-48h post-surgery: 2% vs 0%, p: NS Discharge to 24h post-surgery: 0% vs 0%, p: NS in PACU: 6% vs 4%, p: NS Pts experiencing retching/vomiting: In PACU: 8.2% vs 10.0%, p: NS Discharge to 24h post-surgery: 14% vs 8%, p: NS 24h-48h post-surgery: 6% vs 6%, p: NS Post-recovery oral intake: Good/excellent oral intake (discharge to 24h): 85.7% vs 93.9%, p: NS Good/excellent oral intake (24h to 48h): 85.7% vs 93.9%, p: NS Post-recovery problems: Hospital admission (discharge to 24h): 4% vs 0%, p: NS Hospital admission(24h to 48h): 0% vs 2%, p: NS ER visit for vomiting /hydration: 24h-48h: 0% vs 2%, p: NS discharge to 24h: 4% vs 0%, p: NS	NR

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Olutoye 2003 Single Center	After a minimal fast of 2 h (for clear liquids), all pts received midazolam 0.5 mg/kg per os 15-30 min before induction. Of 216 pts originally enrolled, 1 subject was excluded from analysis after requiring additional surgery, and 8 were excluded because of protocol violations (caudal epidural analgesia, additional intraoperative opioids, or other antiemetics); and 3 pts were lost to followup; 204 pts analyzed. Stomachs suctioned at surgery end, and the trachea extubated when the pt was awake. In the PACU, pain assessed using Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). Pts with severe pain (CHEOPS > 8) received IV morphine (increments of 0.05 mg/kg), those with moderated pain (CHEOPS 5-8) received oral oxycodone (0.1 mg/kg). Mild pain (CHEOPS 3-5) treated with oral acetaminophen 10-15 mg/kg. Pts with postop emesis while still in hospital received rescue: IV ond 0.05 mg/kg, metoclopramide 0.15-0.2 mg/kg, and droperidol 0.05 mg/kg for first, second, and third episodes, respectively. If IV access no longer available, trimethobenzamide (Tigan), 100-200 mg prescribed for rectal administration. Oral intake permitted but not mandatory before discharge(criteria included a fully awake pt who recognized the parents, with stable vital signs, and who was free from pe Nausea, a subjective feeling of emesis, not assessed in this study due to young age of pts. AEs: "There were no differences in the incidence of nonemetic AEs." Snorris 9/12/05: described as 'double blind", but unclear who refers to. Care provider is described as blinded. Unclear if assessor or patient (parent) blinded. Class naïve: NR Screened n-225, 9 declined therefore 216 enrolled; then lost 8 (protocol violation), 3 attrition, 1 second surgery. Therefore 204 analyzed.
Sukhani 2002 Single Center	Solid foods permitted until midnight before the day of surgery, and clear liquids permitted until 3 h before start of the expected surgery. All received oral premedication consisting of midazolam 0.5-0.6 mg/kg (maximum 20 mg), 20-30 min before the anticipated induction. Each patient received an acetaminophen 30 mg/kg suppository, fentanyl 1 microgram/kg IV, and dexamethasone 1 mg/kg (maximum 25 mg) IV before the start of surgery. At the conclusion of surgery, gastric contents were suctioned via an orogastric tube. Because nausea is difficult to assess in children, only retching and vomiting were assessed. This information only includes the H2H portion of this study; the placebo group consisted of 50 patients and their data was not included in this abstraction. SNorris 9/12/05: Class naïve NR; only that couldn't have taken antiemetic in last 24 hours. 1 post randomization exclusion for protocol violation; 2 lost to follow-up after discharge

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Mecklenburg 2006		Pts were excluded if they were 1) under the care of a mental health-care provider, 2) physical status ASA Class III or higher, 3) pregnant, 4) taking medications with antiemetic properties within 48 hours before surgery, 5) presenting for inpatient surgery 6) requiring admission to the hospital for surgical reasons, 7) not receiving general anesthesia.	Dolasetron iv 12.5 mg Ondasetron iv 4 mg		

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Mecklenburg 2006	33.9 82% female NR			

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Results	Adverse Events
Mecklenburg 2006		

Evidence Table 9. Prevention of postoperative nausea and vomiting: Head-to-head trials

Author Year Setting	Comments
Mecklenburg 2006	

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Adults				
Dol vs Ond				
Birmingham 2006 Single Center	Under the care of a mental health-care provider, physical status ASA class III or higher, pregnant, taking medications with antiemetic properties within 48 hours before surgery, presenting for inpatient surgery, requiring admission to the hospital for surgical reasons, not receiving general anesthesia	No/No	NR/NR/100	NR/NR/100
Browning 2004 Single Center	Pts excluded if they were <18, pregnant, received and ASA physical classification of ≥ III, experienced emesis 24 h prior to procedure, or received antiemetic medication or investigational research drug 24 h prior to surgery.	NR/NR	NR/NR/212	NR/NR/212
Paech 2003 Single Center	Pts experiencing preoperative nausea, receiving medication with antiemetic activity or with contraindication to nonsteroidal anti-inflammatory medication or epidural anesthesia were excluded from this study. Women in whom an open procedures was not performed or who underwent unplanned bowel surgery were excluded.	No/NR	NR/NR/120	2/0/118
Tang 2003 Single Center	Exclusion criteria included pregnancy; active menstruation; body weight more that 50% above the ideal body weight; vomiting or retching within 24h before the operation; administration of antiemetic or psychoactive medication within 24h before surgery; a previous history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine, or neurologic disease; alcohol or drug abuse; and impaired renal or hepatic function.	No/No	NR/NR/135	0/0/135
Zarate 2000 Single Center	Pts excluded if they had received an antiemetic medication within 24h before their operation, were pregnant, had clinically significant cardiovascular , neurologic, renal, hepatic, gastrointestinal, or endocrinological diseases, had a history of drug abuse, or were >100% above their ideal body weight	No/No	NR/NR/200	0/0/200
Erhan 2008 Single Center	ASA class III-IV; aged >70 years; BMI >30; pregnancy; smoking; signs of gastrointestinal, endocrine, renal, hepatic or immunological disease; use of opioids or tranquillizers less than 1 week before the operation; treatment with steroids; history of alocohol or drug abuse; history of motion sickness; preoperative diagnosis of gallbladder empyema and previous endoscopic sphincterotomy for common bile duct stones; and conversion to open cholecystectomy.	NR/no opiodis or tranquillizers within 1 week of surgery	NR/NR/80	NR/NR/80

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Adults								
Dol vs Ond								
Birmingham 2006 Single Center	NR	NR	Yes	Yes	Yes	Yes	NR NR NR NR	Unable to determine
Browning 2004 Single Center	Yes	Yes	Yes, although no data given	Yes	Yes	Yes	No No No No	Unable to determine
Paech 2003 Single Center	Yes	Yes	Yes	Yes	No	Yes	Yes No No No	No
Tang 2003 Single Center	Yes	NR	Yes	Yes	Yes	NR, but is "double blind"	Yes No No No	No
Zarate 2000 Single Center	Yes	NR	Yes	Yes	NR, "double blind"	NR	Yes No No No	No
Erhan 2008 Single Center	Yes	Yes	Yes	Yes	Yes	Yes	No No No No	No

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding
Adults					
Dol vs Ond					
Birmingham 2006 Single Center	Unclear	Unable to determine	Fair	No	NR
Browning 2004 Single Center	Unable to determine	Unable to determine	Fair	Yes	NR
Paech 2003 Single Center	Yes	Yes, only 2	Fair	Yes	A small proportion of each study drug was supplied free by the respective pharmaceutical companies (Novartis for trop., Glaxo Wellcome for ond., and Hoechst Marion Roussel for dol.).
Tang 2003 Single Center	Yes	No	Fair	Yes	The clinical research fellowships were supported by departmental resources. This study was also supported by the White Mountain Institute, a not-for-profit private foundation in Los Altos, California (Dr. White is the president).
Zarate 2000 Single Center	Yes	No	Fair	Yes	NR
Erhan 2008 Single Center	NR	No	Fair	Yes	NR

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Kushwaha 2007 Single Center	Gastrointestinal disorders, pregnancy or menstruation, history of motion sickness or previous history of PONV, aged <10 years or >60 years.	NR/NR	NR/NR/125	NR/NR/125
Meyer 2005 Single Center	Pts were excluded for any of the following reasons: 1) the patient declined participation, 2) the physician responsible for patient care considered the study not to be in the best interest of the patient for any reason, 3) the patient was allergic to either primary study drug, or 4) the patient was unable to understand the study.	NR/NR	559/351/92	NR/NR/92
Kortilla 1997 Multicenter	Pts scheduled for post-operative gastric suctioning or pts who had ingested any drug with antiemetic efficacy within 24h before surgery. Other exclusion criteria included clinically significant cardiac or liver disease, abnormal prestudy serum potassium levels, obesity (40% above ideal body weight), nausea and vomiting within 24h prior to surgery, previous treatment with dolasetron mesilate, use of any investigational drug within 30 days of dolasetron administration, or known alcohol abuse.	NR/NR	NR/NR/518	1/3/514
Gran vs Ond				
Bhatnagar 2007	Pts with gastrointestinal disease, those who were menstruating, or those who had received any antiemetic medication within 24 hours of the surgery	No/No	NR/NR/90	0/0/90
Dua 2004 Single Center	Pts with known stomach disorders, history of heartburn, motion sickness, pervious PONV, lower esophageal sphincter disorders, menstruation, uncontrolled hypertension, poorly controlled diabetes, or pre-operative emesis less that 12h prior to surgery were excluded.	None/No	NR/NR/60	NR/NR/NR
Gan 2005 Multicenter	Pts were excluded if they 1) had known hypersensitivity of contraindication to study medications, 2) had chronic nausea and vomiting or experienced retching, vomiting, or moderate or severe nausea in the 24 h before anesthesia, 3) had received an antiemetic drug or a drug with antiemetic properties during the 24 h before anesthesia, 4) had a body mass	No/NR	NR/NR/210	34/0/176

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Kushwaha 2007 Single Center	No	NR	Yes	Yes	NR	NR	No No No No	No
Meyer 2005 Single Center	Yes	Yes	Yes	Yes	Yes	Yes	Yes No Yes No	No
Kortilla 1997 Multicenter	NR	NR	Yes but for weight	Yes	NR	NR	Yes No No No	No
Gran vs Ond								
Bhatnagar 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes No Yes NR	No
Dua 2004 Single Center	Yes	NR	Yes	Yes	Yes	NR	No No No No	NR
Gan 2005 Multicenter	Yes	Yes	Yes	Yes	Yes	Yes	Yes No Yes NR	No

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding
Kushwaha 2007 Single Center	NR	No	Poor	Yes	NR
Meyer 2005 Single Center	Yes	Yes; 51/143=36%; "..47 patients did not receive blinded study drug, and 4 patients chose not to participate."; group assignments of dropouts NR and cannot determine if postrandomization exclusions were evening distributed between groups	Fair	No	NR
Kortilla 1997 Multicenter	Yes	Yes, 1 withdrew after random, before drug	Fair	Yes	Supported by a research grant from Hoechst Marion Roussel
Gran vs Ond					
Bhatnagar 2007	Unclear	No	Fair	No	NR
Dua 2004 Single Center	Unclear	Unable to determine	Fair	No	NR
Gan 2005 Multicenter	Yes	No	Good	No	Roche Laboratories

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Janicki 2006 Hershey Medical Center	Pts were excluded for: pregnancy or breast feeding, use of propofol for maintenance of anesthesia, allergy to study medication, neuroaxial anesthesia, history of vomiting within 24 hours before anesthesia, history of cardia arrhythmia and/or history of antiarrhythmic therapy, and history of vomiting from any organic etiology.	NR/NR	NR/NR/159	6/3/150
Naguib 1996 NR	Patients who were receiving drugs known to have antiemetic effects (such as tricyclic antidepressants, scopolamine, phenothiazines, lorazepam, corticosteroids, and trimethobenzamides. Pts were also excluded if they had experienced nausea or vomiting of it they had taken antiemetic treatment in the 48h before surgery. No premedication was given	No/NA	NR/NR/132	0/0/132
Khan 2005 General hospital	Pts with severe systemic or endocrine disease whom had predisposing factors for delayed gastric emptying, such as diabetes, chronic cholecystitis or neuromuscular disorders	NR/NR	NR/NR/120	NR/NR/120
Oksuz 2007 NR	Those with cardiovascular, pulmonary, renal, hepatic or neurologic diseases were excluded. As well as those receiving drugs know to have antiemetic effects, such as tricyclic antidepressants, scopolamine, phenothiazines, larazepam, corticosteroids, and trimethobenzamides; had experienced nausea or vomiting, or who had received antiemetic treatment in the 48 hours before surgery.	NR/No antiemetic within 48 hours of surgery	NR/NR/75	NR/NR/75
White 2006 Multicenter USA	Pts with history of allergy to any of the potential study medications, pregnancy, breastfeeding, active menstruation, vomiting or retching within 24 h before the operation, administration of antiemetic or psychoactive medication within 24 h before surgery, a history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine or neurologic disease, active alcohol or drug abuse, as well as impaired renal or hepatic function.	NR/No antiemetic or psychoactive medication within 24 hours of surgery	NR/NR/220	15/NR/205
Ondansetron: ODT vs IV				
Demiraran 2005 Single Site Turkey	Those who had experienced nausea or vomiting 24 hours before the study or who were taking antiemetic medication	NR/NR	NR/NR/90	NR/NR/90

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Janicki 2006 Hershey Medical Center	Yes	NR	Yes	Yes	Yes	Yes	Yes No Yes No	Low
Naguib 1996 NR	NR	NR	Yes	Yes	NR, "double blind"	NR	Yes No No No	No
Khan 2005 General hospital	Yes	NR	Yes	Yes	NR	NR	NR NR NR NR	NR
Oksuz 2007 NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR	No
White 2006 Multicenter USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR	No
Ondansetron: ODT vs IV								
Demiraran 2005 Single Site Turkey	Yes	NR	Yes	Yes	Yes	Yes	Yes NR NR NR	NR

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding
Janicki 2006 Hershey Medical Center	NR	NO	Fair	No	Roche Laboratories
Naguib 1996 NR	Yes	No	Fair	Yes	NR
Khan 2005 General hospital	NR	No	Poor	Yes	NR
Oksuz 2007 NR	NR	No	Fair	Yes	NR
White 2006 Multicenter USA	NR	No	Fair	No	White Mountain Institute
Ondansetron: ODT vs IV					
Demiraran 2005 Single Site Turkey	NR	No	Fair	Yes	NR

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Pirat 2005 NR	Pts with history of motion sickness or PONV, preoperative pruritus, treatment with opioids or antiemetics within 48 hours of surgery, hypersensitivity to ondansetron, morphine, or bupivacaine, and contraindication for or refusal or spinal anesthesia. Cases in which dural puncture could not be performed or opioids were required to control intraoperative or postoperative pain were also excluded. No pts were premedicated.	NR/No antiemetic within 48 hours of surgery	NR/NR/150	NR/NR/150
Aprepitant vs ondansetron				
Diemunsch 2007 Multicenter	Exclusion criteria included pregnancy/breastfeeding status, need for a nasogastric or oral-gastric tube, use of neuroaxial- or propofol-maintained anaesthesia, vomiting within 24 h before surgery or of any organic aetiology, allergy to any medications to be used before operation or intra-operatively, pre-established need for intensive care or step-down unit care after operation, evidence of disease or history of illness which according to the investigator rendered the patient inappropriate for the study, abnormal preoperative laboratory values (aspartate aminotransferase >2.5xupper limit of normal, alanine aminotransferase >2.5xupper limit of normal, bilirubin >1.5xupper limit of normal, or creatinine >1.5xupper limit of normal), or need for opioid antagonists or benzodiazepine antagonists. Medications known to induce CYP3A4 were prohibited within 30 days of the study start and CYP3A4 inhibitors were prohibited 7 days before start of study.	No/ no prophylactic antiemetics within 24h before surgery	1004/NR/922	56/0/304 for safety and 866 for efficacy
Gan 2007 Multicenter	Patients who were pregnant or breast-feeding, undergoing surgery requiring routine placement of a nasogastric or oral-gastric tube, or receiving spinal regional or propofol-maintained anesthesia. Pts whom were vomiting of any organic etiology, had vomited for any reason within 24 hours of surgery, or had abnormal laboratory values as specified by the protocol (alanine aminotransferase of aspartate aminotransferase >2.5 x upper limit of normal, bilirubin >1.5 x upper limit of normal, or creatinine >1.5 x upper limit of normal) were also excluded. Those taking medications metabolized by CYP3A4 were excluded.	No/no prophylactic antiemetics within 24 hours before surgery	903/NR805	72/0/766 for safety, 733 for efficacy
Dol vs Gran vs Ond				

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Pirat 2005 NR	Yes	Yes	Yes	Yes	Yes	Yes	NR NR NR NR	No
Aprepitant vs ondansetron								
Diemunsch 2007 Multicenter	Yes	Yes	Yes	Yes	Yes	Yes	Yes No Yes NR	No
Gan 2007 Multicenter	Yes	Yes	Yes	Yes	Yes	Yes	Yes No Yes Yes	No
Dol vs Gran vs Ond								

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding
Pirat 2005 NR	NR	No	Fair	Yes	NR
Aprepitant vs ondansetron					
Diemunsch 2007 Multicenter	30/922 (3.2%) excluded from safety analyses due to no receiving study drug; 56/922 (6.1%) excluded from efficacy analyses; results of sensitivity analyses accounting for excluded patients NR	No	Fair	No	Merck & Co, Inc
Gan 2007 Multicenter	39/805 (4.8%) excluded from safety analyses; 72/805 (8.9%) excluded from efficacy analyses, but results confirmed bases on post hoc sensitivity analyses accounting for excluded patients	No	Fair	No	Merck & Co, Inc
Dol vs Gran vs Ond					

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Bridges 2006 Women's hospital	Allergy to 5-HT_3RA drugs or previous intolerance, pregnant or ≤18 years	NR/NR	NR/NR194	NR/NR/194

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Bridges 2006 Women's hospital	NR	Yes	Yes	Yes	Yes	Yes	Yes No NR No	No

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding
Bridges 2006 Women's hospital	NR	No	Fair	No	NR

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Children				
DoI vs Ond				
Karamanlioglu 2003	Children who received antiemetics or antihistamines in the 24h before surgery were excluded, as were children with diabetes mellitus or gastro-esophageal reflux. Any child unable to swallow the methylene blue capsule or the study drugs or who vomited them before the induction of anesthesia was excluded from the study.	None/NA	NR/NR/150	0/0/150
Olutoye 2003 Single Center	Pts with ASA physical status of ≥ III, a previous history of gastroesophageal reflux, vomiting from organic causes, obesity (>95th percentile of weight for age), emergency surgery, antiemetic therapy within 24h before surgery or the use of neuraxial anesthesia or drugs known to have antiemetic effects (e.g., steroids, propofol). Children undergoing tonsillectomy and adenoidectomy procedures were excluded because they routinely receive steroids at this institution. A history of POV or motion sickness was noted during the preanaesthetic evaluation but did not preclude enrollment.	No/No	NR/225/216	9/3/204
Sukhani 2002 Single Center	Children who received antiemetics, antihistaminics, or psychoactive drugs within 24h before surgery were excluded. Also excluded were children who had a history of diabetes and those who required an iv induction, i.e., those with gastroesophageal reflux, obese children (>150% of ideal body weight), and children with a known history of allergy to any of the drugs used in the study.	No/NR	NR/NR/150	1/2/147

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Children								
Dol vs Ond								
Karamanlioglu 2003	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No
Olutoye 2003 Single Center	Yes	NR	Yes	Yes	Yes	NR	Yes No No No	No
Sukhani 2002 Single Center	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	No

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of postoperative nausea and vomiting

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding
Children					
Dol vs Ond					
Karamanlioglu 2003	Yes	No	Fair	Yes	NR
Olutoye 2003 Single Center	No, lost n=9 for protocol violation, attrition n=3	Yes	Fair	Yes	NR
Sukhani 2002 Single Center	Yes	Yes	Fair	Yes	NR

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Adults: Active-controlled trials				
Dolasetron				
Burmeister 2003 Single Center Germany	RCT, ACT, DB	Elective extracorporeal shock wave lithotripsy (ESWL) Mean duration of ESWL: 27.5 min	ASA I or II pts without obstructive pulmonary disease	A: Dol 12.5 mg iv B: placebo Given 10 min before start of procedure
Granisetron				
Ondansetron				
Doe 1998 Single center US	RCT, ACT DB	Various strabismus surgeries	ASA I-III non-obese pts without premedication with antiemetics	A: Ond 4 mg iv B: Droperidol (Drop) 1.25 mg iv
Fortney 1998 Multicenter North America (pooled results from 2 studies)	RCT, ACT DB	Outpatient procedures <2 h Gyn procedures: 61.0% musculoskeletal: 17.7% Anesth. duration: 56.3 min	ASA I or II status non-pregnant pts with a history of motion sickness and PONV undergoing procedures with highly emetogenic potential; pts also had to be addiction free	A:Ond 4 mg iv B: Droperidol (Dro) 0.625 mg iv C: Dro 1.25 mg iv D: placebo

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Adults: Active-controlled trials					
Dolasetron					
Burmeister 2003 Single Center Germany	NR	NR/ NR	Mean age: 48y Range: 20-77y 57.7% female Ethnicity: NR	History of PONV: 35% History of motion sickness: 27.5% Smoker: 65% Female pts ≤ 50 y: 22.5%	NR/ NR/ 40
Granisetron					
Ondansetron					
Doe 1998 Single center US	Premedication of all pts with midazolam 1-2 mg iv	NR/ No drugs with antiemetic properties nor any opioids allowed prior to surgery	Mean age: 30 y Range: 15-65 y 42% female Ethnicity: NR	NR	NR/ NR/ 45
Fortney 1998 Multicenter North America (pooled results from 2 studies)	During anesthesia after study drug administration, pts allowed to receive fentanyl, alentanil, or midazolam ≤ 2 mg	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 35 y Range: 18-65y 88.2% female Ethnicity: NR	History of PONV: 86.0% History of motion sickness: 61.8%	NR/ NR/ 2061

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Adults: Active-controlled trials			
Dolasetron			
Burmeister 2003 Single Center Germany	NR/ 0/ 40	Pt rating for anagesic properties, A vs B, p=0.99: Excellent: 85% vs 80% Good: 15% vs 20% Fair and Poor : both 0% vs 0% Pt rating for overall quality of anesthesia, A vs B, p=0.32 Excellent: 70% vs 55% Good: 20% vs 20% Fair: 5% vs 15% Poor: 5% vs 10%	Time to discharge, A vs B: 22 min vs 28 min, p<0.05
Granisetron			
Ondansetron			
Doe 1998 Single center US	NR/ NR/ 45	NR	Stay in PACU (min): 53.5 vs 50.2, NS Time from end of surgery to discharge (min): 249.5 vs 266.3, NS
Fortney 1998 Multicenter North America (pooled results from 2 studies)	NR/ NR/ 2061	Overall pt satisfaction with PONV control *A, B, C, D, results* Very satisfied: 68%, 64%, 70%, 60% Somewhat satisfied: 16%, 17%, 15%, 20% Neither satisfied nor dissatisfied: 4%, 5%, 2%, 6% Somewhat dissatisfied: 6%, 7%, 6%, 7% Very dissatisfied: 5%, 5%, 4%, 4% Questionnaire not returned: <1%, 2%, 3%, 3%	Time to home readiness (min): 186 vs 188 vs 207 vs 210, NS

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Gan 2004 Single Center US	ACT DB	Major breast surgery (100%) Duration of surgery: 210.9 min	Consecutive non-pregnant pts of ASA I, II, or II status without pacemakers and who were acupuncture-naïve	A: Ond 4 mg iv + sham electro-acupoint stimulation B: active electro-acupoint stimulation C: placebo + sham electro-acupoint stimulation
Jokela 2002 Multicenter Finland	RCT, ACT DB	Thyroid or parathyroid surgery mean surgery duration: 114 min	Female adult ASA 1-3 patients	A: Ond 16 mg po B: Meto 10 mg po C: Trop 5 mg po All given with midazolam 7.5 mg
Khalil 1999 Single Center US	RCT, ACT DB	Elective middle ear surgery All pts had stomach contents aspirated at end of operation Duration of anesthesia: 204.5min Duration of surgery: 152.7 min	Non-obese and non-mentally retarded adult ASA I and II pts	A: Ond 4mg B: Promethazine (Prom) 25mg C: Ond 2mg + Prom 25mg D: placebo

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Gan 2004 Single Center US	All pts received fentanyl 100 micrograms iv and midazolam 2 mg iv per-operation	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 45.6 y Range: NR 100% female Caucasian: 80% African American: 20%	History of PONV or motion sickness: 38.7%	NR/ NR/ 77
Jokela 2002 Multicenter Finland	Study medication given with midazolam 7.5 mg	NR/ NR	Mean Age: 49.0 y Range: NR 100 % female Ethnicity: NR	History of PONV: 73.2% History of motion sickness: 37.4% Current daily smokers: 22.9%	NR/ NR/ 200
Khalil 1999 Single Center US	Pre-medication with midazolam 2 mg iv	NR / NR	Mean age: Range: 13- 72 y 47.1% female Ethnicity: NR	History of PONV: 21.8% History of motion sickness: 8.0%	NR/ NR/ 87

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Gan 2004 Single Center US	2/ 0/ 75	Mean score for Patient Satisfaction (on scale of 0-10, with 10 being most satisfied) A: 10 (range: 8-10) B: 8.5 (6.2-10) C: 5.5 (3-10) p=0.007 for A & B vs. C	NR
Jokela 2002 Multicenter Finland	21/ NR/ 179	Patient satisfaction (score: 0-10 "most satisfied") A: 9 (range: 0-10) B: 9 (range: 0--10) C: 10 (range: 0-10), p =0.001 when C compared with B	NR
Khalil 1999 Single Center US	NR/ NR/ 87	Patient Satisfaction Score (0: "very dissatisfied" to 10: "very satisfied"): 9.1 vs 8.8 vs 9.2 vs 8.7; NS	Duration of PACU stay (min): 94 vs 87 vs 89 vs 95; NS

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Pan 2008 Two Sites US	RCT, DB	Laparoscopic gynecological surgeries	ASA I-II patients undergoing outpatient laparoscopic gynecological surgeries with general anesthesia; aged ≥18years; having all three patient specific emetic risk factors; ability to follow study protocol instructions; and willing to complete the daily diary	Study group: IV dexamethasone 8mg in 2mL volume after successful intubation, and IV ondansetron 4mg within 15min before tracheal extubation at the end of anesthesia, then ODT of ondansetron 8mg at the time of discharge from PACU and on the morning of postoperative day 1 and 2 at home. Control group: IV placebo of 2mL normal saline after successful intubation, and IV ondansetron 4mg within 15min before tracheal extubation at end of anesthesia, then placebo ODT at discharge and on the morning of postoperative day 1 and 2 at home.
Purhonen 2006 (B) NR	RCT,	Breast surgery	ASA I-III females aged 18-75 yrs scheduled to undergo breast surgery (partial or radical mastectomy, breast reconstruction, or both)	A:30% oxygen in nitrogen and saline 2 ml i.v. B:80% oxygen in nitrogen and saline 2 ml i.v. C:30% oxygen in nitrogen and ondansetron 4 mg i.v.

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Pan 2008 Two Sites US	Preoperative medication consisted of 0-2mg iv midazolam and oral ibuprofen 800mg 1st rescue medication was promethazine 25-50mg iv	NR/NR	Mean age: 34.5 years 100% female Ethnicity NR	Mean weight (kg): 80 Mean height (cm): 163.5	64/60/60
Purhonen 2006 (B) NR	All received oral diazepam 0.15-.02 mg/kg Rescue medication was permitted (droperidol 1.25 mg iv for 1st use, dexamethasone 5mg iv for 2nd use, and ondansetron 4mg iv for 3rd use)	NR/No antiemetics, antihistaminics within 24 hours before surgery	Mean age: 53.33 yrs Range: 18-75 yrs 100% female Ethnicity: NR	BMI: 24.3 History of previous PONV: 30.5% History of motion sickness: 36.4% Nonsmokers: 87% Duration of anesthesia (min): 128 Duration of surgery (min): 99 Type of surgery Mastectomy (partial or radical): 68% Mastectomy and breast reconstruction: 12% Breast reconstruction: 20%	NR/NR/90

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Pan 2008 Two Sites US	NR/NR/60	Overall satisfaction score (0-10) Study group: 9.6 vs Control group: 8.8 Patients most/very satisfied with antiemetic regimen Study group: 87% vs Control group: 83%	Study group vs Control group Patients reporting nausea affecting QOL: 33% vs 60% (p<0.04) Patients reporting emesis affecting QOL: 3% vs 20% (p<0.04) Cumulative modified FLIE scores for nausea: 15.2 vs 23.8 (p<0.02) Cumulative modified FLIE scores for emesis: 9.3 vs 14 (p<0.04)
Purhonen 2006 (B) NR	5/NR/85	Would choose same treatment for future surgery $30O_2$: 79% vs $80O_2$: 76% vs Ond: 89% Would choose a different treatment for future surgery $30O_2$: 7%% vs $80O_2$: 7% vs Ond: 4%	Time from end of surgery to 1st rescue medication use (min) $30O_2$: 341 vs $80O_2$: 266 vs Ond: 344 Incidence of 2nd rescue medication use $30O_2$: 14.3% vs $80O_2$: 24.1% vs Ond: 7.1% Incidence of 3rd rescue medication use $30O_2$: 3.6% vs $80O_2$: 13.8% vs Ond: 0% Time to tolerate fluids (min) $30O_2$: 382 vs $80O_2$: 452 vs Ond: 403 Time to tolerate food (min) $30O_2$: 816 vs $80O_2$: 919 vs Ond: 701 (p<0.05 for $30O_2$ vs $80O_2$)

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Reihner 1999 Single Center Sweden	RCT, ACT DB	Breast surgery Mean anesth. duration: 101.7 min	Non-pregnant, non-obese ASA I or II women	A: Ond 8 mg iv B: droperidol (drop) 1.25 mg iv C:placebo
Sandhu 1999 NR	RCT, PCT DB	Elective gynecologic laparoscopy with std anesthesia (w/o gastric suctioning) surgery duration: 25.0 min Anesthesia duration: 33.1 min	ASA I-II women	A: Ond 8 mg iv B: Dimenhydrinate 50 mg iv C: Placebo
Steinbrook 1996 Single Center US	RCT, DB semi-crossover (see intervention)	Laproscopic cholecystectomy Mean surgery time: 77.4 min	pts scheduled for laproscopic cholecystectomy	A: Drop 0.625 mg iv + metoclopramide 10 mg B: Ond 4 mg + saline Moderate or severe nausea or vomiting in PACU was treated with the cross-over drug

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Reihner 1999 Single Center Sweden	Premedication of all pts with midazolam 4 mg <60kg and 5 mg >60kg im	NR/ NR	Mean age: 54y Range: 18-80 y 100% female Ethnicity: NR	History of PONV: 43.5% History of motion sickness: 21.7% menstrual group (cycle day 1-8): 7.7%	NR/ NR/ 216
Sandhu 1999 NR	NR	NR/ NR	Mean age: 32.7 y Range: NR 100% female Ethnicity: NR		NR/ NR/ 87
Steinbrook 1996 Single Center US	Premedication of all pts with midazolam 1-2 mg iv	NR	Mean age: 43.5 y Range: NR 86% female Ethnicity: NR		NR/ NR/ 215

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Reihner 1999 Single Center Sweden	9/ NR/ 207	NR	Stay in PACU (min): 120 vs 120 vs 120, NS
Sandhu 1999 NR	NR/ NR/ 87	Overall satisfaction score (0 - 10 "satisfied"): PACU: 9 vs 9 vs 9; NS Home: 8 vs 8 vs 8, NS	Mean time to discharge (min): 189 vs 199 vs 205, NS
Steinbrook 1996 Single Center US	15/ NR/ 200	NR	Discharge time (min): 293 vs 288, NS

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Adults: Placebo-controlled trials				
Dolasetron				
Diemunsch 1997 multicenter Europe	RCT, PCT DB	Pts undergoing surgery with general anesth. Gyn. surgery: 63.2% Anesth. duration: 1.73 h	Non-pregnant, Dol naïve ASA I or II pts with no alcohol or drug addiction and normal serum Na and K concentrations before surgery	A: Dol 12.5 po B: Dol 25 po C: Dol 50 po D: Dol 100 po F: placebo
Diemunsch 1998 multicenter Europe	RCT, PCT DB	Patients undergoing major gynecologic surgery: 100% Anesth. Duration: 1.6 hrs	Female patients with ASA physical status I, II and III between 18-60 yrs, weighing 45-100kg	A: Dol 25 mg po B: Dol 50 mg po C: Dol 100 mg po D: Dol 200 mg po E: Placebo
Warriner 1997 Multicenter Canada	RCT, PCT DB	Total abdominal hysterectomy (TAH) (100%) Anesth. duration: 1.5 h	non-pregnant ASA I or II women under gen. anesthesia undergoing TAH	A: Dol 25 po B: Dol 50 po C: Dol 100 po D: Dol 200 po F: placebo
Granisetron				
Ondansetron				
Cherian 2001 Single center UK	RCT, PCT DB	Elective Caesarian section under spinal subarachnoid block	Pregnant women without pre-eclampsia	A: Ond 4 mg iv at end of surgery + 8 mg added to PCA morphine syringe B: nothing in surgery + no Ond in PCA morhpine syringe (placebo group)

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Adults: Placebo-controlled trials					
Dolasetron					
Diemunsch 1997 multicenter Europe	No	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 40.4 y Range: 18-65y 94.7% female Ethnicity: NR	History of PONV: 45.8% History of motion sickness: NR	NR/ NR/ 337
Diemunsch 1998 multicenter Europe	Intramascular or IV morphine and/or NSAIDS were used as postoperative analgesia	NR/NR	Mean age: 43 yrs 100% female White: 96% Black: 1.1% Other: 3.4%	ASA physical status I: 75% mean weight: 68 kg mean height: 163 cm History of PONV: 32% History of motion sickness: 18%	NR/ NR/ 793
Warriner 1997 Multicenter Canada	1 mg lorazepam po or sl the night prior to surgery	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 43.4 Range: 18-70 100% female White: 81.9% Black: 4% Asian: 10.4% Other: 3.7%	History of PONV: 46.8% History of motion sickness: 27.5%	NR/ NR/ 374
Granisetron					
Ondansetron					
Cherian 2001 Single center UK	NR	NR/ NR	NR	NR	NR/ NR/ 81

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Adults: Placebo-controlled trials			
Dolasetron			
Diemunsch 1997 multicenter Europe	NR/ 0/ 337	Patient satisfaction (VAS score: 0 = not at all satisfied to 100 = complete satisfaction) VAS scores not given; the only thing said was that Dol-treated pts were more satisfied with treatment than placebo pts (p<0.003)	NR
Diemunsch 1998 multicenter Europe	4/NR/789	Patient satisfaction VAS scores: 0 mm= not at all satisfied, 100=as satisfied as a pt could be) A: 84.5 mm (p=0.004 vs placebo) B: 97.0 mm (p=<0.001) C: 97.0 mm (p<0.001) D: 96.0 mm (<0.001)	Proportion of patients requiring rescue medication: A: 37% B: 31% (p=0.0011 vs placebo) C: 34% D: 37% E: 48%
Warriner 1997 Multicenter Canada	1/ 0/ 373	Patient satisfaction (VAS score: 0 = not at all satisfied and 100 = as satisfied as pt could be) A: 91.0 (p<0.05 vs placebo) B: 89.8 C: 91.0 (p<0.05 vs placebo) D: 85.0 E: 79.0	NR
Granisetron			
Ondansetron			
Cherian 2001 Single center UK	NR/ NR/ 81	Overall satisfaction with care (% pts): *Good* : A: 85%, B: 87.5% *Moderate* : A: 12%, B: 10% *Poor* : A: 3%, B: 2.5% p = NS between A & B	NR

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Han 2004 Single center Korea	RCT, PCT DB	elective surgery under gen. anesth. Mean duration of anesth: 163.5 min	Male smoking pts ≥ 61y without a history of PONV, motion sickness, or migraine	A: Ond 4 mg iv B: placebo 15 min before anesth. ended A: Ond 16 mg placed in PAC pump B: placebo in PAC pump
Lekprasert 1996 Single center Thailand	RCT, PCT DB	gastrointestinal surgery (laproscopic cholecystectomy (50%), open cholecystectomy (40.2%), appendectomy (7.3%), etc) with general anesth. 80.5% of pts had surgery lasting <2 hrs; 44% had gastric suctioning	ASA I or II status non-pregnant non-drug abusing pts; if women they had to be <100kg and if men <120kg	A: Ond 4 mg iv, prior to induction B: placebo iv
Purhonen 2006 (A) NR	RCT, PCT DB	Gynecologic laparoscopy	ASA I or II female patients scheduled to undergo gynecologic laparoscopy	A: Preoperative placebo tablet, propofol induction, propofol-air/O2 maintenance B: Preoperative 8-mg Ond tablet, thiopentone induction, isoflurane-N2O maintenance C:Preoperative placebo tablet, thiopentone induction, isoflurane-N2O maintenance
Sadhasivam 1999 Single center India	RCT, PCT DB	Modified radical mastectomy Mean anesth. duration: 152 min	ASA I or II non-obese pts	A: Ond 4 mg iv B: placebo at end of surgery

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Han 2004 Single center Korea	NR	NR/NR	Mean age: 67.6 y Range: ≥ 61 y 0% female Ethnicity: NR	Hip surgery: 49% Knee surgery: 22.8%	NR/ NR/ 374
Lekprasert 1996 Single center Thailand	Some premedicated with benzodiazepines (excluding lorazepam) prior to surgery or at induction	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 50.1y Range: 12-75y 74.4% female Ethnicity; NR	Opioid use, A vs B: 51.2% vs 80.4%	NR/ NR/ 82
Purhonen 2006 (A) NR	Fentanyl 1 µg/kg iv or oxycodone for postoperative pain Metoclopramide 10mg iv for rescue medication was permitted	NR/No antiemetics 24 hours before surgery	Mean age: 34.35 yrs 100% females Ethnicity: NR	Mean weight (kg): 64 Mean height (cm): 164.6 History of PONV: 28.6% History of motion sickness: 42% Nonsmoking status: 81.3%	NR/NR/150
Sadhasivam 1999 Single center India	All pts received diazepam 0.2 mg/kg po the night before surgery and 2h before induction	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 45.7 y Range: NR 100% female Ethnicity: NR	History of PONV: 5.6% History of motion sickness: 18.5%	NR/ NR/ 54

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Han 2004 Single center Korea	24/ NR/ 350	Pt satisfaction for analgesia therapy , A vs. B, p = NS for all: "very satisfied": 39.9% vs 42.9% "satisfied": 38.1% vs 38.4% "neither dissatisfied nor satisfied": 18.5% vs 15.8% "Dissatisfied": 3.5% vs 2.8%	
Lekprasert 1996 Single center Thailand	NR/ NR/ 82	Patient Satisfaction levels (p = NS for all comparisons): most satisfied, A vs B: 4.87% vs 21.95% Satisfied, A vs B: 70.73% vs 58.54% Undecided, A vs B: 19.51% vs 17.07% Unsatisfied, A vs. B: 4.87% vs 2.44% Most unsatisfied, A vs B: 0% vs 0%	NR
Purhonen 2006 (A) NR	NR/NR/150	NR	Median cost of anesthetic drugs Prop: $31 vs Ond: $35 vs Pla: $18 Readiness for ward transfer (min) Prop: 61 vs Ond: 90 vs Pla: 64 (p<0.05 for Prop vs Ond) Time to tolerate intake of oral fluids (h) Prop: 3 vs Ond: 3 vs Pla: 3 Time to tolerate intake of food (h) Prop: 6 vs Ond: 6 vs Pla: 7 Time to Walking (h) Prop: 5.8 vs Ond: 6.5 vs Pla: 7.5
Sadhasivam 1999 Single center India	NR/ NR/ 54	Pt satisfaction scores: (0 = "not satisfied" to 10 = "fully satisfied") Ond vs Plac: 8.1 vs 6.1, p = 0.0000	

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Scuderi 1999 Single-center US	RCT, PCT DB	Outpatient surgery with general anesthesia	ASA I, II, or III outpatients	A: Ond 4 mg iv B: placebo
Sun 1997	RCT, PCT DB	ambulatory otolaryngologic procedures (sinus surgery (70.7%), and others) anesth. duration: 93.3 min	Non-pregnant, non-obese non-drug using ASA I or II pts	A: Ond 4 mg iv before induction of anest. + placebo at end of procedure B: placebo at induction + Ond 4 mg iv at end C:placebo + placebo
Tang 1998 US	RCT, PCT DB	Outpatient laproscopic procedures Duration of anesth. : 79.2 min	ASA I or II non-pregnant, non-obese female pts	A: Ond 2 mg iv pre-induction + Ond 2 mg at end of operation B: Ond 4 mg iv pre-induction + placebo at end C: placebo pre-induction + Ond 4 mg iv at end D: placebo + placebo
Thagaard 2003 Single Center Norway	RCT, PCT DB	Elective laproscopy for fundoplication (41%) or cholecystectomy (54%) Mean duration of surgery: 100 min	ASA 1 or II pts	A: Ond 8 mg orally disintegrating tablets bid starting the night after surgery B: placebo

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Scuderi 1999 Single-center US	Premedication with midazolam: 98.8%	NR/ NR	Mean age: 38.2 y Range: 18-65 y 63.3% female White: 80% African American: 18.9% Other: 0.1%	History of risk factors: 58.4%	NR/ NR/ 575
Sun 1997	Premedication of all pts with midazolam 0.02 mg/kg iv	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: Range: 20-70y 46.7% female Ethnicity: NR	History of PONV: 22.7% History of motion sickness: 26.7%	NR/ NR/ 75
Tang 1998 US	Premedication of all pts with midazolam 2 mg iv	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 37.7 y Range: 20-70y 100% female Ethnicity: NR	History of PONV: 30.1% History of motion sickness: 35.2% Last menstrual period: 0-8 days previously: 26.3%	NR/ NR/ 164
Thagaard 2003 Single Center Norway	Pre-medication with midazolam 1-2 mg iv; all pts received droperidol 0.1235mg and Ond 4 mg iv prior to emergence from anesthesia Pain medication after surgery: codeine 60 mg+paracetamol 1000mg up to 4X/day	Ond 4 mg iv prior to end of anesthesia	Mean age: 43.1 y Range: ≥ 18 y 68.7% female Ethnicity: NR	History of PONV: 10.3% History of motion sickness: 40.6%	NR/ NR/ 102

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Scuderi 1999 Single-center US		Satisfaction with control of PONV: #yes/#no, A vs B: 230/7 (97%) vs 212/16 (93%), p = 0.04	Time to discharge from PACU to day hospital (min): 59 vs 58, NS, Time to discharge from PACU to home (min): 87 vs 92, NS
Sun 1997	NR/ NR/ 75	NR	PACU recovery times (min): 73 vs 63 vs 66, NS Hospital discharge times (min): 225 vs 188 vs 203, NS
Tang 1998 US	8/ NR/ 156	Highly satisfied (% pts): 38 vs 36 vs 37 vs 37, NS	*=p<0.05 vs placebo Discharge-ready (min): 198 vs 180 vs 168* vs 213 Actual discharge (min): 234 vs 207 vs 198* vs 243* Caretaker needed (days): 0.9 vs 0.3 vs 0.8 vs 0.8, NS Return to work (days): 4.5 vs 4.5 vs 4.4 vs 5.6, NS
Thagaard 2003 Single Center Norway	6/ NR/ 96	Acute: (4-24h post-op): Overall satisfaction compared with expectation: worse/ similar/ better: 41/ 36/ 23 vs 35/ 42/ 23, p=NS Delayed (24-72 h post op): Overall satisfaction compared with expectation: worse/ similar/ better: 29/ 47/ 24 vs 16/ 51/ 33 , p = NS	Acute: (4-24h post-op): Time to discharge ready (min): 299 vs 277, p=NS Pt rating of general function (1 "all time in bed" to 5 "full normal activity"): 2.4 vs 2.4, p = NS Delayed (24-72 h post op): Pt rating of general function (1 "all time in bed" to 5 "full normal activity"): 3.1 vs 3.2, p = NS

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Trescha 2005 Single Center Germany	RCT, DB	Strabismus	ASA I or II pts scheduled to undergo strabismus surgery	A: 30% inspired oxygen in air plus intravenous administration of saline B: 80% inspired oxygen in air plus intravenous administration of saline C:30% inspired oxygen in air plus 75 µg/kg ondansetron intravenously during induction
Palonosetron				
Candiotti 2008 Multiple Sites USA	RCT, DB	Abdominal or gynecological surgery	ASA I-III patients scheduled to undergo elective laparoscopic abdominal or gynecological surgery of at least 1 hour duration.	A: Palonosetron 0.025mg B: Palonosetron 0.050mg C: Palonosetron 0.075mg D: Placebo
RS-25259				

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Trescha 2005 Single Center Germany	Pre-medicated with midazolam Paracetamol 20 μg/kg for analgesia Rescue medication of dimenhydrinate (1-3 mg/kg) permitted	NR/NR	Mean age: 30.65 Range: 5-79 yrs % female: 55.24% Ethnicity: NR	Pediatric patients (aged <15 years): 31.4% Mean weight (kg): 60.6 Mean height (cm): 160 Duration of surgery (min): 27.3 Current smokers: 30% History of motion sickness: 17.6% History of PONV: 20.5%	373/318/210
Palonosetron					
Candiotti 2008 Multiple Sites USA	Rescue medication was permitted at the discretion of the investigator	NR/NR	Mean age: 37.75 Range: 18-77 years 96% female Ethnicity NR	History of PONV: 64.5% Non-Smoker: 85.2% Mean BMI: 26.75 Gynecological surgery: 74.5% Abdominal surgery: 25.5%	639/574/547
RS-25259					

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Trescha 2005 Single Center Germany	NR/NR/210	No difference in patient satisfaction (numbers NR)	30O2 vs 80O_2 vs OND Use of rescue therapy 0-24h after surgery: 15% vs 12% vs 7% Use of rescue therapy 0-6h after surgery: 10% vs 9% vs 6% Use of rescue therapy 6-24h after surgery: 10% vs 4% vs 1%
Palonosetron			
Candiotti 2008 Multiple Sites USA	48/NR/547	NR	Palonosetron 0.075mg vs Placebo Percentage of patients without functional interference during 0-24h postoperative period Appetite: 44% vs 57% (p=0.018) Sleep: 64% vs 73% Physical activities: 59% vs 65% Social life: 62% vs 73% (p=0.13) Enjoyment of life: 57% vs 66% (p=0.096)
RS-25259			

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Tang 1998 Two Sites US	RCT, DB, PCT	Hysterectomy	ASA I or II pts undergoing abdominal or vaginal hysterectomy with general anesthetic technique	A: RS-25259 0.1 µg/kg B: RS-25259 0.3 µg/kg C: RS-25259 1.0 µg/kg D: RS-25259 3.0 µg/kg E: RS-25259 30 µg/kg F: Placebo

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Tang 1998 Two Sites US	Midazolam 2mg iv was used to premedicate all patients. Rescue medication was permitted	NR/No use of antagonists, antiemetic or psychoactive medications within 24 hours before operation	Mean age: 41 y 100% female Ethnicity: NR	Mean weight (kg): 72.3 Previous PONV: 36.6% Previous motion sickness: 11.5%	NR/NR/218

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Tang 1998 Two Sites US	NR/NR/218	Data not presented, however, statement of "The overall satisfaction with the control of PONV in the first 24 hours after surgery was also similar."	A vs B vs C vs D vs E vs F Use of rescue medication 0-2h after surgery: 22% vs 22% vs 23% vs 20% vs 23% vs 31% Use of rescue medication 0-12h after surgery: 63% vs 56% vs 43% vs 43% vs 46% vs 72% (p<0.05 for C vs F; D vs F; and E vs F) Use of rescue medication 0-24h after surgery: 67% vs 61% vs 54% vs 53% vs 49% vs 75% (p<0.05 for E vs F) Time to first rescue medication use (min): 314 vs 326 vs 381 vs 430 vs 474 vs 234 Use of rescue medication 0-2h after surgery for those with history of PONV: 33% vs 29% vs 46% vs 20% vs 33% vs 29% Use of rescue medication 0-12h after surgery for those with history of PONV: 75% vs 79% vs 62% vs 47% vs 67% vs 79% Use of rescue medication 0-24h after surgery for those with history of PONV: 75% vs 86% vs 62% vs 67% vs 67% vs 79% Use of rescue medication 0-2h after surgery for those with NO history of PONV: 13% vs 19% vs 6% vs 20% vs 19% vs 32% Use of rescue medication 0-12h after surgery for those with NO history of PONV: 53% vs 44% vs 32% vs 40% vs 37% vs 68% (p<0.05 for C vs F and E vs F) Use of rescue medication 0-24h after surgery for those w

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Children: Active-controlled trials				
Ondansetron				
Bach-Styles 1997 Single Center US	RCT, ACT DB	Pediatric pts undergoing opthamalic surgery Anesth. duration: NR	Pediatric pts ASA status I, II, or III	A: Ondansetron (Ond) 0.15 mg/kg iv B: Metoclopramide (Met) 0.25 mg/kg iv C: placebo
Davis, A. 1995 Single Center Saudi Arabia	RCT, ACT DB	Elective strabismus repair surgery w/o gastric suctioning Mean surgery time: 87 min	ASA I or II pediatric and adult pts	A: Ond 75 mcg/kg B: Ond 150 mcg/kg C: Droperidol 75 mcg/kg
Davis, P. 1995 Single Center US	RCT DB	Dental surgery (with stomach suctioning at end)	ASA I and II pediatric pts	A: Ond 100 mcg/kg iv B: Droperidol (drop) 75 mcg/kg iv C: placebo
Litman 1995 Multicenter US	RCT, ACT DB	Strabismus repair Mean anesthesia time: 81.6 min	healthy ASA I and II children without a history of gastric motility disorders	A: Ond 0.15 mg/kg iv B: Droperidol 0.075 mg/kg iv
Rose 1994 Single Center US	RCT, ACT DB	Strabismus repair	ASA I and II pediatric/adolescent pts	A: Ond 0.15 mg/kg iv B: Metoclopramide (meto) 0.25 mg/kg iv C: placebo

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Children: Active-controlled trials					
Ondansetron					
Bach-Styles 1997 Single Center US	NR	NR/ NR	Mean Age: NR Range: 1-17 y 94.7% female Ethnicity: NR	"ANOVA showed no significant difference between the 3 study groups with regard to Age, height, weight, ASA status, history of vomiting, no. of muscles repaired, iv fluids, or duration of surgery." No specifics other than this statement were given.	NR/ NR/ 52
Davis, A. 1995 Single Center Saudi Arabia	Premedication: midazolam 0.5 mg/kg po (Max 10 mg) for children and 5-10 mg diazepam po for adults	NR/ NR	Mean age: 12.4 y Range: NR 39.4% female Ethnicity: NR		NR/ NR/ 213
Davis, P. 1995 Single Center US	All pts premedicated with either midazolam intranasally (0.2-0.3 mg/ kg, max = 5 mg) or po (0.5 mg/ kg, max 15 mg)	NR/ NR	Mean age: 42.7 mos Range: 2-8 yrs % female: NR Ethnicity: NR		NR/ NR/ 102
Litman 1995 Multicenter US	If needed, pts premedicated with midazolam 0.5 mg/kg po	NR/ NR	Mean age: 5.75 y Range: 3-14yrs 40.3% female Ethnicity: NR		NR/ NR/ 57
Rose 1994 Single Center US	All received midazolam 0.5 mg/kg po (max 20 mg) but one who got midazolam 0.2 mg/kg intranasally and one who received diazepam 0.1 mg/kg po	NR/ NR	Mean age: 72 mos Range: 2-17 y 48.9% female Ethnicity: NR		NR/ NR/ 90

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Children: Active-controlled trials			
Ondansetron			
Bach-Styles 1997 Single Center US	NR/ NR/ 52	Satisfaction (% parents): 94% vs 74% vs 74%, NS	Hospital stay (# min): 132 vs 137 vs 132, NS
Davis, A. 1995 Single Center Saudi Arabia	NR/ NR/ 213	NR	Mean discharge times from recovery (min): 44.4 vs 75.3 vs 41, NS
Davis, P. 1995 Single Center US	7/ NR/ 95	NR	PACU length of stay (min): 28.6 vs 39.9 vs 29, NS Hospital length of stay (min): 74 vs 106 vs 85; O>D, p<0.05
Litman 1995 Multicenter US	NR/ NR/ 57	NR	Duration of PACU stay (min): 46.2 vs 54.6, NS Time to discharge (min): 235 vs 258, NS
Rose 1994 Single Center US	NR/ NR/ 90	NR	Time until discharge (min): 111 vs 124 vs 127, NS

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Splinter 1998 Single Center Canada	RCT, ACT DB	Elective tonsillectomy or adenotonsillectomy	healthy children with ASA I or II status and no sleep apnea Anesth. duration: 31.5 min	A: Ond 150 mcg/kg (max 8 mg) iv B: Perphenazine (perp) 70 mcg/kg iv (max 5 mg)
Stene 1996 Single center US	RCT, ACT DB	Tonsillectomy (92.5%) or adenotonsillectomy (7.5%)	ASA I and II pediatric pts	A: Ond 0.15 mg/ kg iv B: Metoclopramide 0.25 mg/ kg iv C: placebo
Granisetron				
Luisi 2006 Brazil University Hospital	RCT, DB	N/A	Patients <20years, with a diagnosis of mestastic or non-mestastic osteosarcoma, who are undergoing chemotherapy treatment in a day hospital	A: Granisetron 50µg/kg B: Metoclopramide 2mg/kg + dimenhydrinate 5mg/kg infusion

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Splinter 1998 Single Center Canada	Pts received either midazolam 0.5 mg/kg (max 15 mg) po before induction or Midazolam 50 mcg/kg (max 3 mg) iv during surgery All received codeine 1.5 mg/kg im	NR/ NR	Mean age: 6.9 y Range: 2-12 y 54.6% female Ethnicity: NR		NR/ NR/ 220
Stene 1996 Single center US	No predication besides oral atropine allowed	NR/ NR	Mean age:6.0 yrs Range: 2- 12 y % female: NR Ethnicity: NR		NR/ NR/ 132
Granisetron					
Luisi 2006 Brazil University Hospital	NR	NR/NR	Mean age: 14 y Range: 7-19 y 42.3% female Ethnicity: NR	NR	NR/NR/26

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Splinter 1998 Single Center Canada	4/ NR/ 216	NR	Mean duration of stay in PAR (min): 46 vs 47, NS Duration of stay in day-case surgical unit (median min): 235 vs 240, p=0.007
Stene 1996 Single center US	12/ NR/ 120	NR	Length of stay (min): 449 vs 485 vs 481, NS n=100 (75.7% of randomized) (study rated poor)
Granisetron			
Luisi 2006 Brazil University Hospital	NR/NR/26	NR	<u>Overall Efficacy (Modified MANE scale)</u> Complete: Met: 10% vs Gran: 62.5% (p<0.0001) Partial: Met: 35% vs Gran: 32.5% Minimum: Met: 42.5% vs Gran: 5% Absence: Met: 12.5% vs Gran: 0%

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Children: Placebo-controlled trials				
Granisetron				
Carnahan 1997 Single center US	RCT, PCT DB	Tonsillectomy and adenoidectomy (T & A) ; pts had gastric suctioning during surgery	Pediatric pts of ASA I or II undergoing elective outpt T & A	A: Gran 0.01 mg/kg iv B: placebo
Cieslack 1996 Single center US	RCT, PCT DB	Outpatient strabismus correction (42.3%), tonsillo-adenoidectomy (19.6%), or dental surgery (34%) using endotracheal gen. anesth. with end-of-surgery stomach suctioning Mean duration of anesth. = 80.5 min	ASA I and II children who had not recently received an drug with an antiemetic effect	A: Gran 10 mcg/kg iv B: Gran 40 mcg/kg iv C: Placebo
Munro 1999 Single-center US	RCT, PCT DB	Strabismus repair surgery with stomach suctioning at end Anesth. duration: 69.6 min	ASA I-II out-patient pediatric pts	A: Gran 20 mcg/kg suspension B: Gran 40 mcg/kg suspension C: placebo
Patel 1997 multicenter US	RCT, PCT DB	Outpt surgeries with gastric suctioning: stabismus surgery (33.8%), tonsillectomy w/ or w/o andenoidectomy (26.1%), herniorrhaphy (31.9%), or orchidopexy (7.9%) Mean duration of anesth.: 57.2 min	ASA I-III pediatric pts without liver or renal disease or vomiting within 24h before surgery	A: Ond 0.1 mg/kg iv if child ≤ 40kg; 4 mg if child >40kg B:placebo
Ondansetron				

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Children: Placebo-controlled trials					
Granisetron					
Carnahan 1997 Single center US	Midazolam 0.5 mg/kg up to 10mg was given 15-30 min before induction	NR/ NR	Mean age: 4.87 y Range: 2-8 y 48.1% female White: 81.5% Black: 11.1% Other: 7.4%	NR	NR/ NR/ 54
Cieslack 1996 Single center US	All pts received midazolam 0.5 mg/kg 15-30 min before induction	NR/ NR	Mean age: 5.2 y Range: 2-16 y 48.4% female Ethnicity: NR		NR/ NR/ 97
Munro 1999 Single-center US	No	NR/ no drugs with antiemetic properties allowed prior to surgery	Mean age: 5.0 y Range: 1-12 y 53.4% female Ethnicity: NR		NR/ NR/ 76
Patel 1997 multicenter US	premedication left up to MD	NR/ no drugs with antiemetic properties allowed within 24h of surgery	Mean age: 5.3y Range: 2-12y 36.8% female Caucasian: 77.8% African American: 13.7% Hispanic: 4.0% Asian: 2.1% Other: 2.3%	Previous history of motion sickness: 8.9% Previous PONV: 6.5%	NR/ NR/ 433
Ondansetron					

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Children: Placebo-controlled trials			
Granisetron			
Carnahan 1997 Single center US	NR/ NR/ 54	NR	Pt discharge time: A: 250.0 (+/- 147.27) min (p<0.05) B: 320.8 (+/-118.22) min
Cieslack 1996 Single center US	NR/ NR/ 97	Mean global parental satisfaction score (0= not at all satisfied; 10=fully satisfied), and % of parents giving a score >8: A: 9.3, 93% score>8 B: 9.1, 97% score>8 C: 8.8, 81%, score>8, p=NS for all comparisons	Discharge readiness (min): 129 vs 108 vs 152 G 10 mg>placebo, p<0.05; otherwise NS
Munro 1999 Single-center US	3/ NR/ 73	NR	Time to discharge readiness (min): 104.8, vs 104.7 vs 124, p<0.05 for both G groups vs placebo
Patel 1997 multicenter US	4/ NR/ 429	NR	Mean time to reach home-readiness (min): 155.7 vs 183.2, p<0.05 Mean time between responsiveness to spoken command until discharge from facility (min): 175.6 vs 214.8, p<0.05
Ondansetron			

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Sennaraj 2002 NR NR	RCT, DB	Strabismus repair under gen. anesthesia Mean anesth. duration: 64.15 min	ASA I or II children who had not received drugs with antiemetic properties within 24h of the study	A: Ond 100 mcg/kg iv at end of procedure + Ond 100 mcg/kg at first signs of PONV (prophylactic) B: placebo at end of procedure + Ond 100 mcg/kg at first signs of PONV (therapeutic)

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Sennaraj 2002 NR NR	No	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 6.6 y Range: 2-15 y 58.7% female Ethnicity: NR	Prior PONV: 28%	NR/ NR/ 150

Evidence Table 11. Prevention of postoperative nausea and vomiting: Active-control and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Sennaraj 2002 NR NR	NR/ NR/ 150	Parental satisfaction score (0= not at all satisfied; 10=fully satisfied): 8.2 vs 6.8, p<0.0001	Mean PACU stay (min): 126.5 vs 141.1, p=0.0002

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Adults: active controlled trials						
Dolasetron						
Burmeister 2003	Unclear; done by using an MS Excel macro	NR	Yes	Yes	Yes	Yes
Ondansetron						
Doe 1998	NR	NR	NR	Yes	NR	Yes
Fortney 1998	NR	NR	Yes	Yes	NR	Yes
Gan 2004	Yes	Yes	Yes, but analysis excluded 2 patients (2.6%) that did not complete the study	Yes	Yes	Yes
Jokela 2002	NR	No, sealed envelope technique	Unclear, excluded 21 patients (10.5%)	Yes	NR	Yes
Khalil 1999	Yes	Yes	Yes	Yes	Yes	Yes
Purhonen 2006 (B) NR	Yes	Yes	Yes	Yes	Yes	Yes
Reihner 1999	NR	Yes	No, intraoperative blood loss significantly lower in ond. group; also, only reported baseline characteristics for 95.8%	Yes	NR	Yes

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
Adults: active controlled trials						
Dolasetron						
Burmeister 2003	Yes	No, No, No, No	NR	NR	NR	Fair
Ondansetron						
Doe 1998	Yes	No, No, No, No	NR	Unclear	No	Fair
Fortney 1998	Yes	Yes, No, No, No	No, No	Yes for satisfaction; No for primary outcome (complete response)	No	Fair
Gan 2004	Yes	Yes, No, No, No	None	No, excluded 2 patients (2.6%)	No	Fair
Jokela 2002	Yes	Yes, No, No, No	None	No, excluded 21 patients (10.5%) who didn't complete due to reoperation (n=6) and unspecified protocol violations (n=15)	No	Fair
Khalil 1999	Yes	No, No, No, No	NR	Yes	No	Fair
Purhonen 2006 (B) NR	Yes	Yes, Yes, Yes, Yes	None	NR	No	Fair
Reihner 1999	Yes	Yes, No, No, No	None	No, excluded 9 pts (4.2%) due to protocol violations	No	Fair

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
Adults: active controlled trials	
Dolasetron	
Burmeister 2003	Aventis
Ondansetron	
Doe 1998	
Fortney 1998	Glaxo Wellcome
Gan 2004	NR
Jokela 2002	NR
Khalil 1999	NR
Purhonen 2006 (B) NR	NR
Reihner 1999	NR

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Sandhu 1999	NR	NR	Yes	Yes	Yes	Yes
Steinbrook 1996	Yes	Yes	Unclear, analysis excluded 15 pts (7.5%) that were converted to open surgery	Yes	Yes	Yes
Granisetron						

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
Sandhu 1999	Yes	No, No, No, No	NR	Unclear	No	Fair
Steinbrook 1996	Yes	Yes, No, No, No	None	No, excluded 15 pts (7.5%)	No	Fair
Granisetron						

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
Sandhu 1999	NR
Steinbrook 1996	NR
Granisetron	

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Adults: placebo-controlled trials						
Dolasetron						
Diemunsch 1997	NR	NR	Yes	Yes	NR	Yes
Diemunsch, 1998	NR	NR	Yes	Yes	Yes	Yes
Warriner 1997	NR	NR	Yes	Yes	NR	Yes
Granisetron						
Ondansetron						
Cherian 2001	Yes	Yes	No, women in ondansetron group "slightly heavier" (significance NR; data NR)	Yes	NR	Yes
Lekprasert 1996	NR	NR	No, fewer pts taking ondansetron received intraoperative opioids and more pts taking ondansetron received gastric content suction	Yes	NR	Yes
Scuderi 1999	Yes	NR	Yes	Yes	NR	Yes

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
Adults: placebo-controlled trials						
Dolasetron						
Diemunsch 1997	Yes	No, No, No, No	NR	Unclear, data NR	No	Fair
Diemunsch, 1998	Yes	Yes, No, No, No	NR	No. excluded 4 patients from efficacy analysis	No	Fair
Warriner 1997	Yes	Yes, No, No, No	None	No, but only excluded 1 patient (0.3%) that didn't undergo surgery	No	Fair
Granisetron						
Ondansetron						
Cherian 2001	Yes	No, No, No, No	NR	Yes	No	Fair
Lekprasert 1996	Yes	No, No, No, No	NR	Yes	No	Fair
Scuderi 1999	Yes	No, No, No, No	NR	Yes	No	Fair

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
Adults: placebo-controlled trials	
Dolasetron	
Diemunsch 1997	Hoechst Marion Roussel
Diemunsch, 1998	Research grant from Hoechst Marion Roussel, Strasbourg, France
Warriner 1997	NR; 3 members of study group affiliated with Hoechst Marion Roussel Canada Research Inc.
Granisetron	
Ondansetron	
Cherian 2001	Not funded by the pharmaceutical industry
Lekprasert 1996	NR
Scuderi 1999	NR

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Sun 1997	NR	Yes	No, fewer pts in the group that received ondansetron first had histories of PONV	Yes	Yes	Yes
Tang 1998	Yes	Yes	Yes, but only gave information about 95.1%	Yes	Yes	Yes
Thagaard 2003	Yes	NR	No: placebo patients were older and more of them were undergoing fundoplication; more ondansetron patients had histories of travel sickness and more were undergoing cholecystectomy	Yes	NR	Yes
Pan 2008 Two Sites US	Yes	Yes	Yes	Yes	Yes	Yes
Purhonen 2006 (A) NR	Yes	Yes	Yes	Yes	Yes	Yes
Trescha 2005 Single Center Germany	Yes	Yes	Yes	Yes	Yes	Yes
Palonosetron						
Candiotti 2008 Multiple Sites USA	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
Sun 1997	Yes	No, No, No, No	NR	Yes	No	Fair
Tang 1998	Yes	Yes, No, No, No	None	No, excluded 8 pts (4.8%) with protocol violations	No	Fair
Thagaard 2003	Yes	Yes, No, No, No	Unclear, No	Excluded 6 pts (5.9%)	No	Fair
Pan 2008 Two Sites US	Yes	Yes, No, Yes, No	No	NR	No	Fair
Purhonen 2006 (A) NR	Yes	Yes, Yes, Yes, Yes	None	NR	No	Fair
Trescha 2005 Single Center Germany	Yes	Yes, NR, NR, NR	NR	NR	No	Fair
Palonosetron						
Candiotti 2008 Multiple Sites USA	Yes	Yes, No, Yes, No	No	Yes	No	Fair

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
Sun 1997	NR
Tang 1998	Glaxo Wellcome
Thagaard 2003	Glaxo Wellcome
Pan 2008 Two Sites US	GSK
Purhonen 2006 (A) NR	NR
Trescha 2005 Single Center Germany	NR
Palonosetron	
Candiotti 2008 Multiple Sites USA	Helsinn Healthcare SA MGI PHARMA Inc

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
RS-25259						
Tang 1998 Two Sites US	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
RS-25259						
Tang 1998 Two Sites US	Yes	No, No, No, No	NR	NR	No	Fair

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
RS-25259	
Tang 1998 Two Sites US	Syntex

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Children: active-controlled trials						
Ondansetron						
Bach-Styles 1997	NR	NR	Yes	Yes	Yes	Yes
Davis, A. 1995	NR	NR	Yes	Yes	Yes	Yes
Davis, P. 1995	Yes	Yes	Yes, but unclear if included 7 pts (6.9%) that were excluded for various reasons	Yes	Yes	Yes
Litman 1995	Yes	NR	Yes	Yes	NR	Yes
Rose 1994	Yes	NR	Yes	Yes	Yes	Yes
Splinter 1998	NR	NR	Yes, but excluded 4 pts (1.8%) with major protocol violations	Yes	NR	Yes
Stene 1996	Yes	Yes	Yes, but excluded 12 pts (9%) with breaches in study protocol	Yes	NR	Yes
Granisetron						
Luisi 2006 Brazil University Hospital	NR	NR	NR	Yes	NR	Yes

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
Children: active-controlled trials						
Ondansetron						
Bach-Styles 1997	Yes	No, No, No, No	Unclear, attrition NR	Yes	No	Fair
Davis, A. 1995	Yes	No, No, No, No	NR	Yes	No	Fair
Davis, P. 1995	Yes	Yes, No, No, No	None	Unclear if included 7 pts (6.9%) that were excluded for various reasons	No	Fair
Litman 1995	Yes	No, No, No, No	NR	Unclear	No	Fair
Rose 1994	Yes	No, No, No, No	NR	Yes	No	Fair
Splinter 1998	Yes	Yes, No, No, No	None	No, excluded 4 pts (1.8%) with major protocol violations	No	Fair
Stene 1996	Yes	Yes, No, No, No	None	No, excluded 41 pts (31%); 12 for protocol breaches, 29 for overnight admission due to airway concerns	Yes, overnight admission due to airway concerns	Poor
Granisetron						
Luisi 2006 Brazil University Hospital	Yes	Yes, No, No, No	Unclear	NR	No	Poor

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
Children: active-controlled trials	
Ondansetron	
Bach-Styles 1997	
Davis, A. 1995	Glaxo provided ondansetron
Davis, P. 1995	NR
Litman 1995	NR
Rose 1994	NR
Splinter 1998	NR
Stene 1996	NR
Granisetron	
Luisi 2006 Brazil University Hospital	NR

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

	Internal Validity					
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Children: placebo-controlled trials						
Ondansetron						
Carnahan 1997	NR	NR	Yes	Yes	Yes	Yes
Cieslack 1996	Yes	Yes	Yes	Yes	NR	Yes
Munro 1999	Yes	NR	Yes, but excluded 3 (3.9%) that refused medication	Yes	Yes	Yes
Patel 1997	NR	NR	Yes, excluded 4 pts (0.9%) who never took study medication	Yes	NR	Yes
Granisetron						
Sennaraj 2002	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

		Internal Validity				
Author Year	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomiz-ation exclusions**	**Quality Rating**
Children: placebo-controlled trials						
Ondansetron						
Carnahan 1997	Yes	No, No, No, No	Unclear	Yes	No	Fair
Cieslack 1996	Yes	No, No, No, No	NR	Yes	No	Fair
Munro 1999	Yes	Yes, No, No, No	None	Yes, if the 3 that didn't take study meds are disregarded	No	Fair
Patel 1997	Yes	Yes, No, No, No	None	No, excluded 14 (3.3%) with protocol violations	No	Fair
Granisetron						
Sennaraj 2002	Yes	No, No, No, No	NR	Yes	No	Fair

Evidence Table 12. Quality assessment of active-control and placebo-controlled trials for prevention of postoperative nausea and vomiting

Author Year	Funding
Children: placebo-controlled trials	
Ondansetron	
Carnahan 1997	NR
Cieslack 1996	NR
Munro 1999	SmithKlein Beecham
Patel 1997	Glaxo Wellcome
Granisetron	
Sennaraj 2002	NR

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Kazemi-Kjellberg, 2001	To systematically review the literature on valid data on any treatment of established PONV symptoms, to critically appraise the data, to test for dose-responsiveness for each drug, and to estimate relative efficacy and likelihood for harm of the various treatments	(End dates not reported) Medline from 1966; Embase from 1974; Cochrane Controlled Trials Register 2000, issue 4	Full reports of randomized comparisons of any therapeutic antiemetic intervention (experimental intervention) with placebo, no treatment, or another antiemetic (control intervention) in vomiting or nauseated postoperative patients.	519 granisetron >1539 ondansetron (N not reported for one study)	6 active control trials 10 placebo-controlled trials

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Kazemi-Kjellberg, 2001		Active-control trials: ondansetron 8 mg vs droperidol 1.25 mg (1 trial) ondansetron 0.1 mg/kg vs droperidol 20 mcg/kg (1 trial) ondansetron 4 mg vs metoclopramide 10 mg (1 trial) granisetron 40 mcg/kg vs droperidol 20 mcg/kg vs metoclopramide 0.2 mg/kg (2 trials) ondansetron 8 mg vs droperidol 1 mg vs alizapride 100 mg (1 trial) Placebo-controlled trials: dolasetron 12.5 mg, 25 mg, 50 mg, or 100 mg (2 trials) granisetron 0.1 mg, 1 mg, or 3 mg (1 trial) 4-10) ondansetron 0.1 mg/kg, 1 mg, 4 mg, 8 mg, or 16 mg (7 trials)

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Main results early efficacy (within 6 hours)	Main results late efficacy (within 24 hours)
Kazemi-Kjellberg, 2001	**Relative risk (95% CI); NNT (95% CI)** Prevention of further nausea Granisetron 0.1 mg: 2.41 (1.56 to 3.73); 4.3 (3.0 to 7.9) Granisetron 1 mg: 2.45 (1.59 to 3.79); 4.2 (2.9 to 7.4) Granisetron 3 mg: 2.56 (1.66 to 3.95); 3.9 (2.7 to 6.6) Ondansetron 8 mg: 2.80 (1.28 to 6.14); 2.0 (1.3 to 4.6) Prevention of further vomiting Dolasetron 12.5 mg: 2.03 (1.46 to 2.82); 3.6 (2.5 to 6.1) Dolasetron 25 mg: 1.85 (1.31 to 2.60); 4.3 (2.8 to 9.0) Dolasetron 50 mg: 1.77 (1.26 to 2.50); 4.7 (3.0 to 11) Dolasetron 100 mg: 1.86 (1.33 to 2.61); 4.3 (2.8 to 8.5) Granisetron 0.1 mg: 2.02 (1.45 to 2.80); 3.7 (2.6 to 6.5) Granisetron 1 mg: 2.20 (1.60 to 3.03); 3.2 (2.3 to 4.9) Granisetron 3 mg: 2.28 (1.66 to 3.13); 3.0 (2.2 to 4.5) Ondansetron 0.1 mg: 1.40 (0.50 to 3.95); NS Ondansetron 1 mg: 1.88 (1.39 to 2.55); 3.7 (2.6 to 6.6) Ondansetron 4 mg: 2.10 (1.58 to 2.79); 3.3 (2.5 to 5.1) Ondansetron 8 mg: 1.84 (1.45 to 2.35); 3.7 (2.7 to 5.8) Ondansetron 16 mg: 3.43 (1.43 to 8.23); 2.6 (1.7 to 6.4) Ondansetron 0.1 mg/kg: 2.27 (1.83 to 2.81); 2.3 (1.9 to 2.9)	**Relative risk (95% CI); NNT (95% CI)** Prevention of further nausea Granisetron 0.1 mg: 2.08 (1.22 to 3.53); 7.3 (4.3 to 24) Granisetron 1 mg: 2.35 (1.41 to 3.93); 5.8 (3.7 to 13) Granisetron 3 mg: 2.88 (1.75 to 4.75); 4.2 (2.9 to 7.2) Prevention of further vomiting Dolasetron 12.5 mg: 2.88 (1.83 to 4.54); 4.8 (3.5 to 7.8) Dolasetron 25 mg: 2.54 (1.59 to 4.04); 6.0 (4.1 to 11) Dolasetron 50 mg: 2.93 (1.86 to 4.61); 4.8 (3.5 to 7.7) Dolasetron 100 mg: 2.54 (1.60 to 4.04); 5.9 (4.1 to 11) Granisetron 0.1 mg: 1.96 (1.30 to 2.95); 5.3 (3.4 to 13) Granisetron 1 mg: 2.35 (1.59 to 3.47); 3.8 (2.7 to 6.5) Granisetron 3 mg: 2.50 (1.69 to 3.68); 3.4 (2.5 to 5.5) Ondansetron 0.1 mg: 1.00 (0.32 to 3.12); NS Ondansetron 1 mg: 2.04 (1.51 to 2.75); 4.8 (3.5 to 7.9) Ondansetron 4 mg: 2.29 (1.73 to 3.02); 4.0 (3.0 to 5.7) Ondansetron 8 mg: 2.23 (1.66 to 3.00); 4.1 (3.1 to 6.2) Ondansetron 16 mg: 3.20 (1.32 to 7.76); 2.9 (1.8 to 8.3) Ondansetron 0.1 mg/kg: 3.14 (2.21 to 4.48); 2.8 (2.2 to 3.7)

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Subgroups	Adverse events
Kazemi-Kjellberg, 2001	No information	Headache was the most frequently-reported adverse event, but no comparison of different antiemetics was made, and results not reported separately by drug. Event rates and relative risks (95% CI) vs placebo by dose: Low dose (dolasetron 12.5 mg, granisetron 0.1 mg, tropisetron 0.5 mg, ondansetron 1 mg): 7.7% vs 10.4%; RR 0.75 (0.51 to 1.10) Medium dose (dolasetron 25-50 mg, granisetron 1 mg, tropisetron 2 mg, ondansetron 4 mg): 9.3% vs 9.3%; RR 1.09(0.78 to 1.52) High dose (dolasetron 100 mg, granisetron 3 mg, tropisetron 5 mg, ondansetron 8 mg): 13.3% vs 9.9%; RR 1.36 (0.98 to 1.88)

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Tramer, 1997	To test the evidence for a dose-response with ondansetron for treatment of PONV and establish whether differences in efficacy between doses are of clinical relevance	Medline (1991-January 22, 1996)	Randomized controlled trials that evaluated the effect of ondansetron compared with a control (placebo, no treatment, or another antiemetic) on established PONV and reported the outcome in dichotomous form.	1,252	Seven randomized controlled trials (4 ondansetron vs placebo, 2 ondansetron vs IV droperidol, 1 ondansetron vs metoclopramide)

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Tramer, 1997	Four trials in 1043 adults (82% female) who complained of nausea or vomited after general anesthesia; one trial in 100 gynecology patients; one trial in 29 vomiting children, one trial in 80 adults undergoing major abdominal surgery.	Four trials of a single iv dose of ondansetron 1 mg, 4 mg, or 8 mg with placebo; One trial of iv ondansetron 8 mg vs iv droperidol 1.25 mg (both antiemetics could be administered up to 3 times in 24 hours); One trial of iv ondansetron 100 mcg/kg vs iv droperidol 20 mcg/kg (children); One trial of iv ondansetron 4 mg vs iv metoclopramide 10 mg

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Main results early efficacy (within 6 hours)	Main results late efficacy (within 24 hours)
Tramer, 1997	**Odds Ratio (95% CI); NNT (95% CI)** Complete control of further nausea or vomiting, or both *Ondansetron vs Placebo* Ondansetron 1 mg: 3.0 (1.8 to 4.8); 3.8 (2.6 to 6.6) Ondansetron 4 mg: 3.5 (2.1 to 5.8); 3.2 (2.3 to 5.2) Ondansetron 8 mg: 3.8 (2.5 to 5.8); 3.1 (2.4 to 4.5) *Ondansetron vs droperidol:* Ondansetron 8 mg X 3 vs droperidol 1.25 mg X 3: 0.7 (0.3 to 1.6); NS Ondansetron 100 mcg/kg vs droperidol 20 mcg/kg: 0.6 (0.1 to 3.4); NS0.7 (0.3 to 1.4); NS Trials combined: 0.7 (0.3 to 1.4); NS *Ondansetron 4 mg vs metoclopramide 10 mg* 2.3 (0.7 to 6.7); NS	**Odds Ratio (95% CI); NNT (95% CI)** Complete control of further nausea or vomiting, or both *Ondansetron vs Placebo* Ondansetron 1 mg: 2.7 (1.8 to 3.9); 4.8 (3.5 to 7.9) Ondansetron 4 mg: 3.2 (2.2 to 4.7); 3.9 (3.0 to 5.7) Ondansetron 8 mg: 3.1 (2.1 to 4.5); 4.1 (3.1 to 6.2) *Ondansetron 4 mg vs metoclopramide 10 mg* 1.8 (0.8 to 4.3); NS

Evidence Table 13. Treatment of established postoperative nausea and vomiting: Systematic reviews

Author Year	Subgroups	Adverse events
Tramer, 1997	No information. 82% of patients in included trials were women.	No information

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Active-controlled trials				
Candiotti 2007 Single Center	RCT Parallel Active	Nonemergency surgery, not otherwise specified	History of PONV: 40% History of motion sickness: 35% No ETOH use: 86% No Smoking: 86% Average BMI: 26.5	Adult females between 18 and 64 years with an ASA I-III status, scheduled to undergo nonemergency surgery, requiring general anesthesia of at least 30 minutes duration

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Active-controlled trials			
Candiotti 2007 Single Center	Patients with known hypersensitivity to 5HT3 drugs, BMI ≥35, significant systemic disease patients who had nausea or vomiting 24 hours before study, any patient taking antiemetics, steroids, H_2 antagonists, anticholinergics, antihistamines, butyrophenones, phenothiazines, or metoclopramide within 24 hours before surgery	a) ondansetron 4mg b) granisetron 1mg c) granisetron 0.1mg	All patients received midazolam 1-2mg, thiopental (3-5mg/kg) was used for induction and succinylcholine (0.5-1mg/kg), rocuronium (0.5-1.2mg/kg). Or vecuronium (0.07-0.1mg/kg) were used to facilitate endotracheal intubation

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Active-controlled trials				
Candiotti 2007 Single Center	no/no	43.08 100% women NR	NR/NR/250	7/NR/88

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Active-controlled trials		
Candiotti 2007 Single Center	Ondansetron vs Granisetron 0.1mg vs Granisetron 1.0mg Efficacy of Rescue Drugs for PONV Complete Response: 57% vs 68% vs 60% Rescue Failure-Further treatment required: 43% vs 32% vs 40% 30-Minute Response to Rescue Drug Nausea score time: 0 min: 6.1 vs 5.5 vs 6.1 Nausea score time: 10 min: 5.2 vs 3.8 vs 5.0 Nausea score time: 20 min: 4.6 vs 3.0 vs 3.9 Nausea score time: 30 min: 3.2 vs 1.8 vs 2.1 Patients with vomiting +/- nausea (in 30-min rescue period) Complete Response: 47% vs 75% vs 43% Rescue Failure-Further treatment required: 53% vs 25% vs 57%	NR

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Coloma 2002 Single Center	DB RCT Parallel Active	Laparoscopic cholecystectomy 68 (76%) Gynecologic laparoscopy 22 (24%)	History of PONV 22(24%) History of motion sickness 15(17%) History of dizziness 18(20%)	Healthy outpatients scheduled for laparoscopic surgery with general anesthesia; patients were enrolled if they complained of nausea or vomiting in the postanesthesia care unit or in the step-down (phase II) recovery unit.
Dabbous 2001 Single Center	DB RCT Parallel Active	Laparoscopic cholecystectomy: 55% Laparoscopic herniorrhaphy: 7% Laparoscopic Appendectomy: 10% Diagnostic Laparoscopy 48: 28%	History of PONV 46 (27%) History of motion sickness 9 (5%)	ASA Class I and II patients undergoing laparoscopic surgery who developed PONV.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Coloma 2002 Single Center	Patients were excluded if they had taken an antiemetic agent within 24 hours prior to the operation, were pregnant, experiencing menstrual symptoms, had previous experience with acustimulaiton therapy, had a permanent cardiac pacemaker, or experienced vomiting or retching within 24 hours before surgery.	a) ondansetron 4mg b) ReliefBand c) combination ondansetron + ReliefBand 4mg	Prophylactic antiemetic (e.g., 10mg IV metoclopramide or 0.625 mg IV droperidol) administered to all patients after induction of anesthesia. Fentanyl intraoperatively and fentanyl and morphine postoperatively
Dabbous 2001 Single Center	Patients receiving pre- or intraoperative antiemetics; postoperative pain scores >5, patients who received postoperative narcotics, pregnant females, patients with a nasogastric tube remaining postoperatively, and sedation scores >1 (degree of sedation was assessed as 1=awake, 2=drowsy, 3=asleep).	a) ondansetron 4 mg b) droperidol 1.25 mg c) metoclopramide 10 mg	All patients were premedicated with glycopyrrolate 0.2 mg IM and diazepam 5 mg PO 45 minutes prior to induction of anesthesia.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Coloma 2002 Single Center	no/no	40 92% women Not reported	268/ 90/ 90	NR/ 7/ 90
Dabbous 2001 Single Center	no/no	44 77% women Not reported	NR/ NR/ 173	NR/ NR/ 173

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Coloma 2002 Single Center	Ondansetron vs Acustimulation vs Combination Complete response at 2 hours Complete response at 2 hours Number (%): 17(57) vs 12 (40) vs 22 (73) Ondansetron vs acustimulation, p: NS Combination vs acustimulation, p: <0.05 Post-treatment retching Post treatment retching Number(%): 10(33) vs 8(27) vs 10(33) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS Post-treatment vomiting Post-treatment vomiting Number(%): 10(33) vs 17(57) vs 8(27) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: <0.05 Time from treatment to rescue antiemetic Time from treatment to rescue antiemetic (minutes) Number(SD): 51(43) vs 63(53) vs 58(37) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS Admitted for PONV Admitted for PONV Number(%): 0(0) vs 0(0) vs 0(0) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS Highest nausea score Highest nausea score (0-10) Score(Range): 5(0-8) vs 5(0-10) vs 6(0-10) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS	ondansetron vs acustimulation pruritus: 3% vs 0% (NS) difficulty voiding: 3% vs 3% (NS) headaches: 0 vs 0 (NS) dizziness: 0% vs 3% (NS) patient felt tingling sensation: 30% vs 57% (NS)
Dabbous 2001 Single Center	ondansetron vs droperidol vs metoclopramide % decrease in nausea scores at 10 minutes: 55.4% vs 41.2% vs 20.2% (p<0.05 between all groups) % decrease in nausea scores at 30 minutes: 84.3% vs 80.0% vs 41.2% (p<0.05 for metoclopramide vs other groups) Need for rescue antiemetic: 5 (8.8%) vs 6 (10.5%) vs 25 (42.3%) p<0.05 for metoclopramide vs other groups, no other statistical differences	ondansetron vs droperidol vs metoclopramide sedation: 0% vs 25% vs 0% headache: 14% vs 10% vs 8% dizziness: 12% vs 10% vs 10% malaise: 12% vs 17% vs 10% agitation: 4% vs 5% vs 5% extrapyramidal symptoms: 0% vs 0% vs 0%

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Fujii 2000 Single center	DB RCT Parallel Active	Abdominal hysterectomy: 76% Vaginal hysterectomy: 5% Salpingo-oophorectomy: 19%	None had a history of motion sickness or previous PONV.	Women undergoing major gynecological operations, ASA physical status I or II, ages 23 to 63, with nausea lasting >10 minutes with or without emesis (vomiting, retching) within 3 hours after recovery from general anesthesia.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Fujii 2000 Single center	Patients with gastrointestinal disease, those who had a history of motion sickness, previous postoperative nausea and vomiting, or both; and those who had taken an antiemetic medication within 24 hours before the operation.	a) granisetron 40mcg/kg b) droperidol 20mcg/kg c) metoclopramide 0.2mg/kg	None reported

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Fujii 2000 Single center	no/no	44 100% women NR	NR/ NR/ 120	0/ 0/ 120

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Fujii 2000 Single center	Granisetron vs droperidol vs metoclopramide Complete control of PONV (no emesis and no rescue medication) for 24 hours 88% vs 55% vs 50% (p=0.002 for granisetron vs droperidol, 0.00? for granisetron vs metoclopramide) No nausea 92% vs 80% vs 75% (p=0.192 for granisetron vs droperidol, 0.06 for granisetron vs metoclopramide) No retching 100% vs 95% vs 90% (p=0.492 for granisetron vs droperidol, 0.11 for granisetron vs metoclopramide) No vomiting 95% vs 77% vs 77% (p=0.047 for granisetron vs droperidol, 0.04 for granisetron vs metoclopramide) Severity of nausea (median and range) 0 (0-4) vs 0 (0-10) vs 0 (0-10) (p=0.011 for granisetron vs droperidol, 0.00? for granisetron vs metoclopramide) Patient satisfaction rating (median and range) 7 (0-10) vs 2.5 (0-10) vs 3 (0-10) (p=0.001 for granisetron vs droperidol, 0.00? for granisetron vs metoclopramide)	Incidence of adverse events (states "such as headache and dizziness): granisetron: 13% droperidol: 13% metoclopramide: 10% (NS) sedation level (median and range): granisetron: 1 (0-5) droperidol: 1 (0-5) metoclopramide: 1 (0-5) p=0.70 No extrapyramidal symptoms observed in any group.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Fujii 2003 Single Center	DB RCT Parallel Active	Partial mastectomy: 12% Partial mastectomy w/axillary dissection: 9% Modified radical mastectomy: 9% Modified Radical mastectomy w/axillary dissection: 69%	History of PONV: 4% History of motion sickness: 9%	Women with ASA physical status I (no organic, physiologic, biochemical, or psychiatric disturbance) who were experiencing nausea and/or emesis after recovery from general anaesthesia for breast surgery.
Unlugenc 2003 Single Center	RCT Parallel Active	Abdominal: 88 (73%) Gynecological: 32 (27%)	No patients with a history of motion sickness or previous postoperative vomiting.	Men and women, ASA Class I and II, ages 18 to 65, who were scheduled for elective gynecological or abdominal surgery under general anesthesia. Patients were included if nausea or vomiting occurred during the first 2 hours in the Postanesthesia Recovery Unit.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Fujii 2003 Single Center	Patients who had gastrointestinal disease, had taken antiemetics within 24 hours before surgery, or who were pregnant, menstruating, or receiving hormonal therapy.	a) granisetron 40mcg/kg b) droperidol 20mcg/kg c) metoclopramide 0.2mg/kg	Patients received no medication before anesthesia. If the patient complained of pain postoperatively, analgesia was provided with indomethacin 50 mg administered rectally.
Unlugenc 2003 Single Center	A history of motion sickness, previous postoperative vomiting, known major organ disease, ASA>II, body weight >100% over ideal, a history of alcohol or drug abuse, or receipt of an antiemetic agent within 24 hours.	a) ondansetron 4mg b) propofol 15mg c) midazolam 1mg d) midazolam 2mg	IV piroxicam (0.5 mg kg -1) for postoperative pain relief. If no pain relief was obtained, increments of fentanyl (0.5-1 mcg -1) IV were given.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Fujii 2003 Single Center	no/no	53 100% women Not reported	80/ 75/ 75	NR/ NR/ 75
Unlugenc 2003 Single Center	no/no	45 53% women Not reported	453/ NR/ 120	NR/ NR/ 120

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Fujii 2003 Single Center	Granisetron vs droperidol vs metoclopramide Emesis free for 24 hours after administration of study drug Number: 88% vs 64% vs 56% droperidol vs granisetron, p: 0.047 metoclopramide vs granisetron, p: 0.013 Severity of nausea (0=no nausea; 10=severe nausea) Median (Range): 4 (4-6) vs 8 (5-10) vs 8 (5-10) droperidol vs granisetron, p: 0.028 metoclopramide vs granisetron, p: 0.025 Nausea in 24 hours after administration of study drug: 12% vs 32% vs 36% droperidol vs granisetron, p: 0.085 metoclopramide vs granisetron, p: 0.047 Retching in 24 hours after administration of study drug Number: 0% vs 4% vs 4% droperidol vs granisetron, p: 0.50 metoclopramide vs granisetron, p: 0.50 Vomiting in 24 hours after administration of study drug Number: 8% vs 16% vs 20% droperidol vs granisetron, p: 0.083 metoclopramide vs granisetron, p: 0.027	Headache was most frequently reported adverse event. Incidence of headache (8%-12%) did not differ between groups. No other clinically significant adverse events were observed in any group.
Unlugenc 2003 Single Center	Ondansetron vs propofol vs midazolam 1 mg vs midazolam 2 mg % change in mean nausea score (1=none; 2=mild; 3=moderate; 4=severe; 5=worst) 5 minutes after treatment: 54.2% vs 54.2% vs 50.0% vs 56.0% 15 minutes after treatment: 56.5% vs 58.3% vs 57.7% vs 60.0% 30 minutes after treatment: 56.5% vs 58.3% vs 57.7% vs 60.0% 60 minutes after treatment: 56.5% vs 58.3% vs 61.5% vs 60.0% 120 minutes after treatment: 56.5% vs 58.3% vs 61.5% vs 60.0% 360 minutes after treatment 56.5% vs 58.3% vs 61.5% vs 60.0% Need for second dose of antiemetic 3.3% vs 13.3% vs 43.3% vs 16.6%	Two patients in ondansetron group (7%) complained of headache after a single dose. No further adverse effects attributable to medication were observed.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Winston 2003 Single Center	RCT Parallel Active	Laparoscopic bilateral tubal ligation 40 (40%) Diagnostic laparoscopy 41 (41%) Operative laparoscopy 19 (19%)	No patients with a history of PONV.	Women with ASA physical status I or II, older than 18 years scheduled to undergo diagnostic laparoscopy, operative laparoscopy, or laparoscopic bilateral tubal occlusion.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Winston 2003 Single Center	Subjects excluded if they reported sensitivity to isopropyl alcohol or ondansetron, had an impaired ability to breathe through the nose, were pregnant or using the medication disulfiram, reported preexisting nausea, or reported any antiemetic use within 24 hours before surgery. Patients who reported a history of significant PONV, defined as nausea or vomiting resistant to antiemetic therapy, or had a history of alcoholism were excluded.	a) inhaled isopropyl alcohol 70% b) ondansetron 4mg	None reported

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Winston 2003 Single Center	no/no	NR 100% women Not reported	NR/ NR/ 100	NR/ NR/ 100

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Winston 2003 Single Center	Ondansetron vs isopropyl alcohol Median verbal numeric rating scale scores (0=no nausea, 10=worst nausea imaginable) first complaint: 8.00 vs 8.00 (p=0.854) 5 minutes: 8.00 vs 3.00 (p=0.002) 10 minutes: 5.00 vs 3.00 (p=0.015) 15 minutes: 5.00 vs 2.00 (p=0.036) 30 minutes: 0.00 vs 1.50 (p=0.469) 45 minutes: 0.00 vs 0.00 (p=0.522) 60 minutes: 0.00 vs 0.00 (p=0.871) Mean time to 50% relief of PON: 27.7 minutes vs 6.3 minutes (p=0.002) Mean stay time in PACU: 60.3 vs 58.4 minutes (NS) Mean stay time in SDS unit: 124.2 vs 139.2 minutes (NS)	Not reported

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Placebo-controlled trials				
Fujii 2004a Single Center	DB RCT Parallel Placebo	Abdominal hysterectomy	No patients with a history of motion sickness and/or PONV	Women ages 33 to 66 years who were categorized as ASA physical status I (no organic, physiologic, biochemical, or psychiatric disturbances) and were experiencing nausea lasting >10 minutes and/or retching or vomiting within 3 hours after recovery from anesthesia in the postanesthetic care unit for abdominal hysterectomy with or without salpingo-oophorectomy.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Placebo-controlled trials			
Fujii 2004a Single Center	Antiemetics given <= 24 hours before surgery, gastrointestinal disease, menstruation, and a history of motion sickness and/or postoperative emetic symptoms.	a) granistron IV 10 mcg/kg b) granistron IV 20 mcg/kg c) granistron IV 40 mcg/kg d) granistron IV 100 mcg/kg e) placebo (saline 5 mL)	None reported

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Placebo-controlled trials				
Fujii 2004a Single Center	no/no	44 100% women NR	105/ 100/ 100	0/ 0/ 100

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Placebo-controlled trials		
Fujii 2004a Single Center	Complete control of emetic symptoms over 24 hours (p vs placebo) granisetron 10 mcg/kg: 35% (p=0.500) granisetron 20 mcg/kg: 85% (p=0.001) granisetron 40 mcg/kg: 85% (p=0.001) granisetron 100 mcg/kg: 80% (p=0.002) placebo: 30% No nausea over 24 hours (p vs placebo) granisetron 10 mcg/kg: 65% (p=1.000) granisetron 20 mcg/kg: 90% (p=0.064) granisetron 40 mcg/kg: 90% (p=0.064) granisetron 100 mcg/kg: 90% (p=0.064) placebo: 65% No vomiting over 24 hours (p vs placebo) granisetron 10 mcg/kg: 70% (p=0.500) granisetron 20 mcg/kg: 90% (p=0.064) granisetron 40 mcg/kg: 90% (p=0.064) granisetron 100 mcg/kg: 90% (p=0.064) placebo: 65% Severity of nausea, median (range); 0=none, 10=severe (p vs placebo) granisetron 10 mcg/kg: 8 (6-10) (p=0.430) granisetron 20 mcg/kg: 5 (4-6) (p=0.038) granisetron 40 mcg/kg: 4.5 (4-5) (p=0.038) granisetron 100 mcg/kg: 8 (6-10) (p=0.038) placebo: 65%: 8 (7-10) Rescue medication used (p vs placebo) granisetron 10 mcg/kg: 20% (p=0.500) granisetron 20 mcg/kg: 0% (p=0.024) granisetron 40 mcg/kg: 0% (p=0.024) granisetron 100 mcg/kg: 0% (p=0.024) placebo: 25%	The most frequent adverse event was headache. Incidence (5%-10%) did not differ significantly between groups (data not reported).

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Fujii 2004b Single Center	DB RCT Parallel Placebo	Laparoscopic cholecystectomy Indication for surgery: Symptomatic cholelithiasis: 77% cholecystic polyp: 12% chronic cholecystitis: 11%	No patients with a history of motion sickness and/or PONV	Male and female patients ages 23 to 68 years with ASA physical status I (no organic, physiologic, biochemical, or psychiatric disturbance) who were experiencing nausea lasting >10 minutes or retching or vomiting with 3 hours after recovery from general anesthesia for laparoscopic cholecystectomy.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Fujii 2004b Single Center	Patients who received antiemetics within 24 hours before surgery, who had gastrointestinal disease, who had a history of motion sickness and/or PONV. Patients who were pregnant, possibly pregnant, breastfeeding, or menstruating.	a) granistron IV 10 mcg/kg b) granistron IV 20 mcg/kg c) granistron IV 40 mcg/kg d) granistron IV 80 mcg/kg e) placebo	Indomethacin 50 mg if the patient experienced pain postoperatively.

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Fujii 2004b Single Center	no/no	47 60% women NR	105/100/100	NR/NR/100

Evidence Table 14. Treatment of established postoperative nausea and vomiting: Comparative clinical trials

Author Year Setting	Results	Adverse events
Fujii 2004b Single Center	Emesis free over 24 hours (p vs placebo) granisetron 10 mcg/kg: 55% (NS) granisetron 20 mcg/kg: 85% (p=0.02) granisetron 40 mcg/kg: 90% (p=0.007) granisetron 80 mcg/kg: 90% (p=0.007) placebo: 50% No nausea over 24 hours (p vs placebo) granisetron 10 mcg/kg: 65% (NS) granisetron 20 mcg/kg: 90% (NS) granisetron 40 mcg/kg: 90% (NS) granisetron 80 mcg/kg: 90% (NS) placebo: 70% No vomiting over 24 hours (p vs placebo) granisetron 10 mcg/kg: 75% (NS) granisetron 20 mcg/kg: 95% (NS) granisetron 40 mcg/kg: 95% (NS) granisetron 80 mcg/kg: 95% (NS) placebo: 80% Severity of nausea, median (range); 0=none, 10=severe (p vs placebo) granisetron 10 mcg/kg: 8 (6-10) (NS) granisetron 20 mcg/kg: 5 (4-6) (p=0.043) granisetron 40 mcg/kg: 5 (4-6) (p=0.043) granisetron 80 mcg/kg: 5.5 (4-5) (p=0.043) placebo: 8.5 (7-10)	The most frequent adverse event was headache. Incidence (5%-10%) did not differ significantly between groups (data not reported). The next most common adverse events were dizziness (≤5%) and constipation (≤5%). Severity of adverse events was not evaluated.

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established postoperative nausea and vomiting

Author Year Setting (subpopulation)	Trial type	Exclusion criteria	Run-in/ Wash out	Screened/ Eligible/ Enrolled
Candiotti 2007 Single Center	Active	Patients with known hypersensitivity to 5HT3 drugs, BMI ≥35, significant systemic disease patients who had nausea or vomiting 24 hours before study, any patient taking antiemetics, steroids, H_2 antagonists, anticholinergics, antihistamines, butyrophenones, phenothiazines, or metoclopramide within 24 hours before surgery	no/no	NR/NR/250
Coloma 2002 Single Center	Active	Patients were excluded if they had taken an antiemetic agent within 24 hours prior to the operation, were pregnant, experiencing menstrual symptoms, had previous experience with acustimulaiton therapy, had a permanent cardiac pacemaker, or experienced vomiting or retching within 24 hours before surgery.	no/no	268/90/90
Dabbous 2001 Single Center	Active	Patients receiving pre- or intraoperative antiemetics; postoperative pain scores >5, patients who received postoperative narcotics, pregnant females, patients with a nasogastric tube remaining postoperatively, and sedation scores >1 (degree of sedation was assessed as 1=awake, 2=drowsy, 3=asleep).	no/no	NR/NR/173
Fujii 2003 Single Center	Active	Patients who had gastrointestinal disease, had taken antiemetics within 24 hours before surgery, or who were pregnant, menstruating, or receiving hormonal therapy.	no/no	80/75/75
Unlugenc 2003, 2004 Single Center	Active	A history of motion sickness, previous postoperative vomiting, known major organ disease, ASA>II, body weight >100% over ideal, a history of alcohol or drug abuse, or receipt of an antiemetic agent within 24 hours.	no/no	453/NR/120
Winston 2003 Single Center	Active	Subjects excluded if they reported sensitivity to isopropyl alcohol or ondansetron, had an impaired ability to breathe through the nose, were pregnant or using the medication disulfiram, reported preexisting nausea, or reported any antiemetic use within 24 hours before surgery. Patients who reported a history of significant PONV, defined as nausea or vomiting resistant to antiemetic therapy, or had a history of alcoholism were excluded.	no/no	NR/NR/100

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established postoperative nausea and vomiting

Author Year Setting (subpopulation)	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Candiotti 2007 Single Center	7/NR/88	Yes	Yes	No similar on age or ETOH use, but similar on all other characteristics	Yes	NR	NR	Yes No Yes No	No
Coloma 2002 Single Center	NR/7/90	Yes	NR	No	Yes	Yes	Yes	Yes No Yes No	No
Dabbous 2001 Single Center	NR/NR/173	Yes	NR	Yes	Yes	Yes	Yes	No No No No	No
Fujii 2003 Single Center	NR/NR/75	Yes	NR	Yes	Yes	Yes	Yes	No No No No	No
Unlugenc 2003, 2004 Single Center	NR/NR/120	Yes	NR	Yes	Yes	Yes	Yes	No No No No	Not reported
Winston 2003 Single Center	NR/NR/100	NR	NR	Yes	Yes	Yes	Yes	No No No No	No

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established postoperative nausea and vomiting

Author Year Setting (subpopulation)	Intention-to-treat analysis	Post randomization exclusions	Quality rating	Controlled group standard of care	Funding
Candiotti 2007 Single Center	Unclear	No	Fair	No	NR
Coloma 2002 Single Center	Yes	No	Fair	Yes	GlaxoSmithKline and Woodside Biomedical
Dabbous 2001 Single Center	Yes (but 24-hour results not reported?)	No	Fair	Yes	Not reported
Fujii 2003 Single Center	Yes	No	Fair	Yes	Not reported
Unlugenc 2003, 2004 Single Center	Unable to determine	Unable to determine	Fair	Yes	Not supported by external funds
Winston 2003 Single Center	Yes	No	Fair	Yes	Not reported

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established postoperative nausea and vomiting

Author Year Setting (subpopulation)	Trial type	Exclusion criteria	Run-in/ Wash out	Screened/ Eligible/ Enrolled
Fujii 2004 Single Center	Placebo	Antiemetics given <= 24 hours before surgery, gastrointestinal disease, menstruation, and a history of motion sickness and/or postoperative emetic symptoms.		105/100/100
Tzeng 2003 Single Center	Placebo	Patients with a history of PONV, motion sickness, or gastrointestinal disorders, a major systemic disease (e.g., hypertension, diabetes mellitus, and morbid obesity), contraindications to epidural anesthesia and analgesia, chronic opioid use, or who had received an antiemetic within 48 hours before surgery. Patients who needed rescue analgesics for pain during surgery were also excluded.		NR/NR/70

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established postoperative nausea and vomiting

Author Year Setting (subpopulation)	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Fujii **2004** Single Center		Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No
Tzeng **2003** Single Center		Yes	NR	unable to determine	Yes	Yes	Yes	Yes No No No	No

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established postoperative nausea and vomiting

Author Year Setting (subpopulation)	Intention-to-treat analysis	Post randomization exclusions	Quality rating	Controlled group standard of care	Funding
Fujii 2004 Single Center	Yes	No	Fair		Not reported
Tzeng 2003 Single Center	No	Yes	Fair		Not reported

Evidence Table 16. Long term uncontrolled intervention studies of safety and adverse events

Author Year Country	Exposure duration	5-HT3 Antagonist	Concomitant medication	Ascertainment techniques	Age (mean) Gender -% female Ethnicity
Adults					
Charbit 2005	Single dose	Ondansetron 4mg iv	NR	ECG readings	45 years 60% female Ethnicity NR
Kirchner 1993	Unclear	Dolasetron 10-50 mg iv	NR	Adverse events checklist (unspecified) was completed 24 hours after last dolasetron dose	46.9 years 32.2% female Ethnicity NR
Watanabe 1995	Unclear; 5.9 courses of chemotherapy (mean)	Granisetron 50 mg/kg iv	NR	NR	22.8 years 84.7% Ethnicity NR
Khoo 1993	Up to 6 days	Ondansetron 1 mg/hr iv plus 8 mg po bid-tid	Dexamethasone	At end of assessment period, patients asked if they experienced any side effects	43 years 20% Ethnicity NR
Manso Ribiero 1993	3-5 days	Ondansetron	NR	NR	NR (62.7% < age 60 years) 53% Ethnicity NR
Marty 1989	24 hours	Ondansetron 8 mg iv, then 1 mg/hr	NR	NR	Median=54 years 35.7% female Ethnicity NR

Evidence Table 16. Long term uncontrolled intervention studies of safety and adverse events

Author Year Country	Hesketh Score Primary malignancy	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed	Safety Outcomes
Adults				
Charbit **2005**	5 NR	NR NR 85	NR NR 85	Significant QTc changes observed during the 15 minutes after antiemetic drug administration (p<0.0001) Maximal QTc lengthening: 17 +/- 9ms (droperidol) vs 20 +/- 13 ms ondansetron (p<0.0001 for both compared to baseline)
Kirchner **1993**	5 Lung	NR NR 31	NR NR 31	Thrombocytopenia: 1 patient Septicemia that led to death: 1 patient Both attributed to cytotoxic chemotherapy and/or cancer
Watanabe **1995**	5 Bone and soft-tissue sarcoma	NR NR 72	NR NR Unclear	One patient reported chest pressure
Khoo **1993**	5 NR	NR NR 25	NR NR 25	Encephalopathy: 1 patient
Manso Ribiero **1993**	Unclear NR	NR NR NR	NR NR 145	Major adverse events (considered unrelated by investigators): 5 patients (included death, shock, respiratory failure, central nervous system hemorrhage and fever, vomiting and jaundice)
Marty **1989**	5 Cancer site=other	NR NR 28	2 0 26	Thrombocytopenia: 3 (11.5%) Another patient experienced palpitations of moderate severity accompanied by throbbing, sweating, and arterial hypertension None of the events were considered due to ondansetron

Evidence Table 16. Long term uncontrolled intervention studies of safety and adverse events

Author Year Country	Exposure duration	5-HT3 Antagonist	Concomitant medication	Ascertainment techniques	Age (mean) Gender -% female Ethnicity
Children					
Craft 1995	Single dose	Granisetron 40 mg/kg iv	None		Mean age NR (range=2-16 yrs) 45% female 97.5% Caucasian 2.5% Asian
Hewitt 1993	3-5 days	Ondansetron iv (dose calculated by surface area; max=8 mg), then 24 mg po (tid)	NR	NR	8.8 years Gender/ethnicity NR
Pinkerton 1990	5 days	Ondansetron 5 mg/m2 iv, then po (dose calculated by surface area; max=24 mg (tid))	NR	NR	9.5 years 50% female Ethnicity NR

Evidence Table 16. Long term uncontrolled intervention studies of safety and adverse events

Author Year Country	Hesketh Score Primary malignancy	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed	Safety Outcomes
Children				
Craft **1995**	Unclear (dosages NR) Acute lymphoblastic leukemia	NR NR 40	NR NR NR	Hyponatremia: 1 patient
Hewitt **1993**	Unclear NR	NR NR 200	25 0 200	Withdrawal due to major adverse events: 3 patients Patient 1: moderate headaches Patient 2: transient nystagmus, diplopia and ataxia Patient 3: renal failure
Pinkerton **1990**	Group A: 5 Group B: 4 Group 3: 4 Solid tumors	NR NR 30	NR NR NR	One child developed hepatitis

Evidence Table 17. Quality assessment of long term uncontrolled intervention studies of safety and adverse events

Author Year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Overall adverse event assessment quality
Kirchner 1993	Unclear	Unclear	No	No	Unclear	No	Poor
Watanabe 1995	Unclear	Unclear	No	No	Unclear	No	Poor
Khoo 1993	Unclear	None	No	No	Unclear	No	Poor
Manso Ribiero 1993	Unclear	Unclear	No	No	Unclear	No	Poor
Marty 1989	Yes	None	No	No	Unclear	No	Fair
Craft 1995	Yes	Unclear	No	No	Unclear	No	Fair
Hewitt 1993	Yes	None	No	No	Unclear	No	Fair
Pinkerton 1990	Unclear	Unclear	No	No	Unclear	No	Poor