

Drug Class Review on Newer Antiemetics

Final Report

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

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INTRODUCTION

Nausea and vomiting are major concerns for patients undergoing chemotherapy and radiotherapy.^{1,2} Risk factors associated with chemotherapy-induced nausea and vomiting include emetogenicity of the chemotherapy regimen, dose level, speed of iv infusion, and patient characteristics including demographics, history of ethanol consumption, and history of prior chemotherapy.³ Factors predictive of radiotherapy-induced nausea and vomiting include site of radiotherapy, in particular, total body irradiation and radiation fields that include the abdomen, total field size, dose per fraction, age, and predisposition for emesis (e.g., history of sickness during pregnancy or motion sickness).² Secondary risks associated with both chemotherapy and radiotherapy-induced nausea and vomiting can include electrolyte imbalances, aspiration pneumonia, interruption of potentially curative therapy, and reduction in quality of life.

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

Finally, nausea and vomiting are symptoms that are also 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 surgery, chemotherapeutic agents, radiotherapy, and pregnancy are thought to be induced by stimulating the dopamine, acetylcholine, histamine, and serotonin neuroreceptors involved in activating specific 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 (e.g., chlorpromazine, perphenazine, prochlorperazine) and metoclopramide and droperidol.¹⁰ A discovery that additional type 3 serotonin receptor-blocking properties were contributing to the effect of one of the dopamine antagonists, metoclopramide, eventually led to the development of the newer antiserotonergic drugs.¹¹ There are currently four 5-HT₃ receptor antagonists approved for use in the United States and Canada (Table 1). The most recent research has focused on the potential role of Substance P in inducing emesis by binding to tachykinin neurokinin (NK₁) receptor sites and this led to the development of the novel substance P receptor antagonist, aprepitant.¹²

Table 1. Antiemetic Drug Indications and Recommended Doses

| Generic Name | Trade Name | FDA Approved Indications and Dosage in Adults | FDA Approved Indications and Dosage in Children |
|--------------|------------|--|---|
| Aprepitant | Emend® | Chemotherapy: Day 1: 125 mg po once Days 2 & 3: 80 mg po once <i>Emend is to be given for 3 days in conjunction with a regimen containing a 5HT3-antagonist and a corticosteroid</i> | Chemotherapy: Dose determined by doctor |
| Dolasetron | Anzemet® | Chemotherapy: 100 mg po once (up to 1 hr before chemo) 1.8 mg/kg iv once (up to 30 min before chemo); Alternatively, a fixed dose of 100mg iv can be administered over 30sec. PONV, prevention: 100 mg po once (up to 2 hrs before surgery) 12.5 mg iv once (15 min. before anesthesia ends) PONV, established: 12.5 mg iv once (at onset of symptoms) | Chemotherapy (for children 2-16years): 1.8 mg/kg po & iv once, max. 100mg (up to 30 min before chemo) PONV, prevention: 0.35 mg/kg iv once , max. 12.5 mg (15 min before anesthesia ends) 1.2 mg/kg po once , max. 100mg (up to 2 hrs before surgery) PONV, established: 0.35 mg/kg iv once, max. 12.5mg (at onset of symptoms) |
| Granisetron | Kytril® | Chemotherapy: 2 mg po once (up to 1 hr before chemo) 0.10mg/kg iv once (up to 30 min before chemo) PONV, prevention: 1 mg iv once (before induction or before reversal of anesthesia) PONV, established: 1 mg iv once Radiation: 2 mg po once | Chemotherapy: 0.10 mg/kg iv once (up to 30 min before chemo) |
| Ondansetron | Zofran® | Chemotherapy: <i>Moderately emetogenic:</i> 8 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given twice daily <i>Highly emetogenic:</i> single 24 mg tablet 30 min before chemo; 32 mg iv once (30 min before chemo) or 0.15 mg/kg tid (1 st dose is infused 30 min before chemo starts) PONV, prevention: 4 mg iv once (immediately before induction of anesthesia) 16 mg po (tablet or orally disintegrating tablet) once (1 hr before anesthesia induction) (20 mL if oral solution given) PONV, established: 4 mg iv or im once (at onset of symptoms) Radiation: 8 mg po (tablet or orally disintegrating tablet) X3 (10 mL X3 if oral solution given) (1 st dose 1-2 hours before radiation) | Chemotherapy <i>Moderately emetogenic:</i> for patients aged 12 years and above, the dosage is the same as in adults; for patients 4-11 years the dose is 4 mg po (tablet or orally disintegrating tablet) OR 10 mL oral solution given three times daily 0.15mg/kg iv once (30 min before chemo) PONV, prevention (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV): 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg PONV, established (the iv form is approved for use in patients 1 month to 12 years; the other forms have not been studied in children for PONV): 0.1 mg/kg iv once if ≤40 kg; 4 mg iv once if >40 kg |
| Palonosetron | Aloxi® | Chemotherapy: 0.25 mg iv once (up to 30 minutes before chemo) | Chemotherapy: Dose determined by doctor |

po = (*per os*) orally
iv = intravenous
im = intramuscular

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 (DERP). The participating organizations of DERP 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:

Key Question 1: What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting?

Key Question 2: What is the comparative tolerability and safety of Newer Antiemetics when used to treat or prevent nausea and/or vomiting?

Key Question 3: Are there subgroups of patients based on demographics (age, racial groups, gender), pregnancy, other medications, or co-morbidities for which one Newer Antiemetic is more effective or associated with fewer adverse events?

Inclusion Criteria

Population(s):

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

- Chemotherapy*
- Radiation Therapy
- Post-Operative
- Pregnancy

* In this report, we use the emetogenicity classification scale that Hesketh defined in 1997 and modified in 1999^{13, 14} 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 emetogenic 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 – i.e., it classifies the chemotherapeutic agents according to the likelihood that the patient will experience emesis. Chemotherapeutic agents rated as “1” on this scale have a low emetogenic potential, while agents rated as “5” are considered to be severely emetogenic (a >90% chance of emesis in patients).

Interventions

Aprepitant (Emend®) - oral

Dolasetron (Anzemet®) – oral, injectable

Granisetron (Kytril®) - oral, injectable

Ondansetron (Zofran®) – oral (tablet and orally disintegrating tablet), injectable

Palonosetron (Aloxi®) – injectable

Effectiveness outcomes

Treatment of Established Post-Operative 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 post-operatively
 - Late: within or close to 24 hours post-operatively
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - Early: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, delay until first emetic episode, number of emesis-free days

Prevention of Post-Operative Nausea and/or Vomiting

- Success: absence of vomiting and/or retching in the post-operative period.
 - Acute: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching) in the post-operative period.
 - Acute: within or close to 6 hours post-operatively
 - Late: within or close to 24 hours post-operatively
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, 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
 - during the first 24 hours of chemotherapy administration
 - acute/early vomiting and/or retching induced by highly emetogenic chemotherapy
 - acute/early vomiting and/or retching induced by moderately emetogenic chemotherapy
 - after the first 24 hours of chemotherapy administration
 - delayed/late vomiting and/or retching induced by highly emetogenic chemotherapy
 - delayed/late vomiting and/or retching induced by moderately emetogenic chemotherapy
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - during the first 24 hours of chemotherapy administration
 - acute: induced by highly emetogenic chemotherapy
 - acute: induced by moderately emetogenic chemotherapy
 - after the first 24 hours of chemotherapy administration
 - delayed: induced by highly emetogenic chemotherapy

- delayed: induced by moderately emetogenic chemotherapy
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, serious emetic sequelae, worst day nausea/ vomiting and/or retching, delay until first emetic episode, number of emesis-free days

Prevention Radiation Induced Nausea and/or Vomiting

- Success: absence of vomiting and/or retching
 - Acute: during the first 24 hours of onset of radiotherapy
 - Delayed: after the first 24 hours of onset of radiotherapy, or after consecutive radiotherapy doses given during several days
- Success: absence of any emetic event (nausea, vomiting and/or retching, or nausea and vomiting and/or retching)
 - Acute: during the first 24 hours of onset of radiotherapy
 - Delayed: after the first 24 hours of onset of radiotherapy, or after consecutive radiotherapy doses given during several days
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes, degree of nausea, or number of or need for rescue medication, 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 and/or retching, or nausea and vomiting and/or retching)
- Rhodes index or visual analog scale assessments of symptom severity
- Fetal outcome
- Other: patients' satisfaction or QOL, number of vomiting and/or retching episodes per period of time, number of or need for rescue medication, serious emetic sequelae, number of emesis-free days, re-hospitalization episodes and/or duration.

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.

Safety outcomes

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

Study designs

1. For effectiveness, controlled clinical trials and good-quality systematic reviews.
2. For safety, in addition to controlled clinical trials, observational studies will be included.

The benefit of the RCT 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.^{15, 16} However, RCTs can vary in quality, and often suffer from limitations in generalizability to the larger patient population. Observational study designs are thought to have greater risk of introducing bias, although they typically represent effects in a broader section of the overall patient population. While it has been shown that some observational studies and RCTs of the same treatments have similar findings, there are also multiple example of situations where this has not been true and the question of what type of evidence is best has not been resolved.^{17, 18} While RCTs 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, we searched the Cochrane Central Register of Controlled Trials 4th Quarter 2004), Cochrane Database of Systematic Reviews, MEDLINE (1966 to February Week 1 2005), EMBASE (2nd Quarter 2005), and CancerLit (1974 to March 2005) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). We have attempted to identify additional studies through searches of reference lists of included studies and reviews, the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

Two reviewers independently assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. 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 was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a “carryover effect” (from the first treatment) in studies without a washout period, or “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, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.^{19,20} 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 in one or more categories were rated “poor-quality”; trials that met all criteria were rated “good-quality”; the remainder were rated “fair-quality.” A fatal flaw occurs when there is evidence of bias or confounding in the trial, for example when randomization and concealment of allocation of random order are not reported and baseline characteristics differ significantly between the groups. In this case, randomization has apparently failed and for one reason or another bias has been introduced.

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. Those studies considered only *probably* valid are indicated as such using a “fair-poor” rating. 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. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will 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.

Appendix B also shows the criteria we used to rate observational studies. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair-quality if they met three to five criteria and poor-quality if they met two or fewer criteria.

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

Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive two different ratings: one 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.

Evidence Synthesis

Effectiveness versus Efficacy. Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, 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 highly selected populations in efficacy studies. Examples of “effectiveness” outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allow for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also 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 other practice settings. They often restrict options, such as combining therapies or switching drugs, that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use objective measures of effect 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.

Data Presentation. We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated one pharmacologic treatment of newer antiemetics against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis. No meta-analyses were conducted in this review due to heterogeneity in treatment regimens, use of concomitant medications, outcome reporting and patient populations.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

RESULTS

Overview

We identified 3,272 articles from literature searches and reviews of reference lists. This includes citations from dossiers submitted by three pharmaceutical manufacturers: Merck (aprepitant, Emend®), Sanofi Aventis (dolasetron mesylate, Anzemet®), GlaxoSmithKline (ondansetron HCl, Zofran®). After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained copies of 477 full-text articles. After re-applying the criteria for inclusion, we ultimately included 193 publications (165 studies and 28 duplicate data or background publications). Of these 165 trials we analyzed, 72 trials were included in our chemotherapy section, 58 trials were included in the prevention of post-operative nausea and vomiting section, 20 were included in the treatment of post-operative nausea and vomiting section, thirteen were included in the radiation section, and two were included in the pregnancy section. The flow of study inclusion and exclusion is detailed in Figure 1.

Summary of main findings

- **Overview**
 - No effectiveness study was identified for inclusion in this review
 - Direct comparative evidence is available only for the efficacy and safety of newer antiemetics in the prevention of nausea and vomiting post-operatively or that associated with chemotherapy
 - Evidence of the efficacy and safety of newer antiemetics in the treatment of post-operative and radiation-associated nausea and vomiting is based primarily on indirect comparisons from placebo-controlled and active-controlled trials.
 - Evidence of the efficacy and safety of newer antiemetics in the treatment of nausea and vomiting associated with pregnancy is extremely limited and restricted to one trial of ondansetron compared to promethazine
- **Direct Comparative efficacy and safety: Main findings from head-to-head trials**
 - **Dolasetron vs ondansetron:** No consistent differences in rates of Complete Response or adverse events in trials of adults undergoing emetogenic chemotherapy (3 trials) or following various surgical procedures in trials of adults (5 trials) or children (3 trials).
 - Ondansetron was associated with significantly higher rates of abnormal vision and dizziness in only one of three trials in adults undergoing emetogenic chemotherapy that reported these adverse events
 - Dolasetron was associated with significantly higher rates of constipation and diarrhea in that same trial
 - **Granisetron vs ondansetron:** No consistent differences in rates of Complete Response or adverse events following emetogenic chemotherapy in trials of adults (18 trials) or children (1 trial) or in trials of adults undergoing various surgical procedures (2 trials)
 - Ondansetron was associated with significantly higher rates of abnormal vision and dizziness in one of three trials in adults undergoing emetogenic chemotherapy

- **Dolasetron vs granisetron:** No differences in rates of Complete Response (acute or delayed) or adverse events in adults undergoing emetogenic chemotherapy (1 trial)
- **Granisetron iv vs po formulations:** No differences in rates of Complete Response (acute or delayed) or adverse events in adults undergoing emetogenic chemotherapy (1 trial)
- **Ondansetron iv vs po oral solution formulations:** No differences in rates of Complete Response (acute or delayed) or adverse events in children undergoing emetogenic chemotherapy (1 trial)
- **Palonosetron vs dolasetron (1 trial) or ondansetron (1 trial):** Acute and delayed complete response rates for palonosetron were noninferior to those for dolasetron and ondansetron in adults undergoing emetogenic chemotherapy. Palonosetron superiority in complete response rates was indicated for delayed emesis relative to dolasetron (NNT=7) and for both acute and delayed emesis relative to ondansetron (NNT=9 and 6).
- **Indirect Comparative efficacy and safety: Findings from active-controlled and placebo-controlled trials**
 - **Prevention and Treatment of Post-Operative Nausea and Vomiting**
 - Indirect evidence suggests no differences between dolasetron, granisetron, and ondansetron for prevention of further nausea and vomiting when used to treat established post-operative nausea and vomiting in adults. Limited indirect evidence also suggests no difference in patient satisfaction and the occurrence of headache.
 - Indirect evidence to compare the complete response rates of granisetron and dolasetron in preventing PONC are too limited to make conclusions at this time.
 - No conclusions can be made regarding the indirect comparative effects of dolasetron versus granisetron in prevention of PONV, or dolasetron, granisetron and ondansetron on post-operative patient satisfaction or duration of hospital stay outcomes.
 - **Prevention of nausea and vomiting related to chemotherapy:**
 - **Aprepitant:** Direct or indirect comparative evidence for aprepitant is not available. Evidence of the efficacy and safety of aprepitant when added to granisetron or ondansetron comes only from placebo-controlled trial in adults undergoing emetogenic chemotherapy.
 - **Ondansetron:** There were generally no differences between ondansetron and other antiemetics in their effects on rating scale scores measuring quality of life in women with breast cancer
 - **Prevention of nausea and vomiting related to radiation**
 - 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-controlled and placebo-controlled trials due to heterogeneity in patient populations, comparators, radiotherapy regimens and outcome reporting
 - **Prevention of nausea and vomiting related to pregnancy**
 - **Ondansetron:** No direct or indirect comparisons are available. One trial of ondansetron and promethazine in hospitalized women with hyperemesis

gravidarum does not provide evidence of comparative efficacy and/or safety among newer antiemetics

- **Safety in observational studies**
 - **Pregnancy:** There were no differences between ondansetron and other antiemetics or other non-teratogenic drugs in live births, number of malformations, birth weight, or gestational age at birth in 176 women that were exposed to treatment during gestational weeks 5-9
 - **Chemotherapy:** Reports of single cases of serious adverse events associated with dolasetron, granisetron and ondansetron come only from poor-quality uncontrolled studies and do not offer any comparative information.
- **Comparative efficacy and safety in subgroups**
 - **Chemotherapy:** Evidence from one post-hoc subgroup analysis suggests that granisetron may be associated with significantly higher rates of vomiting than ondansetron in chemotherapy patients with a predisposition to nausea/vomiting (history of motion sickness, pretreatment with emetogenic chemotherapy).

Detailed Assessment

Key Question 1.

What is the comparative effectiveness of Newer Antiemetics in treating or preventing nausea and/or vomiting?

Prevention of Chemotherapy-Related Nausea and Vomiting

Adults

Direct comparisons

The majority of head-to-head trials conducted in adults undergoing chemotherapy regimens directly compared granisetron and ondansetron.²¹⁻⁵² Table 2 below summarizes the numbers of head-to-head trials comparing granisetron and ondansetron and other 5-HT₃ antagonists and aprepitant.⁵³⁻⁶³ The primary efficacy endpoint in a majority of trials was the proportion of patients that achieved a “complete response.” Definitions of “complete response” varied across trials but was generally a composite outcome involving any two or more of the following improvement indicators: no emesis; no nausea; no rescue medication use. In general, there were no consistent differences between any combination of dolasetron, granisetron, and ondansetron. Palonosetron was associated with significantly higher acute and delayed complete response rates, however, when compared to dolasetron (NNT=10 and 7) and ondansetron (NNT=9 and 6).^{61, 62}

Twenty-six percent of head-to-head trials were rated poor quality due to combinations of probable biases including lack of blinding; inadequate randomization and allocation concealment methods, often evidenced by uneven distribution of baseline prognostic factors; and analyses that excluded proportions of patient populations that exceeded acceptable limits (>15%).^{23, 29-32, 34, 35, 41, 43, 44, 48, 58}

Sources of heterogeneity across trials included: (1) chemotherapy regimen – number of courses and emetogenicity level; (2) antiemetic regimen – dosage level, route,

schedule; (3) concomitant prophylactic therapy with corticosteroids; (4) patients – distribution of gender, age, primary malignancies; and (5) outcome reporting.

Table 2. Numbers of head-to-head (HTH) trials in adults undergoing chemotherapy*

| | Aprepitant | Dolasetron | Granisetron | Ondansetron | Palonosetron |
|---------------------|------------|------------|-------------|-------------|--------------|
| Aprepitant | ***** | | | | |
| Dolasetron | | ***** | | | |
| Granisetron | | 2 (1) | po vs iv=1 | | |
| Ondansetron | | 4 | 31 (11) | ***** | |
| Palonosetron | | 1 | | 1 | ***** |

*Numbers refer to studies found and discussed in report, and the numbers in parentheses refer to poor quality studies; Abbreviations: po-by mouth, orally; iv-intravenous

Granisetron vs ondansetron

There were very few differences between granisetron and ondansetron, regardless of chemotherapy regimen, antiemetic regimen, use of concomitant corticosteroid therapy, patient population, or outcome reporting method.^{21, 22, 25-28, 33, 36-40, 42, 45-47, 49-52} Dosage levels ranged widely for both granisetron (po 1 and 2 mg; iv 10 mcg/kg and 3 mg) and ondansetron (iv 2-32 mg). Dosage level inequities between treatment groups also did not seem to have an impact on comparative efficacy. In general, there were no differences between granisetron and ondansetron the most optimal outcomes, rates of acute or delayed complete response.^{25, 26, 28, 36, 37, 39, 40, 46, 49}

Complete response – acute. Only half of the trials reported complete response at 24 hours.^{25, 26, 28, 36, 37, 39, 40, 46, 49} Table 3 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 one or combination of demographic, prognostic, or outcome factors.

Complete response – delayed. Half again as many trials reported *delayed* complete response rates and there were no significant differences between granisetron and ondansetron (Table 3).^{25, 26, 37, 40, 49} In general, complete response rates declined after the first 24 hours. There was one exception to this. In one trial, complete response rates (no emesis or nausea) for granisetron and ondansetron were numerically higher by day 6 (74.5% vs 71.4%, NS) than they were at 24 hours (67.3% and 66.5%, NS).²⁵ A possible explanation for this is that this is the only study in which oral metoclopramide 20 mg 6 hourly together with intramuscular dexamethasone 8 mg twice daily was introduced to participants on days 2-6. This is in contrast to the other studies that reported delayed complete response rates, in which emesis prophylaxis was either discontinued after day 1 or continued using the same 5HT3-antagonist regimen.

Table 3. Complete response rates in adults undergoing chemotherapy*

| Trial | Treatments Concomitant prophylaxis | Hesketh Score Primary malignancy | % female Mean age | Complete response rates (% pts) | |
|---|---|---|----------------------|---------------------------------|--|
| | | | | Acute (≤ 24 hrs) | Delayed (> 24 hrs) |
| <i>No emesis, nausea or use of rescue medication</i> | | | | | |
| Gralla 1998 (n=1054) | G 2 mg po QD O 32 mg iv QD DEX or MPR optional | 5 Respiratory+ Intrathoracic | 34% 61.7 yrs | 54.7% vs 58.3% NS | NR |
| Perez 1998 (n=1085) | G 2 mg po QD O 32 mg iv QD Both + DEX/MPR/PR | 3 or 4 Breast | 80% 55.6 yrs | 59.4% vs 58% NS | 46.7% vs 43.8%, NS (48 hrs) |
| Navari 1995 (n=987) | G 10 or 40 µg/kg iv QD O 0.15 mg/kg iv TID | 5 Lung | 36% 62.3 yrs | 38% vs 41% vs 39%; NS | NR |
| <i>No emesis or nausea</i> | | | | | |
| Del Favero 1995 (n=966) | G 3 mg iv QD O 8 mg iv QD Both + DEX | 5 Lung | 32% 61 yrs | 67.3% vs 66.5% NS | 74.5% vs 71.4%, NS (day 6) |
| <i>No emesis and none-mild nausea</i> | | | | | |
| Walsh 2004 (n=96) | G 10 µg/kg iv QD O 0.15 mg/kg iv Q8 hrs CC med use NR | 3-5 Non-Hodgkin's lymphoma/ Hodgkins | 16% 52 yrs | 83% vs 90% NS | 50% vs 46%, NS (day 6) |
| Noble 1994 (n=309) | G 3 mg iv QD O 8 mg iv TID; SP 8- and 16 hrs CC med use NR | 3-4 Head/neck | 23% 51.8 yrs | 91.5% vs 89.1% NS | 39.2% vs 37.3%, NS (results from Cycle 1, over 5 days) |
| <i>No emesis or rescue medication</i> | | | | | |
| Park 1997 (n=97) | G 3 mg iv QD O 8 mg iv, Q8 hrs, then 8 mg po Q12 hrs for 5 days | 5 Stomach | 47% 51 yrs | 53.2% vs 45.8% NS | Days 2-7: 29.8% vs 27.1%, NS |
| Spector 1998 (n=371) | G 10 µg/kg iv QD O 24 mg po (tablet) QD | 5 Lung | 44% 64 yrs | 51% vs 58% NS | NR |
| <i>No nausea or rescue medication</i> | | | | | |
| Fox-Geiman 2001 (n=102) | G 1 mg po Q12 hrs O 8 mg po Q8 hrs O 32 mg iv QD All + DEX | 4 Bone Marrow Transplant | 72% 47 yrs | 92% vs 95% vs 92%, NS | 47% vs 48% vs 49%, NS (over 8 days) |

*Abbreviations: G-granisetron; O-ondansetron; DEX-dexamethasone; MPR-methylprednisolone; PR-prednisolone; CC-concurrent; po-by mouth, orally; iv-intravenous; QD-once a day; TID-three times daily; NR-not reported; NS-not significant

Other emesis and nausea outcomes. There were generally no differences between granisetron and ondansetron in complete protection from acute or delayed emesis OR nausea, respectively.^{21, 22, 25, 27, 38, 42, 45, 47, 50-52} The exceptions are as follows. More adults with breast cancer (98% female; mean age=44) undergoing Hesketh level 3 chemotherapy and prophylactic iv granisetron 3 mg experienced complete control of emesis at 24 hours (73.7% vs 38.8%, p=0.035) and during days 2-5 (73.7% vs 33.3%, p=0.014) than those taking iv ondansetron 8 mg (n=54).⁵⁰ Nausea outcomes were not reported.

Fewer participants taking iv granisetron 3 mg QD experienced “nausea+emesis control failure” (47% vs 80%, p=0.03) and “emesis control failure” (27% vs 47%, p=0.04) than those taking iv ondansetron 8 mg bid after 10 days in one study of 45 participants with lymphoma (33% female; mean age=38 years).⁴⁵ Use of blinding in this study is unclear. Ondansetron 8 mg (iv on day 1, then po) was superior to iv granisetron 3 mg in the proportion of patients with complete protection from nausea (55% vs 40%, p<0.009) on the worst of days 1-5 in a trial of women with breast cancer (n=48, mean age=50.3 years).⁴⁷

Participant satisfaction and preference outcomes. There were no differences between granisetron and ondansetron in patient satisfaction across two trials^{46, 47} and mixed results for patient preference across an additional two trials.^{21, 37} More patients preferred iv granisetron 3 mg over iv ondansetron 24 mg in one crossover trial of mostly males (77%) with head/neck cancer (combined treatment sequences: 34% vs 25.6%; p=0.048). When treatment sequences were considered separately, however, patient preferences correlated with which treatment was received first.³⁷ More patients with breast cancer (68% female) preferred iv ondansetron 32 mg over iv granisetron 3 mg (45% vs 30%, p<0.01) in another trial.²¹

Dolasetron vs ondansetron

Results from two good-quality trials demonstrated no differences between dolasetron and ondansetron in 24-hour complete response rates (no emesis or rescue medication use), either when both were dosed intravenously⁵⁴ or orally,⁵³ at the recommended levels. In contrast, iv ondansetron 32 mg (recommended dosage) was superior to iv 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.⁵⁵ This difference was not observed after 7 days 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 4 and Evidence Tables 1 and 2).

Table 4. Outcomes from HTH trials of dolasetron vs ondansetron in adults

| Trial (Sample size) Quality | Treatment Total dose in mg (frequency) | | | 1° malignancy % female Mean age Emetogenicity* | Complete response rates (% pts no emesis or rescue medication use) | | Nausea (VAS scores) | | Satisfaction or QOL |
|--------------------------------------|--|---|-------------|---|---|------------------------------|---|--|---|
| | D | O | CC Med | | Acute (≤ 24 hrs) | Delayed (> 24 hrs) | Acute (≤ 24 hrs) | Delayed (> 24 hrs) | |
| Fausser 1996 (n=398) Good | po 100 or 200 (QD) | po O 24- 32 (flexible: 8 mg tid or qid) | None | Breast 61.2% 53.2 yrs Levels 3, 4 | 60.5 vs 76.3 vs 72.3, NS | NR | Change from baseline: 3.5 vs 0 vs 3, NS | NR | Satisfaction (mean VAS): 55-99 vs 98, NS |
| Hesketh 1996 (n=609) Good | iv 1.8 or 2.4 mg/kg (QD) | iv O 32 (QD) | None | Lung 38% 62 yrs Level 5 | 44.4% vs 40% vs 42.7, NS | NR | Median: 10 vs 22 vs 16, NS | NR | Satisfaction (median VAS): 92 vs 85.5 vs 84, NS |
| Lofters 1997 (n=696) Fair | Acute: iv 2.4 mg/kg (QD) Delayed: po 200 mg (QD) | Acute: iv O 32 (QD) Delayed: po O 16 (8 mg bid) | Dex 8 mg | Breast 71% 55 yrs Level 3 | 57% vs 67%; p=0.013 | 7 days: 36% vs 39%, NS | Mean VAS: 13.1 vs 10.1; p=0.051 | Mean VAS after 7 days: 11.0 vs 8.87, NS | Global QOL (EORTC QLQ- 30): No significant changes (data NR) |

*Hesketh Score; EORTC QLQ-30=European Organization for Research and Treatment of Cancer

Abbreviations: VAS-visual analog score; QOL-quality of life; po-by mouth, orally; iv-intravenous; QD-once a day; BID-twice a day; TID-three times daily; QID-four times daily; NR-not reported; NS-not significant

Dolasetron vs granisetron

There were no significant differences in efficacy outcomes between dolasetron and granisetron in one good quality trial (n=474) of mostly men receiving high-dose cisplatin (≥ 80 mg/m²) for head/neck malignancies (Evidence Tables 1 and 2).⁵⁷ IV dolasetron 1.8 or 2.4 mg/kg and iv granisetron 3 mg, both given once, were comparable with regard to percentages of patients with 24-hour complete responses (54% vs 47% vs 48%, NS) and no nausea (VAS ≤ 5 mm: 41% vs 41% vs 41%, NS).⁵⁷ There were also no significant group differences in the percentages of patients that investigators rated as having good or excellent global antiemetic efficacy (61% vs 62% vs 62%, NS). Patient satisfaction was described as being measured using a VAS, but outcomes were not reported.

Palonosetron

Single doses of IV palonosetron 0.25 mg were noninferior to IV dolasetron 100 mg⁶¹ and IV ondansetron 32 mg⁶² for acute and delayed complete response rates in head-to-head trials involving primarily females (77%) undergoing *moderately* emetogenic (Hesketh 2001 levels 3-4) chemotherapy for breast cancer (60.2%) (Table 5 and Evidence Tables 1 and 2). Further, superiority was indicated for complete response rates for palonosetron for all but the comparison to dolasetron at 24 hours post-dose.⁶¹ No significant differences in *acute* satisfaction (mean VAS scores) or quality of life (Functional Living Index-Emesis questionnaire overall scores) were reported. IV palonosetron was superior in improving *delayed* quality of life (days 2-5) and

patient satisfaction (on some but not all of days 2-5) when compared to iv dolasetron or iv ondansetron. In both trials, patients were allocated to treatment using a non-random, “deterministic” method designed to minimize group differences in gender, chemotherapy history, and use of corticosteroids. Bias is not suspected, however, as FDA checked the analyses using permutation methods and substantiated the results (http://www.fda.gov/cder/foi/nda/2003/21-372_Alox_Statr.pdf).

No differences between iv palonosetron 0.25 mg and iv ondansetron 32 mg in acute or delayed complete response rates or patient satisfaction/QOL were found in a trial (protocol 99-05) that is discussed in an FDA review (http://www.fda.gov/cder/foi/nda/2003/21-372_Alox_Medr_P5.pdf), but that is not yet fully published.⁶⁴ Patients were 51% female and undergoing highly emetic chemotherapy (Hesketh level 5); other characteristics were not reported.

Table 5 Outcomes from HTH trials of palonosetron in adults**

| Trial Protocol# | IV treatment (mg) QD | | | 1° malignancy Emetogenicity* | % female Mean age Ethnicity | Complete response (% pts no emesis or rescue medication use) | | Satisfaction (Mean VAS 1-100) | | QOL (Mean FLIE overall score: 1-1800) | |
|-----------------------------|----------------------|----------------|------------|------------------------------|-------------------------------------|--|--------------------------------------|-------------------------------|---------------------------------|---------------------------------------|-----------------------------|
| | P | D or O | CC med | | | Acute (24 hr) | Delayed (Days 2-5) | Acute (24 hr) | Delayed (Days 2-5) | 24 hr | Delayed (Days 2-5) |
| Eisenberg 2003 99-04 | 0.25 n=189 | D 100 n=191 | DEX MPR | Breast Levels 3, 4 | 82% 54 yrs 31.3% white | 63 vs 52.9; p=0.049 | 54 vs 38.7; p=0.004 NNT=7 | 95 vs 90, NS | Day 4: 97 vs 93, p=0.0217 | 1686 vs 1629, NS | 1672 vs 1599, p=0.393 |
| Gralla 2003 99-03 | 0.25 n=189 | O 32 n=185 | None | Breast (57%) Levels 3, 4 | 72.1% 55.4 yrs 98.9% white | 81 vs 68.6; p=0.0085 NNT=9 | 74.1 vs 55.1, p<0.001 NNT=6 | 97 vs 97, NS | 98 vs 94, p=0.0152 | 1587 vs 1721, NS | 1740 vs 1680, p=0.014 |
| Aapro 2003 99-05 (abstract) | 0.25 n=223 | O 32 n=221 | DEX MPR | NR Level 5 | 51% NR NR | 59.2 vs 57, NS | 45.3 vs 38.9, NS | NS (data nr) | NS (data nr) | NS (data nr) | NS (data nr) |

*Hesketh classification schema¹⁴

**Abbreviations: P-palonosetron; D-dolasetron; O-ondansetron; CC-concurrent ; DEX-dexamethasone; MPR-methylprednisolone; VAS-visual analog score; QOL-quality of life; NNT-number needed to treat; NS-not significant; NR-not reported

Granisetron IV vs granisetron PO

There were no significant differences in efficacy outcomes between iv granisetron and po granisetron in one fair-quality trial (n=60) of participants (65% female) who were to undergo emetogenic chemotherapy (Hesketh levels 3 or 5) as a conditioning regimen for progenitor cell transplantation (PBPCT) or bone marrow transplantation (BMT).⁶³ Similar proportions of patients were completely free from emesis at 24-hours (6.9% vs 9.1%, NS) taking either iv or po dosages of granisetron (1 mg every 12 hours). Concomitant dexamethasone was allowed for the last 17 patients due to a protocol amendment designed to enhance the efficacy of granisetron.

Indirect comparisons

Head-to-head trials lacked evidence for aprepitant and quality of life/functional capacity outcomes. Numerous placebo- and active-controlled trials were reviewed to address these gaps

(Appendix C). No placebo- or active-controlled trials were found that reported functional capacity outcomes in this population.

Aprepitant

Aprepitant has been studied in fair-quality placebo-controlled trials as an add-on to “standard therapy” (granisetron or ondansetron plus dexamethasone) for the prevention of highly⁶⁵⁻⁶⁹ or moderately⁷⁰ emetic chemotherapy-induced nausea and vomiting (Evidence Tables 3 and 4). Two of these were the pivotal trials included in the manufacturers submission to FDA.^{65, 68} The most common cancer type represented across all trials was lung cancer. In all studies, a significantly higher proportion of patients receiving the aprepitant regimen had a complete response (no emetic episodes and no use of rescue medication) compared with patients receiving standard therapy in the acute and delayed phases of treatment. Additionally, Functional Living Index-Emesis (FLIE) scores indicated that CINV impacted daily life to a lesser degree over six days in patients taking aprepitant relative to those receiving standard therapy.^{65, 68, 70}

Quality of life

Five fair-quality, active-controlled trials of ondansetron reported the effects of antiemetic treatment on quality of life in women undergoing moderately-severely emetogenic chemotherapy. (Table 6 and Evidence Tables 5 and 6).⁷¹⁻⁷⁵ 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 US), but not prochlorperazine and the quality of life associated with ondansetron versus metoclopramide is less clear.^{71, 72, 74}

Table 6. Quality of life outcomes in active-controlled 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 six 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: O-ondansetron; po-by mouth, orally; iv-intravenous; QOL-quality of life; EORTC-European Organization for Research and Treatment of Cancer; QLQ-C30-Quality of Life Questionnaire (EORTC); FLIE-Functional Living Index-Emesis; BID-twice a day

Children

Direct Comparisons

Four head-to-head trials included children (Evidence Table 1 and 2).^{52, 76-78} One was rated 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, often evidenced by uneven distribution of baseline prognostic factors; and analyses that excluded a proportion of the original patient population.⁷⁷

There were no differences between iv ondansetron and iv granisetron in teens (mean age=16.9 years)⁷⁶ or between the iv and oral solution forms of ondansetron in younger children aged 8 years (see Table 7).⁷⁸ One thing to note about the White 2000 study is related to the treatment regimen.⁷⁸ After receiving the loading doses reflected in the table below, all patients then received 4 mg of ondansetron oral solution plus 2-4 mg of oral dexamethasone every 6-8 hours for up to 8 days. All patients also received 4 mg of oral ondansetron oral solution twice daily for the 2 days that followed cessation of the chemotherapy. Chemotherapy level (Hesketh system) is unknown because the dosages for chemotherapy agents were not reported. Something to note about the Forni 2000 study is that the evaluation of efficacy outcomes was based on patient *days* as the unit of measurement (n=717), rather than the number of patients randomized (n=90).⁷⁶ This brings into question whether the distribution of mean patient characteristics remained balanced between groups in this type of analysis. This is unknown as this information was not reported.

A subgroup analysis of 51 (26%) participants under age 18 (mean age NR) also suggested no differences between iv granisetron and iv ondansetron in protection from emesis or nausea.⁵² 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 VAS 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.

Table 7. Outcomes in HTH trials of children*

| Trial (Sample size) Quality | Treatment Total dose in mg (once daily) | | | 1° malignancy % female Mean age Emetogenicity* | Complete response rates (% pts no vomits/retches) | | Nausea | | Adverse events |
|---|--|---------------------------------|-------------------------------|--|--|---------------------------------------|------------------------|------------------------------------|---|
| | Group 1 | Group 2 | CC Med | | Acute (≤ 24 hrs) | Delayed (> 24 hrs) | Acute (≤ 24 hrs) | Delayed (> 24 hrs) | |
| White 2000 (n=428) Fair | iv O 5 mg/m ² | O oral solution 8 mg | po dex 2- 4 mg | Variety (NR) 42% 8 yrs Moderate-High | 81 vs 78; NS | Worst of all days: 62 vs 62, NS | None: 73 vs 70; NS | ≥ 10 days None: 52 vs 56, NS | No difference s Any AE: 24 vs 25; NS |
| Forni 2000 (n=90; patient days=717) Fair | iv G 2 mg/m ² | iv O 5.3 mg / m ² | iv dex 8 mg/m ² | Osteosarcoma of extremity 31% 16.9 yrs Level 5 | 62.9% vs 58.3% (NS) of patient days (237 vs 240)NR | NR | NR | NR | NR |

* Abbreviations: G-granisetron; O-ondansetron; dex-dexamethasone; iv-intravenous; po-by mouth, orally; AE-adverse events; NS-not significant; NR-not reported; CC= concomitant

Prevention of Nausea and Vomiting Associated with Radiation

Adults

Direct Comparisons

The only study comparing newer antiemetics in patients undergoing total body irradiation conducted an analysis of each drug (granisetron and ondansetron) compared to a historical control group.⁷⁹ Using this analysis, no differences were found between the drugs on 3 outcome measures, but granisetron was superior to control in complete nausea control on Day 0, where ondansetron, at a lower than recommended dose, was not statistically superior to control on this outcome measure (see Table 8). Because this analysis used a historical control group rather than directly comparing the drugs, any inferences about indirect comparative efficacy should be made with caution.

There were no significant differences between granisetron and ondansetron on any outcome measure upon direct comparison, however, based on our own analyses using the Fisher's exact test (StatsDirect software).

Table 8. Granisetron and ondansetron outcomes following TBI**

| Outcome | Granisetron 2 mg n=18 | Ondansetron 8 mg n=15 | Historical control n=90 | Statistically Significant vs Historical Control? | | Direct comparison G vs O* |
|--|-----------------------------|-----------------------------|-------------------------------|---|-----|---------------------------------|
| | | | | G | O | |
| <i>Complete emetic control – no emesis/rescue medication (% pts)</i> | | | | | | |
| Day 0 | 61.1 | 46.7 | 2 | Y | Y | NS |
| Day 3 | 62.5 | 66.7 | 18.9 | n/a | n/a | NS |
| Overall | 27.8 | 26.7 | 0 | Y | Y | NS |
| <i>Complete nausea control – no nausea/rescue medication (% pts)</i> | | | | | | |
| Day 0 | 44.4 | 26.7 | 2.2 | Y | N | NS |
| Day 3 | 37.5 | 66.7 | 10.3 | n/a | n/a | NS |
| Overall | 11.1 | 13.3 | 0 | N | N | NS |

*Calculated by OHSU EPC using StatsDirect

**Abbreviations: G-granisetron; O-ondansetron; NS-not significant

Indirect comparisons

We included a number of placebo-controlled and active-controlled trials of dolasetron, granisetron and ondansetron (Evidence Tables 7 and 8).^{2, 80-89} Four of these trials of granisetron⁸⁷ and ondansetron,⁸¹⁻⁸³ plus one incompletely published trial of ondansetron versus metoclopramide,⁹⁰ were previously analyzed in a good quality systematic review.⁹¹ The Tramer et al review (1998) did not make any indirect comparisons and noted that the evidence was limited by variability in underlying risk (wide ranges in placebo response rates), clinical settings, comparators, radiotherapy regimen, and endpoints. Conclusions were that (1) ondansetron is consistently efficacious in preventing acute vomiting after total body or upper abdominal radiation (NNT 2.5),^{82, 90} (2) limited evidence suggests that ondansetron is efficacious in preventing acute nausea,^{82, 90} (3) and that there were no differences between granisetron or ondansetron and any placebo- or active-comparators in delayed protection from vomiting or nausea.^{82, 87, 90}

Our review adds to the Tramer et al review in a few areas. First, we included trials that have been published since the final search date for the Tramer et al review (since January 1997)^{2, 80, 89} We also included some earlier trials that were not in the Tramer et al review for unknown reasons.^{2, 80, 85, 86, 88, 89} Despite adding fair-quality trials, we were also unable to make any indirect comparisons due to the variability described above. With regard to acute outcomes (Table 9 below), our review adds evidence that both dolasetron⁸⁶ and granisetron⁸⁰ provide superior control of vomiting and nausea compared to placebo in patients undergoing abdominal radiation. Likewise, no clear superiority of granisetron versus placebo⁸⁰ or ondansetron versus various active comparators^{83, 88} in patients undergoing abdominal radiation in their effects on delayed protection was found.

Further, our review adds a trial that compared the oral disintegrating tablet form (ODT) of ondansetron to placebo in patients undergoing abdominal radiation and ondansetron ODT was associated with superior rates of treatment success on various measures.²

Finally, our review adds a placebo-controlled trial of IV ondansetron 8 mg that the previous review excluded, which involves patients undergoing a bone marrow transplantation conditioning regimen that involves concomitant non-emetogenic chemotherapy (melphalan 110 mg/m²) and single fraction total body irradiation (TBI) (10.5 Gy).⁸⁴ Results of this trial suggest that IV ondansetron was superior to placebo during but not 6-12 hours after TBI in preventing these patients from any emetic event or nausea/retching.

Table 9. Summary of findings from placebo-controlled and active-controlled trials in patients undergoing radiation

| Treatment | Control | # trials | Acute (≤ 24 hours) | | Delayed (> 24 hours) | |
|-------------|----------------|----------|--------------------------|----------|-------------------------|----------------|
| | | | Vomiting | Nausea | Vomiting | Nausea |
| Dolasetron | Placebo | 1 | Superior | Superior | - | - |
| | Active | 0 | n/a | n/a | n/a | n/a |
| Granisetron | Placebo | 1 | Superior | Superior | Mixed | Mixed |
| | Metoclopramide | 1 | Superior | - | No differences | - |
| Ondansetron | Placebo | 4 | Mixed | Mixed | Mixed | No differences |
| | Various | 4 | Superior | Superior | Mixed | No differences |

Children

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

Prevention of Post-Operative Nausea and Vomiting (PONV)

Adults

Direct Comparisons

Seven trials comparing 5HT₃ antagonists used prophylactically to prevent PONV in adults were found, all were rated fair quality (see Table 10 below).⁹²⁻⁹⁸ Complete information on these studies and the quality assessments are in Evidence Tables 9 and 10. The patient populations varied in terms of surgical procedures included in these trials, from those described as “superficial surgical procedures”, to gynecologic-oncology surgical procedures. Only one study included pre-treatment with dexamethasone and droperidol.⁹⁵ Study sizes ranged from 60 to 518. Dosing ranged in these studies, from 4 to 8 mg of ondansetron, 12.5 to 50 mg dolasetron and 1 to 3 mg granisetron. As can be seen in the discussion below, dose response was not seen other than between the 25 and 50 mg doses of dolasetron.

Dolasetron versus Ondansetron

Five trials in adults compared dolasetron IV with ondansetron IV.⁹²⁻⁹⁶ The complete response rates were not significantly different between the 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 4 mg of ondansetron was used in each trial, the dolasetron dose varied more. In 4 studies, 12.5 mg was included, in 2 a 25 mg dose, and in one a 50 mg dose. The 50 mg dose was found to be superior to the 25 mg dose on total response rates at 24 hours (complete response plus no nausea), and both the 50 mg dose and ondansetron 4 mg were superior to 25 mg dolasetron on complete response (no emesis plus no rescue medication use) at 24 hours.⁹³ Differences were not found between 12.5 and 50 mg doses of dolasetron and 4 or 8 mg doses of ondansetron in another study.⁹⁹

Granisetron versus Ondansetron

Two trials compared granisetron IV (differing doses) and ondansetron 4 mg IV, one in women undergoing radical mastectomy (using 1 mg granisetron),⁹⁷ and the other in patients undergoing laparoscopic cholecystectomy (using 3 mg granisetron) of whom 22% were male.⁹⁸ No significant differences were found between the drugs on complete response at 24 hours in either study. The proportions free of PONV varied in the trials, with total response at 24 hours in 75-80% in the trial of mastectomy patients, and 52-66% in the cholecystectomy patients.

Indirect Comparisons

The head-to-head trials (above) compared granisetron and dolasetron to ondansetron but not to each other. These head-to-head trials did not allow indirect comparison of these drugs because they included different patient populations, and differing dose regimens of the antiemetic drugs. There are numerous placebo-controlled and active-controlled trials of dolasetron, granisetron and ondansetron for prevention of post-operative nausea and vomiting in adults and children (Appendix D).

While several good-quality systematic reviews published between 1995 and 1999 that evaluated a large proportion of the trials of ondansetron versus placebo or other antiemetic treatments, none reviewed the newer drugs and none made indirect comparisons.¹⁰⁰⁻¹⁰⁵

Dolasetron and granisetron in placebo-controlled trials

A small proportion of placebo-controlled trials allowed indirect comparisons between dolasetron and granisetron because they included similar populations of adults¹⁰⁶⁻¹⁰⁹ and reported similar outcomes. Complete response was generally defined as no vomiting or rescue medication use. Rates of complete response to placebo were similar across trials and this suggests a reasonable level of homogeneity in patient characteristics.

These comparisons (see Table 10 below) suggest that 1 and 3 mg of IV granisetron has higher absolute response rates than 25 mg or PO or IV dolasetron, even when comparing studies with similar placebo response rates. These are the doses most commonly used in the head-to-head trials of these drugs versus ondansetron. However, this indirect comparison is based on only one trial of granisetron. Indirect comparisons from the head-to-head trials do not provide more information, because the doses used in trials of dolasetron in similar patients were different, and no patients in the granisetron trials were undergoing gynecologic surgery.

Table 10. Indirect comparisons of PONV prophylaxis in placebo-controlled trials

| Trial (Sample Size) | Treatment | Mean age % female | Complete Response Rates | |
|---|---|----------------------|-------------------------|---------|
| | | | Treatment | Placebo |
| Adult women undergoing major gynecologic surgery | | | | |
| Diemunsch 1998 (n=789) | Dolasetron 25, 50, 100, or 200 mg oral | 43.0 years 100% | 45% | 35% |
| | | | 57% | |
| | | | 51% | |
| | | | 47% | |
| Warriner 1997 (n=374) | Dolasetron 25, 50, 100, or 200 mg oral | 43.3 years 100% | 36% | 29.3% |
| | | | 40.5% | |
| | | | 54.1% | |
| | | | 49.3% | |

| | | | Complete Response Rates | |
|-------------------------|---|-------------------|---------------------------------------|-------|
| Graczyk 1997 (n=635) | Dolasetron 12.5, 25, or 50 mg IV | 32 years 100% | 50% 52% 56% | 31% |
| Wilson 1996 (n=527) | Granisetron 0.1 mg, 1.0 mg and 3.0 mg IV | 47.4 years 96% | 44.7% 63.4% 61.7% | 33.8% |

Satisfaction and hospital stay outcomes: Ondansetron

None of the head-to-head trials of adults undergoing surgery reported quality of life, patient satisfaction, or resource utilization outcomes. To examine indirectly how newer antiemetics compare on such outcomes, we relied on placebo and active-controlled trials (Evidence Tables 11 and 12).^{108, 110-140} Table 11 summarizes the main findings.

Indirect comparisons between dolasetron and ondansetron in adults are limited due to differences in populations and method of outcome measurements. Table 11 below summarizes the findings of these trials on these measures. Indirect comparison of placebo-controlled trials would seem to indicate that dolasetron results in better satisfaction and shorter hospital stays when compared to placebo than when ondansetron is compared to placebo.

Table 11. Effects of antiemetics on post-operative satisfaction and hospital stay outcomes in adults

| Antiemetics | Comparators (Total # trials) | Satisfaction (# trials) | Hospital or PACU Stay (# trials) | Surgery types |
|--|---|------------------------------------|---|----------------------|
| Dolasetron ^{108, 116, 139} | Placebo (3) | Dolasetron superior (3) | Dolasetron superior (1) | Various |
| Ondansetron ^{112, 117-121, 125, 127, 128, 131, 133-138} | Placebo (8) | No differences (5/7) | No differences (3/4) | Various |
| | Other antiemetics (8) | No differences (5) | No differences (5) | |

Children

Direct comparisons

Dolasetron versus Ondansetron

Two trials compared IV dolasetron and IV ondansetron,^{141, 142} and one trial compared oral dolasetron and ondansetron in children undergoing surgical procedures.¹⁴³ Dosing was based on weight in all 3 trials, and was similar, but not identical in the 2 trial of the intravenous formulations. Two of the studies included tonsillectomy surgeries,^{142, 143} while a third excluded these because they routinely receive steroid prophylaxis.¹⁴¹ Of the 2 studies including tonsillectomies, 1 pre-treated children with dexamethasone¹⁴² and the other did not.¹⁴³ No significant differences were found between the drugs based on complete response at 24 hours. Complete response rates varied from 52% to 86%, with the higher rates seen in the trial using dexamethasone pre-treatment. Individual studies assessed shorter-term efficacy (0-6 hours),

longer-term efficacy (48 hours), and effect on vomiting only, but again no differences were found.

Table 12. Prevention of PONV: Complete response at 24 Hours**

| Adults | Intervention | Surgery Type | Complete Response |
|--|--|---|---|
| Dolasetron versus Ondansetron (IV) | | | |
| Paech 2003 | Dolasetron 12.5 mg Ondansetron 4mg | Gynecologic, including oncologic | 17% vs 20%, NS |
| Browning 2004 | Dolasetron 12.5mg Ondansetron 4mg | Gynecologic | NS * |
| Tang 2003 | Dolasetron 12.5mg Ondansetron 4mg | "superficial surgical procedures" | 98% vs 98%: NS |
| Zarate 2000 | Dolasetron 12.5 mg or 25mg Ondansetron 4mg or 8mg | ENT | D 12.5: 74% D25: 73% O4: 76% O8: 72% NS |
| Korttilla 1997 | Dolasetron 25mg or 50mg Ondansetron 4mg | Misc General (50% laparoscopic, 77% gynecologic) | D25: 51% D50: 71% O4: 64% D50 or D25 vs O4: NS D50 or O4 vs D25: p=0.05 |
| Granisetron versus Ondansetron (IV) | | | |
| Dua 2004 | granisetron 1mg Ondansetron 4mg | Modified Radical Mastectomy | O4: 60% G1: 75% NS |
| Naguib 1996 | granisetron 3mg vs Ondansetron 4mg | laparoscopic cholecystectomy | O4: 66% G3: 52% NS |
| Children | | | |
| Dolasetron versus Ondansetron | | | |
| Karamanlioglu 2003 | Dolasetron 1.8 mg/kg PO Ondansetron 0.15 mg/kg PO | elective strabismus (47%), middle ear, adenotonsillectomy or orchiopexy surgery | D: 68% O: 52% NS |
| Sukhani 2002 | Dolasetron 0.5mg/kg IV Ondansetron 0.15 mg/kg IV | tonsillectomy or adenotonsillectomy with DEX pretreatment | D: 86% O:92% NS |
| Olutoye 2003 | Dolasetron 0.35 or 0.70mg/kg IV Ondansetron 100 mcg/kg IV | Superficial Ambulatory Surgeries (89% Herniorrhaphy) | D350: 73% D700: 73% O100: 78% NS |

*Incidence/degree of nausea, incidence of emesis; **Abbreviations: O-ondansetron; D-dolasetron; G-granisetron; DEX-dexamethasone; PO-by mouth, orally; IV-intravenous; NS-not significant

Indirect comparisons

Dolasetron and granisetron in placebo-controlled trials of children

Just as for the population of adults undergoing surgery, placebo-controlled trials of dolasetron and granisetron for prevention of post-operative nausea and vomiting in children were reviewed for possible indirect comparisons of these antiemetics (Appendix D). Evidence was insufficient to reach conclusions about the comparative efficacy of dolasetron and granisetron from the only two placebo-controlled trials that involved similar enough populations (i.e., strabismus surgery) and outcome reporting methods to make indirect comparisons.^{140, 144} Dolasetron was given at the lowest end of the range in one study that compared a weight-dependent dosage strategy (0.35 mg/kg IV) and a fixed dose strategy (12.5 mg IV) to placebo in 118 children and reported complete response rates of 62%, 64% and 33%, respectively.¹⁴⁰ Response rates appear larger in the trial of granisetron 20, 40, and 80 mg compared to placebo (40% vs 83% vs 87% vs 33%) in 120 children, but the two trials are not necessarily suitable for indirect comparison due to the differences in dosage levels.¹⁴⁴

Satisfaction and hospital stay outcomes: Ondansetron

As in the head-to-head trials of adults undergoing surgery, no head-to-head trials of children undergoing surgery reported quality of life, patient satisfaction, or resource utilization outcomes. Again, we relied on fair-quality placebo and active-controlled trials to examine indirectly how newer antiemetics compare on such outcomes (Evidence Tables 11 and 12).^{110, 111, 113-115, 122-124, 126, 129, 130, 132} The results of these trials are summarized in the table below and seem to show that ondansetron results in better satisfaction when compared to placebo than does granisetron. However, direct comparisons are needed to confirm such conclusions.

Table 13. Effects of antiemetics on post-operative satisfaction and hospital stay outcomes in children

| Antiemetics | Comparators (Total # trials) | Satisfaction (# trials) | Hospital or PACU Stay (# trials) | Surgery types |
|---|---|------------------------------------|---|-----------------------|
| Dolasetron ¹⁴⁰ | Placebo (1) | NR | No differences (1) | Strabismus surgery |
| Granisetron ^{111, 113, 123} | Placebo (3) | No differences (1) | Granisetron superior (3) | Various |
| Ondansetron <small>110, 114, 115, 122, 124, 126, 129, 130, 132</small> | Placebo (2) | Ondansetron superior (1) | Ondansetron superior (2) | Various |
| | Other antiemetics (7) | No differences (1) | No differences (5/7) | |

Treatment of Established Post-Operative Nausea and Vomiting

Adults

Direct Comparisons

No head-to-head studies of Treatment of Established PONV were found.

Indirect Comparisons

We identified two good-quality systematic reviews of active- and placebo-controlled trials in patients with established PONV (Evidence Table 13).^{145, 146} One included only studies of ondansetron;¹⁴⁶ the other included studies of ondansetron, granisetron, and dolasetron.¹⁴⁵ To supplement evidence from these reviews, we included 6 active- and 2 placebo-controlled trials that were published subsequent to or were not included in these reviews (Evidence Tables 14 and 15). Four of six active-control trials included ondansetron,¹⁴⁷⁻¹⁵⁰ and two included granisetron.^{151, 152} One placebo-controlled trial included ondansetron¹⁵³ and the other included granisetron.¹⁵⁴

Results of Systematic Reviews

A review published in 1997¹⁴⁶ included randomized controlled trials of ondansetron versus placebo (3 trials),¹⁵⁵⁻¹⁵⁷ versus droperidol (2 trials),^{158, 159} and versus metoclopramide (1 trial).¹⁶⁰ All but one trial¹⁵⁹ was conducted in adults, and 82% of patients were women. The main outcome measure was complete control of further nausea, vomiting, or both, and results are presented for early (within 6 hours) and late (within 24 hours) efficacy. This review does not provide comparative information about different antiemetics, but it does provide estimates of complete response rates for ondansetron.

Ondansetron at all doses (1 mg, 4 mg, and 8 mg) was more effective than placebo at both early and late time points. The numbers needed to treat for early efficacy compared with placebo were 3.8 for 1 mg, 3.2 for 4 mg, and 3.1 for 8 mg. Over 24 hours, numbers needed to treat were 4.8 for 1 mg, 3.9 for 4 mg, and 4.1 for 8 mg. There was no difference between ondansetron and droperidol for early efficacy, and no difference between ondansetron and metoclopramide for both early and late efficacy.

A more recent review¹⁴⁵ included trials of dolasetron^{161, 162} and granisetron (1 trial)¹⁶³ in addition to ondansetron (8 trials).^{155-157, 164-168} This review separated results by prevention of further nausea and prevention of further vomiting, reporting early (within 6 hours) and late efficacy (within 24 hours). Studies that did not report nausea and vomiting results separately were not analyzed.

For prevention of further vomiting in vomiting patients, numbers needed to treat were similar for dolasetron, granisetron, and ondansetron. For early efficacy, the numbers needed to treat for dolasetron (12.5 mg to 100 mg) ranged from 3.6 to 4.7, for granisetron (0.1 mg to 3 mg) they ranged from 3.0 to 3.7, and for ondansetron (1 mg to 16 mg) they ranged from 2.3 to 3.7. For late efficacy, numbers needed to treat were 4.8 to 6.0 for dolasetron, 3.4 to 5.3 for granisetron, and 2.8 to 4.8 for ondansetron.

Comparative data for prevention of further nausea were limited; no study of dolasetron reported this outcome, and the only data for ondansetron for early efficacy are at the 8 mg dose. Comparing ondansetron 8 mg to the highest dose of granisetron (3 mg), ondansetron was more effective (78% vs 42%, NNT 2.0 vs 3.9). Confidence intervals overlapped, however, indicating the difference was not statistically significant. Granisetron was less effective for prevention of further nausea than prevention of further vomiting; conversely, ondansetron 8 mg was more effective for prevention of further nausea than vomiting.

Placebo-controlled trials: Early Efficacy

Table 14 shows complete response rates for early efficacy from placebo-controlled trials of dolasetron and ondansetron.^{155-157, 161, 162} No study of granisetron reported this endpoint. The numbers needed to treat versus placebo were lower for ondansetron, but confidence intervals overlap; therefore a significant difference between the drugs cannot be assumed.

Table 14. Dolasetron vs ondansetron for treatment of established PONV: Complete response in placebo-controlled trials (within 6 hours)

| Drug, dose | Population, Type of Surgery | Treatment group response rate | Placebo group response rate | Risk Difference (95% CI) NNT |
|---|--|-------------------------------|-----------------------------|------------------------------|
| Dolasetron | | | | |
| DIEMUNSCH, 1997 ¹⁶¹ (12.5 MG TO 100 MG) | 100% women Mean age 37 Laparoscopy, laparotomy, or vaginal hysterectomy | 155/227 (68.3%) | 28/54 (51.9%) | 16% (2% to 31%) 6.1 |
| Kovac, 1997 ¹⁶² (12.5 MG TO 100 MG) | 83% women Mean age 34 Gynecologic, orthopedic, ENT, breast, other | 256/499 (51.3%) | 33/121 (27.3%) | 24% (14% to 33%) 4.2 |
| Ondansetron | | | | |
| DuPen, 1992 ¹⁵⁶ (1 mg, 4 mg, or 8 mg) | 11% women Mean age 33 Surgery type not reported | 217/371 (58.5%) | 39/129 (30.2%) | 28% (18% to 37%) 3.5 |
| Bodner, 1991 ¹⁵⁵ (8 mg) | 100% women Mean age 31 Diagnostic laparoscopy or laparoscopic tubal ligation | 17/35 (48.6%) | 3/36 (8.3%) | 40% (20% to 58%) 2.5 |
| Larjani, 1991 ¹⁵⁷ (8 mg) | 94% women Mean age 36 Surgery type not reported | 14/18 (77.8%) | 5/18 (27.8%) | 50% (17% to 73%) 2.0 |

Placebo-controlled trials: Late Efficacy

Table 15 shows complete response rates at late time points from the 4 placebo-controlled trials (2 granisetron, 2 ondansetron) that reported this outcome.^{153, 154, 156, 164} The studies varied in their baseline risk, as indicated by a wide range of placebo response rates. Risk differences compared with placebo ranged from 16% to 41%. Confidence intervals again overlapped and statistically significant differences between granisetron and ondansetron cannot be assumed.

Table 15. Granisetron vs ondansetron for treatment of established PONV: Complete response in placebo-controlled trials (within 24 hours)

| Drug, dose (dose level) | Population, Type of Surgery | Treatment group response rate | Placebo group response rate | Risk Difference (95% CI) NNT |
|---|--|-------------------------------|-----------------------------|------------------------------|
| Granisetron | | | | |
| Fujii 2004a ¹⁵⁴ (10 mcg, 20 mcg, 40 mcg, or 100 mcg/kg) | 100% women Mean age 44 Abdominal hysterectomy | 57/80 (71%) | 6/20 (30%) | 41% (17% to 60%) 2.4 |
| Fujii 2004b ¹⁵³ (10 mcg, 20 mcg, 40 mcg, or 80 mcg/kg) | 60% women Mean age 47 Laparoscopic cholecystectomy | 64/80 (80%) | 10/20 (50%) | 30% (7% to 52%) 3.3 |
| Ondansetron | | | | |
| Claybon, 1994 ¹⁶⁴ (1 mg, 4 mg, or 8 mg) | 85% women Mean age 33 Surgery type not reported | 137/328 (42%) | 28/108 (26%) | 16% (5% to 25%) 6.3 |
| DuPen, 1992 ¹⁵⁶ (1 mg, 4 mg, or 8 mg) | 11% women Mean age 33 Surgery type not reported | 166/371 (45%) | 19/129 (15%) | 30% (21% to 37%) 3.3 |

Placebo-controlled trials: Need for Rescue Antiemetics

Only four placebo-controlled trials reported separately the need for rescue antiemetics (Table 16).^{154, 155, 161, 163} Rates for ondansetron and granisetron were similar. In one study of dolasetron, there was no difference between placebo and treatment groups. The number of patients needing rescue antiemetics was low in the placebo group in this study (18.5%) indicating that this may have been an unusual patient population and results may not be generalizable to other patient groups.

Table 16. Need for rescue antiemetics in placebo-controlled trials of established PONV

| Drug, dose | Treatment | Placebo | Risk difference (95% Confidence Interval) | NNT |
|--|--------------------|-------------------|---|-----|
| Ondansetron | | | | |
| Bodner, 1991 ¹⁵⁵ (8 mg) | 15/35 (42.9%) | 31/36 (86.1%) | -43% (-22% to -61%) | 2.3 |
| Dolasetron | | | | |
| Diemunsch, 1997 ¹⁶¹ (12.5 to 100 mg) | 34/227 (15.0%) | 10/54 (18.5%) | -3.5% (-6.2% to +16.5%) | NS |
| Granisetron | | | | |
| Taylor, 1997 ¹⁶³ (0.1 to 3 mg) | 164/386 (42.5%) | 89/133 (66.9%) | -24% (-14% to -33%) | 4.1 |

| Drug, dose | Treatment | Placebo | Risk difference (95% Confidence Interval) | NNT |
|--|------------------|----------------|--|------------|
| Fujii, 2004a ¹⁵⁴ (10 to 80 mcg/kg) | 4/80 (5%) | 5/20 (25%) | -20% (-4% to -42%) | 5.0 |

Placebo- and active-controlled trials: Patient satisfaction

No study of treatment of established PONV reported patient satisfaction as a primary endpoint, but limited information on this outcome is reported in four active-controlled^{147, 148, 152, 165} and one placebo-controlled trial.¹⁶¹

In three studies, patients were more satisfied with ondansetron^{148, 165} or granisetron¹⁵² than with metoclopramide or droperidol. It is not possible to make an indirect comparison of ondansetron versus granisetron from these studies because they used different methods to measure patient satisfaction.

In a study comparing ondansetron to acustimulation, there was no difference in patient satisfaction rates between treatment groups.¹⁴⁷ The evidence for dolasetron is from one placebo-controlled trial.¹⁶¹ Patients were more satisfied with dolasetron than placebo as measured by a visual analogue scale.

Children

Direct Comparisons

No head-to-head studies of Treatment of Established PONV were found.

Indirect Comparisons

The evidence for treatment of established PONV in children is limited to two trials of ondansetron: one placebo-controlled trial in 375 children ages 2 to 12 years¹⁶⁶ and one active-controlled trial (versus droperidol) in 29 children ages 2 to 10 years.¹⁵⁹ 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.¹⁶⁶ Ondansetron was superior to placebo at 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, $p < 0.001$) time points. Fewer ondansetron patients needed rescue medication (9% ondansetron vs. 27% placebo within 2 hours; 17% ondansetron vs 51% placebo within 24 hours).

In a small active-control trial,¹⁵⁹ the difference between ondansetron 0.1 mg/kg and droperidol 2.0 mg/kg for early efficacy (complete control of PONV within 4 hours) was not significant (75% for ondansetron vs 84.6% for droperidol; odds ratio 0.60, 95% CI 0.10 to 3.4). Late success and need for rescue medication was 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 non-comparative for our purposes.^{169, 170} The only trial identified compared ondansetron and

promethazine in 30 women hospitalized with hyperemesis gravidarum and found no differences on any outcome measure.

Key Question 2.

What is 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 pre-specified and were inadequately defined. Ascertainment techniques were generally inadequately defined and it was not possible to determine whether they were non-biased and accurate. Specifically, it was often unclear as to whether the adverse events reported included those that investigators considered “unrelated”, and how this was determined. It was also unclear as to whether adverse event reporting included all levels of severity and how these were defined. All of these factors likely contribute to the wide ranges of event rates seen in these trials and these outcomes should be interpreted with caution.

Prevention of Chemotherapy-Related Nausea and Vomiting

Adults

Tolerability

The majority (82%) of trials reported adverse event outcomes and there were generally no statistically significant differences.^{21, 22, 25, 27, 28, 33, 36-40, 42, 45-47, 49, 52-55, 57, 61-63} Proportions of patients with at least one adverse event ranged from 33.8-58% for dolasetron, 28-87.1% for granisetron, 24-85.8% for ondansetron, and 61-66.5% for palonosetron. Rates of withdrawals were rarely reported and ranged from none^{49, 54, 61} to less than 3% for both granisetron and ondansetron.³⁷ Headache, constipation and diarrhea were the most common adverse events and rates (ranges) are shown in the table below.

Table 17. Rates (ranges) of most common AE's in HTH trials*

| Comparison | Headache | Constipation | Diarrhea |
|------------|--------------------------|------------------------|---|
| G vs O | 1.4%-53.3% vs 1.3%-33.3% | <1-20% vs 0.4-30% | 3-12% vs 0-9.8% |
| D vs O | 18.8-43.7% vs 14.5-36.5% | 1.3-39.4% vs 1.3-32.1% | 16.3% vs 8.2% p=0.0001 ⁵⁵ |
| D vs G | 22-28% vs 23% | NR | 11-13% vs 6% |
| P studies | 4.8-15.4% vs 5.3-16.5% | 1.6-9.2% vs 1.6-6.2% | 1-1.6% vs 2.1% |
| G iv vs po | 8% vs 8% | 0% vs 2% | NR |

*Abbreviations: G-granisetron; O-ondansetron; D-dolasetron; P-palonosetron; po-by mouth, orally; iv-intravenous; NR-not reported

Ondansetron was associated with significantly higher rates of dizziness and abnormal vision than either granisetron⁴⁰ or dolasetron⁵⁵ in one trial of each comparison that used higher doses of ondansetron (32 mg IV)(Table 18). Two other trials reported insignificant differences in dizziness rates for granisetron and ondansetron.^{22, 52} One trial compared ondansetron (IV or

oral) and dolasetron (IV or oral) in 696 patients and reported higher rates of constipation (39.4% vs 32.1%; $p=0.044$) for ondansetron and higher rates of diarrhea (16.3% vs 8.2%; $p=0.001$) and abdominal pain (15.7% vs 9.6%, $p=0.015$) for dolasetron.⁵⁵

Table 18. Rates of dizziness and abnormal vision in HTH trials with ondansetron*

| Study (sample size) Treatments | Dizziness | Abnormal vision |
|--|-------------------------|--------------------------|
| Lofters 1997 (n=696) D: iv 2.4 mg/kg QD OR po 200 mg QD O: iv 32 mg OR po 8 mg bid | 14% vs 25.5%; $p<0.001$ | 4.1% vs 14.2%; $p<0.001$ |
| Perez 1998 (n=1085) G: po 2 mg QD O: iv 32 mg QD | 5.4% vs 9.6%, $p=0.011$ | 0.6% vs 4.2%, $p<0.001$ |
| Chiou 2000 (n=61) G: po 1 mg QD O: iv 3 mg tid | 8% vs 3.8%, NS | NR |
| Orchard 1999 (n=187) G: iv 10 µg/kg Q12 hrs O: iv 0.15 mg/kg load along with a 0.03 mg/kg/h drip | 4.4% vs 2%, NS | NR |

*Abbreviations: G-granisetron; O-ondansetron; D-dolasetron; po-by mouth, orally; iv-intravenous; QD-once a day; tid-three times daily; NS-not significant; NR-not reported

Rates of death were not different between po dolasetron and po ondansetron,⁵³ iv dolasetron and iv ondansetron,⁵³ or between iv or po granisetron in 3 trials⁶³ The deaths were attributed to the patients' underlying disease process.

Serious adverse events

Serious adverse event rates reported in trials in patients undergoing chemotherapy were not significantly different for iv dolasetron or granisetron (6% vs 7% vs 5%, NS).⁵⁷ Only two adverse events were rated as being related to antiemetic treatment and these were angina/MI/acute pulmonary edema in one patient and fever/abdominal pain in another, both associated with granisetron. Rates of hospital admission for fluid administration were not significantly different for iv dosages of granisetron 3 mg and ondansetron 32 mg (0.8% vs 0.8%, NS) and there were no emergency admissions.²¹

Reports of serious adverse events outside of the trial setting come only from uncontrolled studies of dolasetron,¹⁷¹ granisetron,¹⁷² and ondansetron¹⁷³⁻¹⁷⁵ in adults (Evidence Tables 16 and 17). These studies were generally poor quality, lacking detail regarding patient selection processes, ascertainment methods, and adverse event descriptions and 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.

Children

Tolerability

Evidence regarding comparative tolerability of newer antiemetics in children is severely limited and indicates no differences in adverse event rates for oral solution and iv forms of ondansetron.⁷⁸ IV and oral solution forms of ondansetron were associated with similar rates of any adverse event (24% vs 25%, NS), abdominal/gastrointestinal discomfort (4% vs 3%, NS), fever/pyrexia (3% vs 3%, NS), and diarrhea/headache (2% vs 2%, NS) in a trial of 428 children undergoing moderate to severely emetogenic chemotherapy for hematological malignancies (mean age=8 years).⁷⁸

Serious adverse events

Reports of serious adverse events in observational studies of granisetron¹⁷⁶ and ondansetron^{177, 178} in children (Evidence Tables 16 and 17) suffered from similar methodological flaws as those discussed above.

Prevention and Treatment of Post-Operative Nausea and Vomiting

Adults

Only 3 of 10 studies of 5HT₃ antagonists in preventing PONV reported on adverse events experienced by participants.^{92, 93, 97} Of these only 2 reported adequate data to make a comparison between the drugs.^{93, 97} In these studies, no differences in the rate of overall adverse events or any particular adverse event was found between dolasetron or granisetron versus ondansetron.

The most frequent adverse event reported in trials of established PONV was headache. Three placebo-controlled trials of ondansetron,¹⁵⁵⁻¹⁵⁷ two of dolasetron,^{161, 162} and one of granisetron¹⁶³ 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^{153, 154} did not report the numbers of patients with headache in each group, but noted that the incidence of headache did not differ from placebo.

The Kazemi systematic review¹⁴⁵ did not report comparative information for adverse events separately by individual antiemetic, but an analysis of headache versus 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.

Children

No comparative information on the adverse events in children is available. Indirect evidence is extremely limited. In a placebo controlled trial in children,¹⁶⁶ 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 (NS).

Patients Undergoing Radiation

Adults

Direct comparisons

Our own post-hoc analyses suggested no differences between oral granisetron 2 mg and oral ondansetron in tolerability in 34 patients undergoing hyper-fractionated total body irradiation (TBI).⁷⁹ Similar rates of patients had adverse experiences that were possibly/probably related to study medication (38.9% vs 25%, NS). The most frequently reported adverse experiences were headache (27.8% vs 18.8%, NS) and diarrhea (22.2% vs 6.3%, NS). Two patients in each treatment group experienced severe adverse events. These were both headache in the granisetron group and one episode each of severe infection and nervousness in the ondansetron group.

Indirect comparisons

Placebo-controlled and active-controlled trials of dolasetron, granisetron, or ondansetron did not provide any opportunity to conduct indirect comparisons due to heterogeneity in populations, comparators, radiotherapy regimens, and adverse event reporting.^{2, 80-89} Conclusions from a previous systematic review⁹¹ of earlier trials of granisetron⁸⁷ and ondansetron^{81-83, 90} were that these drugs are associated with increased incidence of headache and constipation. The additional placebo-controlled and active-controlled trials of granisetron⁸⁰ and ondansetron^{85, 86, 88, 89} we reviewed also reported headache and constipation as being the most common significant adverse events.

Pregnant Patients

Short Term Tolerability

In a study of ondansetron versus promethazine in women with hyperemesis gravidarum, significantly more women experienced sedation with promethazine compared to ondansetron.¹⁶⁹ 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.¹⁷⁹ The study enrolled 188 pregnancies with exposure to ondansetron, with exposure during weeks 5-9 of gestation. The women had all been treated for nausea and vomiting associated with pregnancy. Loss to follow-up in this group was 6%. This study used 2 comparison groups, women exposed to other antiemetics during, and women exposed to other non-teratogenic 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 the groups in number of live births, proportion of infant with deformities, birth weight and other measures.

Key Question 3

Are there subgroups of patients based on demographics (age, racial groups, gender), pregnancy, other medications, or co-morbidities 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 by only a few studies and focused only on protection against post-operative and emetogenic chemotherapy-related nausea/vomiting.^{21, 25, 26, 28, 36, 46, 53, 54, 57, 78} Safety comparisons in subpopulations were lacking in most studies.

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

Co-morbidities 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 in the study did not analyze the effects in these subgroups, however.

Demographics

There were no differences between dolasetron or granisetron and ondansetron, or between each other, in rates of complete emetic control in subpopulations based on age or gender in adult patients aged 18 to 94 years undergoing emetogenic chemotherapy for a variety of cancer types.^{25, 28, 36, 40, 46, 53, 54, 57} These drugs also appear to work well in preventing post-operative nausea/vomiting (PONV) and no differences were found in trials that included primarily women in (4 of 10 studies) or those that included more males.

There were also no differences between ondansetron IV and oral solution formulations in rates of complete or major control of emesis in subpopulations based on age in children aged 1-17 years undergoing moderate-highly emetogenic chemotherapy for treatment of various cancer types.⁷⁸

In the adult populations studied for PONV, the mean ages of patients in dolasetron versus ondansetron studies was 45 years, and in granisetron versus ondansetron studies, 42 years. While these means include both older and younger patients, from these data it is not clear if differences among the drugs exist in these age groups, particularly safety comparisons in older patients are lacking. Similarly, in the pediatric populations, the mean ages ranged from 6 to 9, so for younger children and adolescents very little comparative information is available and what exists is not stratified by age.

Other medications

There were no differences between ondansetron and either dolasetron or granisetron in rates of complete emetic control in subpopulations based on use of concomitant medications in patients undergoing emetogenic chemotherapy for a variety of cancer types (e.g., corticosteroids,^{28, 40} H2-receptor antagonists,²⁵ opioids,²⁵ benzodiazepines,^{25, 54} or NSAIDs²⁵).

Concomitant medications that were disallowed or used as part of anesthesia, pre-anesthesia or post-op pain control also varied in trials of PONV prevention, with some excluding drugs often used as pre-anesthetics or anesthetics known or thought to have antiemetic properties. Overall, higher rates of complete response were seen in trials that included use of dexamethasone pre-operatively, and lower rates were associated with gynecologic surgeries and

lower doses of the 5HT3 antagonist. Differences between dolasetron, granisetron, and ondansetron in subpopulations based on concomitant medication use cannot be seen from these data.

Prognostic factors

Evidence from a post-hoc subgroup analysis of a trial in patients receiving emetogenic 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 emetogenic chemotherapy).²⁵ IV granisetron 3 mg was associated with lower rates of complete protection from emesis in patients with motion sickness when compared to those without (16.9% vs 43%; $p < 0.0001$); whereas, iv ondansetron 24 mg was associated with similar rates of complete protection regardless of the presence of motion sickness (19.9% vs 30%, NS).²⁵ IV granisetron was also associated with significantly lower rates of protection from vomiting than IV ondansetron in a subgroup of patients previously treated with emetogenic chemotherapy.²⁵ Authors note that these outcomes may be due to chance, given that the numbers of patients in these subgroups were relatively small.

SUMMARY

Table 19. Overall Summary Table

| Treatments | Quality of evidence | Conclusions |
|--|--|--|
| Key Question 1: Effectiveness or Efficacy | | |
| Dolasetron vs ondansetron | | |
| IV vs IV | Adults | |
| | Chemotherapy (2 trials): Fair | No differences in complete delayed response. Mixed results on complete response at 24 hours: ondansetron superior in one of two trials |
| | Prevention of PONV (5 trials): Good | No differences in complete response at 24 hours. Indirect comparisons of functional outcomes were inconclusive. |
| | Children | |
| | Prevention of PONV (2 trials): Fair | No consistent differences in complete response at 24 hours |
| | Prevention of PONV (3 trials): Fair-Poor | <i>Indirect</i> comparisons suggest that ondansetron may be superior to dolasetron in reducing duration of hospital stay. |
| | Treatment of established PONV (1 systematic review, 7 trials) Fair | <i>Indirect</i> comparisons suggest that dolasetron and ondansetron are similarly efficacious for complete response at early time points (within 6 hours). |
| PO vs PO | Adults | No differences in complete response at 24 hours. Rates of complete delayed response were not reported. |
| | Chemotherapy (1 trial): Fair-Poor | |
| | Children | |
| | Prevention of PONV (1 trial): Fair-Poor | |
| Comparisons of all formulations | Adults: Prevention of PONV (10 trials): Fair | <i>Indirect</i> comparisons suggest that dolasetron may be superior to ondansetron in improving patient satisfaction and decreasing duration of hospital stay. |

| Treatments | Quality of evidence | Conclusions |
|-----------------------------------|--|---|
| Granisetron vs ondansetron | | |
| IV vs IV | Adults | |
| | Chemotherapy (5 trials): Good | No differences in acute/delayed complete response rates |
| | Radiation (1 trial) Poor | No difference in acute/delayed complete response |
| | Prevention of PONV (2 trials): Fair | No differences in rates of complete response at 24 hours |
| | Children | |
| | Chemotherapy (1 trial): Fair-Poor | No differences in rates of acute complete response. Rates of complete delayed response were not reported. |
| | Prevention of PONV (5 trials): Fair-Poor | <i>Indirect</i> comparisons suggest that ondansetron may be superior to granisetron in increasing patient satisfaction. <i>Indirect</i> comparisons do not suggest any differences in effects on hospital stay. |
| | Treatment of established PONV (1 systematic review, 4 trials) Fair | <i>Indirect</i> comparisons suggest that granisetron and ondansetron are similarly efficacious for complete response at late time points (within 24 hours), and for need for rescue antiemetics. |
| PO vs PO | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences in acute/delayed complete response rates |
| IV vs PO | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences in rates of complete response at 24 hours |
| PO vs IV | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences in acute/delayed completed response rates |
| Dolasetron vs granisetron | | |
| IV vs IV | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences in rates of 24-hour complete response. Rates of complete delayed response were not reported. |
| | PONV Prevention in women undergoing gynecologic surgery (4 trials) Fair-Poor | <i>Indirect</i> comparisons are limited and are not adequate to establish a difference in response rates between these drugs.. |
| | Children | |
| | PONV Prevention in patients undergoing strabismus surgery (2 trials): Fair-Poor | <i>Indirect</i> comparisons were not adequate to establish a difference in response rates between these drugs. |

| Treatments | Quality of evidence | Conclusions |
|--|---|---|
| Palonosetron vs dolasetron | | |
| IV vs IV | Adults Chemotherapy (1 trial): Fair-Poor | Complete response rates: Palonosetron noninferior in acute/delayed complete response rates |
| Palonosetron vs ondansetron | | |
| IV vs IV | Adults Chemotherapy (1 trial): Fair-Poor | Palonosetron superior in acute/delayed complete response rates |
| Granisetron | | |
| IV vs PO | Adults Chemotherapy (1 trial): Fair-Poor | No differences in rates of 24-hour complete response |
| Ondansetron | | |
| IV vs PO oral solution | Children Chemotherapy (1 trial): Fair-Poor | No differences in proportions of patients with no vomiting within and beyond 24 hours |
| IV | Pregnancy - Poor 1 Active-controlled trial | No direct or indirect comparisons possible. Ondansetron was not found superior to promethazine |
| Key Question 2: Tolerability and safety | | |
| Dolasetron vs ondansetron | | |
| IV vs IV | Adults Chemotherapy (2 trials): Fair | Ondansetron associated with higher rates of dizziness and blurred vision than dolasetron. Dolasetron associated with higher rates of diarrhea, and abdominal pain while ondansetron had higher rates of constipation. No other differences found. |
| | Prevention or Treatment of PONV (1 trial): Fair-Poor | No differences |
| | Children Prevention of PONV (2 trials): Poor | Not reported |
| PO vs PO | Adults Chemotherapy (1 trial): Fair-Poor | No differences |
| | Children Prevention of PONV (1 trial): Poor | Not reported |
| Granisetron vs ondansetron | | |

| | | |
|------------------------------------|---|--|
| IV vs IV | Adults | |
| | Chemotherapy (5 trials): Good | No differences |
| | Prevention of PONV (1 trial): Fair-poor | No differences |
| | Radiation (1 trial) Poor | No difference |
| | Children | |
| | Chemotherapy (1 trial): Fair-Poor | No differences |
| PO vs PO | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences |
| IV vs PO | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences |
| PO vs IV | Adults | |
| | Chemotherapy (2 trials): Fair-Poor | Ondansetron associated with higher rates of dizziness and blurred vision than granisetron when higher doses used, no difference when lower doses of ondansetron used. No other differences |
| Dolasetron vs granisetron | | |
| IV vs IV | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences |
| Palonosetron vs dolasetron | | |
| IV vs IV | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences |
| Palonosetron vs ondansetron | | |
| IV vs IV | Adults | |
| | Chemotherapy (1 trial): Fair-Poor | No differences |
| Granisetron | | |
| IV vs PO | Adults | No differences in rates of 24-hour complete response |
| | Chemotherapy (1 trial): Fair-Poor | |
| Ondansetron | | |
| IV vs PO oral solution | Children | |
| | Chemotherapy (1 trial): Fair-Poor | Not reported |
| IV | Pregnancy - Poor | |
| | 1 Active-controlled trial and 1 observational study | No evidence compared to other newer antiemetics. Ondansetron associated with less sedation than Promethazine. There were no differences between ondansetron and other older antiemetics in birth outcomes. |

| Treatments | Quality of evidence | Conclusions |
|--|---|--|
| Key Question 3: Effectiveness, efficacy, tolerability and safety in subgroups | | |
| Dolasetron vs granisetron vs ondansetron | | |
| | Adults aged 18-94 undergoing chemotherapy (subgroup analyses in 8 trials): Good | No differences in complete response rates in subpopulations based on age, gender or use of concomitant medications. |
| Ondansetron vs granisetron | | |
| IV vs IV | Adults undergoing chemotherapy: (subgroup analysis in 1 trial): Fair-poor | Ondansetron superior to granisetron in complete response rates in subpopulations based on a predisposition to nausea/vomiting (motion sickness, previous treatment with emetogenic chemotherapy) |
| Ondansetron | | |
| IV vs PO oral solution | Children aged 1-17 years undergoing chemotherapy (subgroup analyses in 1 trial): Fair-poor | No differences in complete response rates in subpopulations based on age. |

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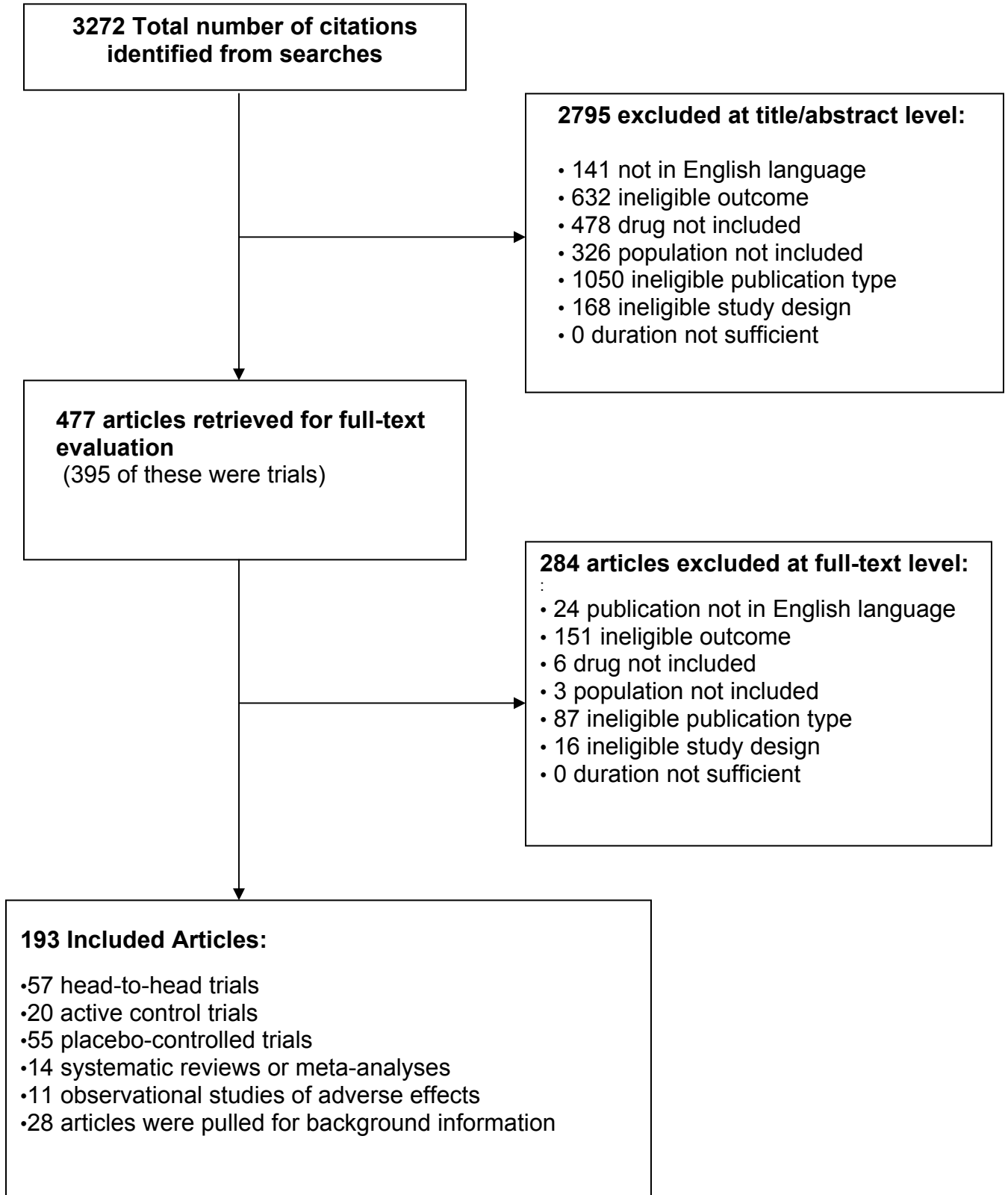
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Figure 1. Results of literature search



Appendix A. 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)

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)

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and “The Database of Abstracts of Reviews of Effects (DARE)” in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of “good”, “fair” or “poor”. Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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.

For 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 numbers, birth dates or weekdays
 - 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
 - Other approaches sequence to clinicians and patients
 - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
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 the 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 (i.e., 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 followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of followup? (Give numbers at each stage of attrition.)

*For Studies Reporting Complications/Adverse Effects***Assessment of Internal Validity**

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?
2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in 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 non-biased and accurate ascertainment of events (independent ascertainment; validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)
5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,

i.e., 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 search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of 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 (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Placebo-controlled and active-controlled trials for prevention of chemotherapy-related nausea and vomiting

1. On the relationship between nausea and vomiting in patients undergoing chemotherapy. Italian Group for Antiemetic Research. *Support Care Cancer*. May 1994;2(3):171-176.
2. Aapro MS, Thuerlimann B, Sessa C, de Pree C, Bernhard J, Maibach R. A randomized double-blind trial to compare the clinical efficacy of granisetron with metoclopramide, both combined with dexamethasone in the prophylaxis of chemotherapy-induced delayed emesis. *Annals of Oncology*. 2003;14(2):291-297.
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9. Anonymous. Delayed emesis induced by moderately emetogenic chemotherapy: do we need to treat all patients? The Italian Group for Antiemetic Research. *Annals of Oncology*. 1997;8(6):561-567.
10. Anonymous. Ondansetron versus metoclopramide, both combined with dexamethasone, in the prevention of cisplatin-induced delayed emesis. The Italian Group for Antiemetic Research. *Journal of Clinical Oncology*. 1997;15(1):124-130.
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13. Ballatori E, Roila F, Salinaro F, et al. Ondansetron (OND) vs metoclopramide (MTC) both combined with dexamethasone (DEX) in the prevention of cisplatin (CDDP)-induced delayed emesis. The Italian Group for Antiemetic Research. *Supportive Care in Cancer*. 1996;4(251).

14. Barrenetxea G, Schneider J, Mar Centeno M, Romero H, De la Rica M, Rodriguez-Escudero FJ. Chemotherapy-induced emesis: Management of early and delayed emesis in milder emetogenic regimens. *Cancer Chemotherapy and Pharmacology*. 1996;38(5):471-475.
15. Beck T, York M, Chang A, et al. Oral ondansetron 8 MG BID is as effective as 8 MG TID in the prevention of nausea and vomiting associated with cyclophosphamide-based chemotherapy. *Breast Cancer Research & Treatment*. 1996;37(Suppl):92-92.
16. Beck TM. The pattern of emesis following high-dose cyclophosphamide and the antiemetic efficacy of ondansetron. *Anti-Cancer Drugs*. 1995;6(2):237-242.
17. Beck TM. Efficacy of ondansetron tablets in the management of chemotherapy-induced emesis: Review of clinical trials. *Seminars in Oncology*. 1992;19(6 SUPPL. 15):20-25.
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23. Bonnetterre J, Chevallier B, Metz R, et al. A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, fluorouracil, and doxorubicin or epirubicin chemotherapy. *Journal of Clinical Oncology*. 1990;8(6):1063-1069.
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29. Bremer K, Hans K, Harjung H, Kurrle E, Uhlenbusch R. Granisetron (Gran), a selective 5-HT₃-antagonist, compared to alizapride plus dexamethasone (comp) as antiemetics during five-day-cycles of cytotoxic chemotherapy. *Ann-Oncol*. 1990;1(Suppl):110.
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Appendix D. Placebo-controlled and active-controlled trials for prevention of PONV

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Appendix E. Abbreviations Used in Report

| | |
|--------------|--|
| A | aprepitant |
| ACT | active controlled trials |
| AEs | adverse events |
| bid | twice a day |
| BMT | bone marrow transplantation |
| CC | concomitant |
| CI | confidence interval |
| Cyclo | cyclophosphamide |
| d | day |
| D | dolasetron |
| DERP | Drug Effectiveness Review Project |
| DEX | dexamethasone |
| Dox | doxorubicin |
| e.g. | for example |
| EORTC QLQ 30 | European Organization for Research and Treatment Center, Quality of Life Questionnaire |
| Epir | Epirubicin |
| FDA | Food and Drug Administration |
| FLIE | Functional Living Index-Emesis |
| G | granisetron |
| HCl | hydrogen chloride |
| hr | hour |
| HTH | head-to-head |
| i.e. | that is |
| im | intramuscular |
| iv | intravenous |
| kg | kilograms |
| m(os) | month |
| mcg | microgram |
| meto | metoclopramide |
| mg | milligrams |
| min | minute |
| mL | milliliter |
| MPR | Methylprednisolone |
| NCI | National Cancer Institute |
| NK1 | tachykinin neurokinin |
| NNT | number needed to treat |
| NR | not reported |
| NS | not significant |
| NSAIDs | non-steroid anti-inflammatory drugs |
| O | ondansetron |
| ODT | oral disintegrating tablet |
| P | palonosetron |
| PBPCT | peripheral blood progenitor cell transplantation |
| PCT | placebo controlled trials |
| po | (<i>per os</i>) orally |
| PONV | post-operative nausea and vomiting |

| | |
|-------|-----------------------------|
| PR | predniselone |
| qd | once a day |
| qid | four times daily |
| QOL | quality of life |
| RCT | randomized controlled trial |
| RT | radiotherapy |
| TBI | total body irradiation |
| tid | three times daily |
| U.K. | United Kingdom |
| U.S. | United States |
| ULN | Upper Limit of Normal |
| VAS | visual analog score |
| vs | versus |
| wk | week |
| y(rs) | year |