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[Intervention Review]

Serotonin receptor antagonists for highly emetogenic chemotherapy in adults

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ABSTRACT

Background

Serotonin receptor antagonists (5-HT_3 RAs) are used to control chemotherapy-induced emesis. Although they have the same general mechanism of action (blockade of serotonin receptors), they have different chemical structures and may have different effects.

Objectives

To compare efficacy of different serotonin receptor antagonists (5-HT_3 RAs) in the control of acute and delayed emesis induced by highly emetogenic chemotherapy.

Search methods

We searched CENTRAL, the Specialised Register of the Cochrane PaPaS Group, PubMed, EMBASE, and LILACS databases. Our most recent search was in March 2009.

Selection criteria

Randomised trials comparing 5-HT_3 RAs in an adult cancer population.

Data collection and analysis

We extracted information from the included studies on the control of acute and delayed nausea and vomiting, either as a single or a combined outcome. Where appropriate, we combined the results of similar trials. We carried out sensitivity and subgroup analyses to test the robustness of our findings.

Main results

We included 16 randomised trials (7808 participants). Nine of the trials compared granisetron versus ondansetron. No other drug comparison was studied in more than one trial. The meta-analyses of the granisetron versus ondansetron trials found similar results for the two drugs on acute vomiting (eight trials, 4256 participants, odds ratio (OR) 0.89; 95% CI 0.78 to 1.02), acute nausea (seven trials, 4160 participants, OR 0.97; 95% CI 0.85 to 1.10), delayed vomiting (three trials, 1119 participants, OR 1.00; 95% CI 0.74 to 1.34) and delayed nausea (two trials, 1024 participants, OR 0.96; 95% CI 0.75 to 1.24). Granisetron and ondansetron showed similar effects on headache and diarrhoea, with the possible exception of less constipation associated with ondansetron.

One study of 1114 participants comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone showed superiority of palonosetron in controlling delayed vomiting (OR 1.45; 95% CI 1.14 to 1.85) and delayed nausea (OR 1.63; 95% CI 1.27 to 2.10). Complete

response for delayed nausea and vomiting was also in favour of the combination palonosetron and dexamethasone (OR 1.63; 95% CI 1.29 to 2.07).

Authors' conclusions

Ondansetron and granisetron appear to be equivalent drugs for the prevention of acute and delayed emesis following the use of highly emetogenic chemotherapy.

According to one single trial the combination of palonosetron and dexamethasone was superior to granisetron and dexamethasone in controlling delayed emesis. However, more evidence is needed before palonosetron could become the candidate 5-HT_3 RA for the control of delayed emesis induced by highly emetogenic chemotherapy.

PLAIN LANGUAGE SUMMARY

Serotonin receptor antagonists to prevent nausea and vomiting after chemotherapy

Nausea and vomiting are among the most distressing side effects associated with chemotherapy for cancer patients. The search for the best way to prevent these symptoms is ongoing. The development of a group of drugs that act as highly selective antagonists for the serotonin (5-HT_3) receptors which may trigger the symptoms was a major step forward. These anti-emetic drugs, called serotonin receptor agonists (5-HT_3 RAs, for short), gave better control than a commonly used drug, metoclopramide.

Today, the use of 5-HT_3 RAs in the patient's treatment plan, either alone or in combination with other drugs, is regarded as the 'gold standard' alongside chemotherapy that is known to cause many patients to experience nausea and vomiting. There are several 5-HT_3 RAs, and although they have different chemical structures they all work in similar ways by blocking the serotonin receptors**.** However, it is worthwhile knowing if there are important differences in the effects of 5-HT_3 RAs, which include ondansetron, granisetron, tropisetron, dolasetron and palonosetron. This systematic review set out to compare these drugs to see if one of them is more effective. However, we found only a small number of trials evaluating tropisetron, dolasetron, ramosetron and palonosetron, so we cannot be sure about how they rank against the other drugs. Most of the trials compared granisetron versus ondansetron and so we were only able to combine the results of trials of this comparison. We found that the effects of granisetron and ondansetron were similar. We were able to study their effects on several outcomes and found similarities for acute vomiting, acute nausea, combined acute nausea and vomiting, delayed vomiting, delayed nausea and the combination of delayed vomiting and nausea. The two drugs were also similar for adverse events, including common side effects such as headache and diarrhoea, with the possible exception of less constipation with the use of ondansetron. This evidence shows that ondansetron and granisetron can be regarded as equivalent drugs for the prevention of acute and delayed nausea and vomiting for patients receiving chemotherapy. There is not enough evidence to know whether any of the different 5-HT_3 RAs have similar or different effects. Therefore, the choice of which 5-HT_3 RA to use for the prevention of acute nausea and vomiting should be influenced by local conditions, including the costs of the drugs and the ease with which they can be provided. One large study of 1114 participants comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone showed palonosetron to be better at controlling delayed vomiting and delayed nausea. Palonosetron and dexamethasone combined appeared to be good at delaying nausea and vomiting. As the results from a single trial are limited, and also because another trial comparing palonosetron with ondansetron showed a lack of benefit, however, further evidence is needed before palonosetron can be recommended as the 5-HT_3 RA of choice for the prevention of delayed nausea and vomiting.

BACKGROUND

Description of the condition

Nausea and vomiting are among the most distressing side effects associated with chemotherapy in cancer patients. However, the magnitude of the problem is not always fully appreciated by physicians and nurses. A survey of a group of women with breast cancer treated with chemotherapy highlighted the underestimates (Grunberg 2003).

Severe nausea and vomiting can cause metabolic disturbances secondary to dehydration and malnutrition. This in turn can interfere with the clinical course of the patient's disease and with their acceptance of chemotherapy. The patient's perception of adequate control of nausea and vomiting is an essential part of any cancer management plan. Inadequately controlled emesis significantly impairs quality of life and increases the risk of non-compliance with the chemotherapy programme (Hesketh 1999).

Vomiting is a partially understood, complex mechanism based on the interaction between humoral factors, afferent fibres, as well as inhibition and excitation of somatic and visceral musculature (Ettinger 1995). The vomiting centre in the brain medulla, which is responsible for the co-ordination of emesis, is deemed to be activated by afferent impulses from the chemoreceptor trigger zone (CTZ), the vestibular apparatus, the mid brain, the limbic system and the pharynx or gastrointestinal tract (Siegel 1981). Following activation of the vomiting centre, efferent impulses to the salivation centre, abdominal muscles, respiratory centre and cranial nerves lead to vomiting (Craig 1987). The understanding of the physiology of emesis has been greatly accelerated by the identification of specific neurotransmitter receptors that play a pivotal role in drug-induced emesis. Several critical receptors which trigger the act of vomiting when stimulated by chemotherapeutic agents, their metabolites or released neurotransmitters have been identified in the central nervous system (CNS) and in the gastrointestinal (GI) tract (Borison 1983; Tack 2000).

Activation in the brain medulla of either the vomiting centre or the CTZ is mediated through dopamine, opioid, histamine, acetylcholine, neurokinin (NK-1) or serotonin receptors (Ettinger 1995). Acute emesis caused by cytotoxic drugs is associated with an increase in the concentration of serotonin in the intestine and the brainstem. However, the current hypothesis about chemotherapy-induced nausea and vomiting (CINV) is that chemotherapy-induced serotonin release from enterochromaffin cells in the gut results either in direct interaction with CNS serotonin receptors or in the stimulation of $5HT_3$ receptors on afferent vagal fibres in the gut. This then generates impulses to the centre of vomiting in the lateral reticular formation in the medulla (ASHP 1999; Cubeddu 1990). The validity of this pathogenic model is supported by the fact that anti-emetic agents which bind to CTZ and peripheral receptors are the most effective in the prevention of CINV (Gralla 1991). Delayed nausea and vomiting is less well understood and may involve mechanisms other than those mediated through serotonin receptors (Kris 1994; Rudd 1994).

How the intervention might work

The first receptors targeted by drug research have been dopamine receptors, which are found in high concentration in the CTZ. Phenothiazines were the first chemical substances known to antagonise dopamine receptors. They showed some weak anti-emetic activity, associated with hypotension and other important side effects (Moertel 1963). The introduction of the benzamide, metoclopramide represented a substantial improvement in the prevention of CINV (Gralla 1981). However, despite the high affinity with dopamine receptors resulting in their full saturation, this chemical agent was found to be consistently efficacious at elevated doses only, raising uncertainty about its mechanism of action (Strum 1982).

The characterisation of the serotonin receptors and the demonstration of a moderate affinity of metoclopramide for the binding of the correspondent type 3 ($5\text{-}HT_3$) suggested that the prevention of emesis by this drug at high doses could be ascribed to a blockade of the serotonin receptors (Fozard 1978). The development of highly selective antagonists for the $5\text{-}HT_3$ receptors marked a substantial improvement in the control of CINV because of the better therapeutic index compared with metoclopramide and the absence of the extrapyramidal reactions adversely mediated by dopamine receptors binding (Cubeddu 1994). The first selective $5\text{-}HT_3$ RA, ondansetron, was approved in 1991, followed by granisetron in 1993, tropisetron in 1994, dolasetron in 1997 and palonosetron in 2003.

The various $5\text{-}HT_3$ RAs are characterised by different chemical structures but have the same general mechanism of action: blockade of serotonin receptors (Koeller 2002)**.** However, selectivity of $5\text{-}HT_3$ receptors binding is somewhat different among the $5\text{-}HT_3$ RAs. For example, granisetron strongly and very selectively binds to $5\text{-}HT_3$ receptors, whereas ondansetron displays 20% of unselective non-$5HT_3$ binding (Blower 2003). Good bio-availability in the range of 50% to 80% is common to all these drugs with no substantial differences in absorption between intravenous and oral administration (Balfour 1997). The terminal half-life of the $5\text{-}HT_3$ RAs differs. Palonosetron has the longest (40 hours) compared with the shortest for ondansetron (three to five hours). Hepatic metabolism of the $5\text{-}HT_3$ RAs is mediated through drug oxidation by different isoenzymes of the citochrome P450 (CYP1A2, CYP2D6 and CYP3A4) (Davis 2001).

Granisetron is the only drug of this class not metabolised by the CYP2D6 pathway but primarily via the CYP3A family (Bloomer 1994). This difference might be important for individual patients, considering that the CYP2D6 enzyme is characterised by genetically polymorphic variants with altered function. However, from a pharmacokinetic perspective, slow or fast metabolic pathways of the $5\text{-}HT_3$ RAs can prevail in the individual patient, resulting in either lower or enhanced plasma concentration of the drug (Blower 2002; Kaiser 2002).

The potential different impact of different dosages of drugs is based on theoretical considerations about serotonin receptor saturation associated with this class of drugs (Blower 2002). However, as long as the minimum efficacious dose of the drug is administered, it is currently believed that greater doses will not result in greater efficacy. Concerning the route of administration, both oral and intravenous administration are currently considered equivalent in terms of efficacy (Gralla 1998; Perez 1998).

The toxicity profile of 5-HT_3 receptor antagonists is modest. Commonly reported toxicities include headache in 10% to 15% of patients and constipation in 10% to 15% (Schwartzberg 2007).

Recently aprepitant (Emend), a novel neurokinin-1 antagonist (NK-1), was introduced for the prevention of CINV. This drug blocks the neurokinin receptor and enhances the activity of 5-HT_3 RAs with a complementary mechanism of action (Navari 2004). Aprepitant in association with ondansetron and dexamethasone provided a higher degree of emesis control relative to acute and delayed CINV than ondansetron and dexamethasone alone following high-dose cisplatin chemotherapy (Hesketh 2003).

According to the recent guidelines of the Multinational Association of Supportive Care in Cancer (MASCC 2008) and the American Society of Clinical Oncology (ASCO 2006), the prevention of acute nausea and vomiting in the setting of highly emetogenic chemotherapy should be based on a combination of one 5-HT_3 RA, dexamethasone and aprepitant (the MASCC level of confidence and consensus is high and the ASCO (American Society of Clinical Oncology) level of evidence is high and has a grade recommendation of A). In the setting of cisplatin chemotherapy, prevention of delayed vomiting and nausea should be based on the combination of aprepitant and dexamethasone (MASCC level of confidence high, level of consensus moderate; ASCO level of evidence II and grade of recommendation A)

Why it is important to do this review

This review seeks to identify important differences in the effects of the various 5-HT_3 RAs. This would help in choosing which drug to use. For example, granisetron, dolasetron, palonosetron and tropisetron do not require dose adjustment in patients with hepatic impairment (Hoechst 1999; Palmer 1994; Rhoda 1993; TML 2004) but a dose reduction of ondansetron is recommended in patients with severe hepatic failure because of significantly reduced clearance of the drug (Blake 1993; Figg 1996). The differences might be relevant for the care of individual patients and although there are two earlier systematic reviews comparing granisetron with ondansetron in the setting of highly emetogenic chemotherapy (Del Giglio 2000; Mendarte 2000), an up-to-date systematic review assessing the clinical efficacy of the various 5-HT_3 RAs is warranted.

OBJECTIVES

The primary objective of this review is to investigate the clinical efficacy of different serotonin receptor antagonists (5-HT_3 RAs) in the control of acute and delayed emesis induced by highly emetogenic chemotherapy.

The secondary objectives are to examine eligible studies for information on adverse events and to assess if there are important differences in the adverse events caused by the different anti-emetic agents.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) where randomisation is explicit and appropriate, with at least 20 participants per treatment group and data on at least one of the outcome measures were eligible. We included cross-over randomised studies if information for the first phase of the study was available. This is because of the likelihood of a carry-over effect in cross-over studies of anti-emetics. We excluded trials with inadequate allocation concealment, such as allocation generated by alternation, use of case record numbers, dates of birth or day of the week, or by any other procedure which is transparent before allocation. We included studies published only as abstracts or that were unpublished if sufficient information on study design, patients characteristics, interventions and outcomes was available. Otherwise they were excluded or included with reservation.

Types of participants

We included cancer pa- older than 16 years undergoing highly emetogenic chemotherapy. Highly emetogenic chemotherapy included those cytotoxic drugs for which emesis is expected to occur in more than 90% of chemotherapy administrations in the absence of anti-emetic prophylaxis. We used the Antineoplastic Agents Emetic Risk Classification, adopted by the American Society of Clinical Oncology, to identify the relevant forms of chemotherapy (ASCO 2006).

We excluded studies of nausea and vomiting associated with moderately emetogenic chemotherapy, radiotherapy, autologous or allogeneic bone marrow transplantation, or surgery.

Types of interventions

Given that placebo-controlled trials are unethical in the setting of highly emetogenic chemotherapy, we considered any 5-HT_3 RA compared with any other drug of this class for study inclusion according to the following combinations:

- 5-HT_3 RAs as single anti-emetic treatment versus a different 5-HT_3 RA as single anti-emetic treatment;
- 5-HT_3 RAs in combination with corticosteroids versus a different 5-HT_3 RA in combination with corticosteroids;
- 5-HT_3 RAs in combination with corticosteroids and aprepitant versus a different 5-HT_3 RA in combination with corticosteroids and aprepitant;
- 5-HT_3 RAs as single anti-emetic treatment versus the same 5-HT_3 RA as single anti-emetic treatment but with different dosing and dosing schedules.

Types of outcome measures

Primary outcomes

The primary outcome is acute nausea and vomiting.

Secondary outcomes

1. Delayed nausea and vomiting.
2. Adverse effects.

- We analysed vomiting by using the proportion of participants with complete absence of vomiting or retching, either documented by direct observation or according to patients' diaries.
- We analysed nausea by using the proportion of participants with complete absence of nausea, with or without mild nausea as documented in participants' diaries.
- We analysed total control of nausea and vomiting (i.e. complete absence of nausea and vomiting) by using the proportion of participants with complete absence of vomiting and absence of nausea, with or without mild nausea.
- We analysed adverse events by using the proportion of participants experiencing minor or severe adverse events, or both.
- Acute events were those occurring within 24 hours of chemotherapy.
- Delayed events were those occurring after 24 hours but within seven days of chemotherapy. Where data were given on a daily basis, we used the rate for the worst day.
- At least three days of follow up were required for a trial to be included in the evaluation of delayed nausea and vomiting. We recorded data for acute and delayed nausea and vomiting separately.

Search methods for identification of studies

Electronic searches

The search strategy was based on the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) and the Cochrane Pain, Palliative Care and Supportive Care (PaPaS) Cochrane Review Group. The search was built on three concepts: cancer, chemotherapy and 5-HT_3 RA anti-emetic agents. The intervention-related concept (i.e. the anti-emetic therapy) and the condition-related concept (i.e. the cancer chemotherapy) were combined. The intervention-related concept was searched using the Boolean term OR to combine the different 5-HT_3 RAs. The search strategy terms for the condition-related concept were built up by combining terms for neoplasm and cancer chemotherapy with the OR term. As the review is focused on highly emetogenic chemotherapy regimens, cisplatin (the most representative drug of this category), was searched for specifically.

The search terms were based in part on searches employed in other narrative and systematic reviews, as well the citations in relevant papers already identified. The search was based on the relevant controlled-vocabulary terms for the specific database, along with free text words and phrases. To ensure maximum sensitivity, the names of the different 5-HT_3 RAs and surrogate terms for anti-emetics were used. As noted above, these were combined with the OR term. However, to increase specificity in the search for reports of trials that directly compared at least two 5-HT_3 RAs (i.e. the focus of this review), a search in which pairs of 5-HT_3 RAs are combined with the AND term and these pairs are combined with the OR term was also run.

The following electronic databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue1), the Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group Specialised Register, PubMed, EMBASE and LILACS. The search strategy used to search MEDLINE is detailed in Appendix 1.

The search covered the time period from January 1990 to March 2009. No language restrictions were applied. Although the review concerns participants older than 16 years, no age limits were applied in the initial search. In databases other than CENTRAL we used the highly sensitive search strategy for identifying RCTs (Dickersin 1994).

Searching other resources

We searched Internet databases of grey literature (SIGLE) and ongoing trials as follows:

1. the meta-register of controlled trials - international database of ongoing and completed trials (www.controlled-trials.com);
2. the International Standard Randomised Controlled Trial Number (ISRCTN) Register (www.controlled-trials.com);
3. the National Research Register - database of ongoing and recently completed research projects funded by, or of interest to, the UK National Health Service (www.doh.gov.uk);
4. the National Cancer Institute Clinical Trials service (www.cancer.gov);
5. the Information on Clinical Trials and Human Research Studies database containing information about US federally and privately supported clinical research in human volunteers (http://clinicaltrials.nci.nih.go);
6. the Clinical Trials Centre of the National Health and Medical Research Council of Australia website (www.ctc.usyd.edu.au); and
7. the Clinical Trials Register of Trials Central (www.trialscentral.org/index.html).

We also searched the websites of the following large co-operative research groups in cancer and pharmaceutical companies:

1. the European Organisation for Research and Treatment of Cancer (EORTC) website (www.eortc.be);
2. the Eastern Co-operative Oncology Group website (www.ecog.dfci.harvard.edu);
3. the Southwest Oncology Group website (www.swog.org); and
4. the Glaxo Wellcome Register of Clinical Trials (www.gsk.com).

Before handsearching potential relevant journals, the Cochrane Collaboration's Master List of Journals (www.cochrane.us/cochraneemainpage.asp) was checked to determine which journals or conference proceedings have already been handsearched within The Cochrane Collaboration. We handsearched the conference proceedings of the American Society of Clinical Oncology (1994 to August 2007), the American Society of Hematology (1994 to 2007) and the European Society of Medical Oncology (ESMO) (1995 to 2007). We checked the references in the studies identified in the search for additional studies. We also contacted authors of clinical trials, experts in the field and pharmaceutical companies (GlaxoSmithKline, Novartis Farma, Roche, Italfarmaco, Sanofi Aventis) for additional unpublished or ongoing trials.

Data collection and analysis

Trial selection

Two review authors (AB and EM) worked independently to identify potentially relevant trials from the records retrieved in the searches of the bibliographic databases. Using the full text of each study, two review authors (AB and EM) independently classified trials for inclusion in the review as eligible or not eligible, according to an eligibility form which contained the following questions:

1. Is the study described as randomised?
2. Were the participants adults (> 16 years of age)?
3. Did the participants in the study have malignant neoplasms?
4. Did the participants in the study receive highly emetogenic chemotherapy?
5. Did the study document acute or delayed emesis?
6. Were both groups treated with one 5-HT_3 RA?

Studies had to meet all of the above criteria to be eligible. We identified any duplicate studies. We resolved any controversies by consensus between the two review authors.

Quality assessment

Two review authors (AB and EM) independently assessed the methodological quality of the included trials according to the following domains: concealment of allocation, double-blinding, intention-to-treat analysis and loss to follow up.

Each study was also assessed using the zero to five-point scale described by Jadad 1996, as summarised below.

1. Was the study described as randomised? (1 = yes; 0 = no)
2. Was the study described as double-blind? (1 = yes; 0 = no)
3. Were withdrawals and drop-outs described? (1 = yes; 0 = no)
4. Was the method of randomisation well-described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate
5. Was the double-blinding well-described and appropriate? (1 = yes; 0 = no); deduct one point if inappropriate.

Two unblinded review authors (AB and EM) independently assessed the quality of the included trials. They discussed any disagreements until consensus was reached. We assessed quality using an in-house assessment form that has not been validated.

The following criteria were assessed:

1. satisfactory randomisation method;
2. concealment of allocation;
3. treatment allocation masked from participants;
4. treatment allocation masked from clinicians;
5. treatment allocation masked from outcome assessors;
6. similarity of prognostic factors at baseline;
7. description of number of withdrawals, drop-outs and losses to follow up; and
8. intention-to-treat (ITT) analysis.

For the purposes of this review, we defined important prognostic factors as age, gender, previous chemotherapy-related emesis, alcohol consumption, stage of disease and performance status.

We explored the influence of the quality criteria in a sensitivity analysis.

Data extraction

Following validation of a pilot version of the data extraction form using a small sample of studies, two review authors (AB and EM) independently extracted the following data on study design, participant characteristics, interventions and outcomes.

1. General information: title; authors; source; contact address; country; language and year of publication; duplicate publications; sponsor and trial setting.
2. Trial characteristics: study design, objective of the study; type of study (single-/multi-centre, parallel/cross-over, open/blind); description of randomisation; description of concealment; ITT analysis (yes/no); information on participants excluded after randomisation (yes/no); number of participants randomised; number of evaluable participants; description of reasons for exclusions (yes/no); country where the study was performed; funding (yes/no).
3. Participants: age range; gender; performance status; type of cancer; setting of study; previous chemotherapy; type of chemotherapy; setting inpatient or outpatient.
4. Intervention: anti-emetic drugs (5-HT_3 RAs), concomitant corticosteroids (yes/no); dose and schedule of anti-emetic drugs.
5. Outcomes: definition; proportion of participants with no acute vomiting or acute nausea, or delayed vomiting or delayed nausea; proportion of participants with complete absence of acute nausea and vomiting or complete absence of delayed nausea and vomiting (ie. total control of nausea and vomiting). Where data were given on a daily basis, the rate for the worst day was chosen. Proportion of participants with non-severe adverse events, i.e. headache, constipation, diarrhoea, dizziness,ECG modifications. Proportion of participants with severe adverse events.

One review author entered the data into The Cochrane Collaboration Review Manager 5.0 (RevMan) software program (RevMan 2008) and a second review author checked these data. Disagreements were resolved by discussion and consensus.

Statistical considerations

Where appropriate, we combined the results of trials using RevMan 5.0. For dichotomous variables, we calculated an odds ratio (OR) with 95% confidence intervals (CI) for individual studies. We pooled similar studies using a fixed-effect meta-analysis to estimate the OR and its 95% CI. We treated three-arm trials comparing two different doses of one drug with another active comparator as two separate trials with the participants of the single active comparator split into two equal parts.

In the meta-analyses, we assessed heterogeneity using the chi-squared test ($P < 0.1$ was considered statistically significant). If heterogeneity was found, we used a random-effects model. We investigated sources of heterogeneity. We assessed the robustness of the overall results and causes of heterogeneity by sensitivity and subgroup analyses as described below.

In a meta-analysis of at least four trials, we generated a funnel plot to examine the presence of bias. We investigated possible causes of any asymmetry. We carried out ITT analyses where possible.

Sensitivity and subgroup analysis

We analysed the clinical and methodological diversity of the included studies, as well as the statistical heterogeneity, according to the following criteria.

Subgroup analysis

1. Trials based on different 5-HT_3 RAs doses:
   a. trials based on ondansetron 8 mg versus trials based on ondansetron > 8 mg;
   b. trials based on granisetron 1 mg once daily versus trials based on granisetron 3 mg once daily.
2. Trials employing concomitant corticosteroids versus trials employing single drug anti-emetic prophylaxis.
3. Trials based on cisplatin > 70 mg/m^2 versus trials based on cisplatin 50 to 70 mg/m^2.

Sensitivity analysis

1. Open and single-blind studies versus double-blind studies.
2. Studies with available and per protocol analysis versus studies with ITT analysis.
3. ITT analysis with imputed data (worst case/best case scenario).
4. Studies with chemotherapy-naive participants versus studies including participants already treated with chemotherapy.
5. Exclusion of trials using discordant routes of administration for pairs of serotonin receptor antagonists.
6. Trials incorporating mild nausea in the outcome versus trials considering only more severe nausea.

RESULTS

Description of studies

Results of the search

We identified 25 randomised trials that met our eligibility criteria.

Included studies

We included 16 RCTs for a total of 7808 participants. These studied granisetron, ondansetron, tropisetron, ramosetron, palonosetron and dolasetron (Aapro 2006; Audhuy 1996; Del Favero 1995; Gebbia 1994; Gralla 1998; Hesketh 1996; Kang 2002; Mantovani 1996; Martoni 1996; Marty 1995; Navari 1995; Noda 2002; Park 1997; Ruff 1994; Saito 2009; Spector 1998). All trials were reported in English.

Nine trials evaluated granisetron versus ondansetron (Del Favero 1995; Gebbia 1994; Gralla 1998; Mantovani 1996; Martoni 1996; Navari 1995; Park 1997; Ruff 1994; Spector 1998). However, only isolated trials were available comparing granisetron or ondansetron respectively with tropisetron, ramosetron, palonosetron and dolasetron.

Excluded studies

We excluded nine out of the 25 studies. We excluded four studies because of inadequate outcome assessment (Barrajon 2000; Bianchi 1996; Chua 2000; Koizumi 2003). We excluded two studies because of protocol deviation (Raynov 2000) and unavailability (Tsukuda 1995). We excluded one study because of very poor methodological quality (Nakamura 1999). We excluded one study because it included paediatric participants (Forni 2000). We excluded one study because it included participants treated with moderately emetogenic chemotherapy (Zhaocai 2008).

Risk of bias in included studies

Allocation

All trials were described as randomised. In eight studies, we judged the randomisation method to be adequate (Audhuy 1996; Del Favero 1995; Hesketh 1996; Kang 2002; Marty 1995; Navari 1995; Noda 2002; Saito 2009). However, in the other eight studies the randomisation process was unclear. Four trials showed an adequate concealment of allocation (Del Favero 1995; Hesketh 1996; Noda 2002; Park 1997), whereas in the remaining 12 studies the quality of concealment of allocation was unclear. For the six meta-analyses that we were able to perform, allocation concealment was classified as unclear in eight out of the nine trials. It was judged to be adequate in one trial.

With the exception of two trials (Mantovani 1996; Martoni 1996), the distribution of prognostic factors at baseline was well-balanced in the study groups.

Blinding

Eleven studies were double-blind concerning participants and clinicians (Aapro 2006; Audhuy 1996; Del Favero 1995; Gralla 1998; Hesketh 1996; Marty 1995; Navari 1995; Noda 2002; Ruff 1994; Saito 2009; Spector 1998). One trial was designed to have blinding of the participants only (Kang 2002). We were not able to determine blinding in the other trials (Gebbia 1994; Mantovani 1996; Martoni 1996; Park 1997). In all but one trial (Aapro 2006) the blinding of outcome assessors was not clarified. Sensitivity analysis for open and single-blind studies did not lead to any important changes to the outcomes analysed.

Incomplete outcome data

Withdrawals, drop-outs and losses to follow up were stated in all trials and accounted for less than 10% of every study population.

When assessing all of the trials contributing to the six meta-analyses, eight out of nine trials reported an ITT analysis with almost all randomised participants being analysed for the intended outcomes (Del Favero 1995; Gralla 1998; Mantovani 1996; Martoni 1996; Navari 1995; Park 1997; Ruff 1994; Spector 1998). The remaining trials were analysed on an available case basis with no major imbalances between the study groups. Therefore, the relatively small amount of missing data and the balance of losses between the comparison groups means that attrition bias should not, in principle, threaten the validity of our findings. This is also supported by the sensitivity analysis in which studies with available and per protocol analysis were excluded. Furthermore, we performed a worst case-best case scenario analysis to assess the influence of the excluded data and none of the results were importantly different from the pooled data reported.

Selective reporting

We used funnel plots only for the comparison between granisetron and ondansetron on acute emesis, because of the insufficient

number of trials in other settings. This revealed a possible lack of small trials favouring ondansetron (Figure 1; Figure 2).

Figure 1.

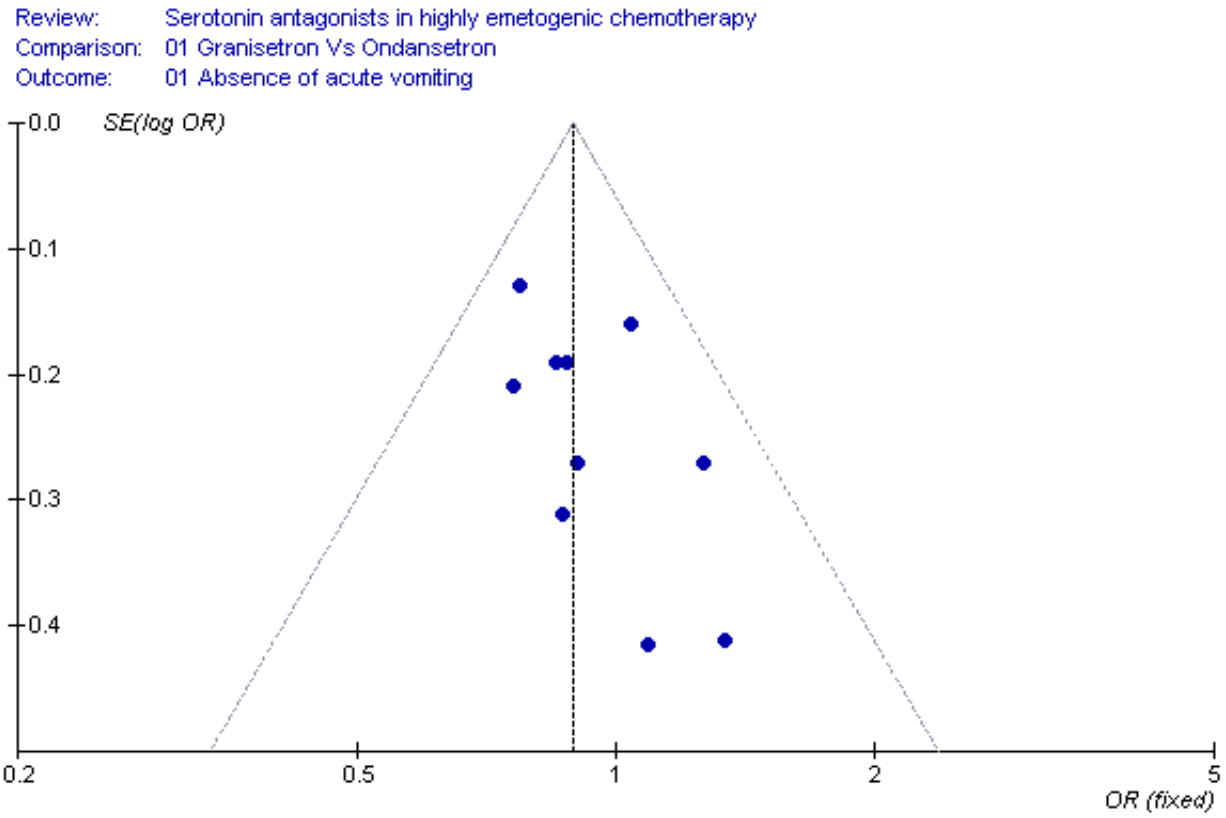
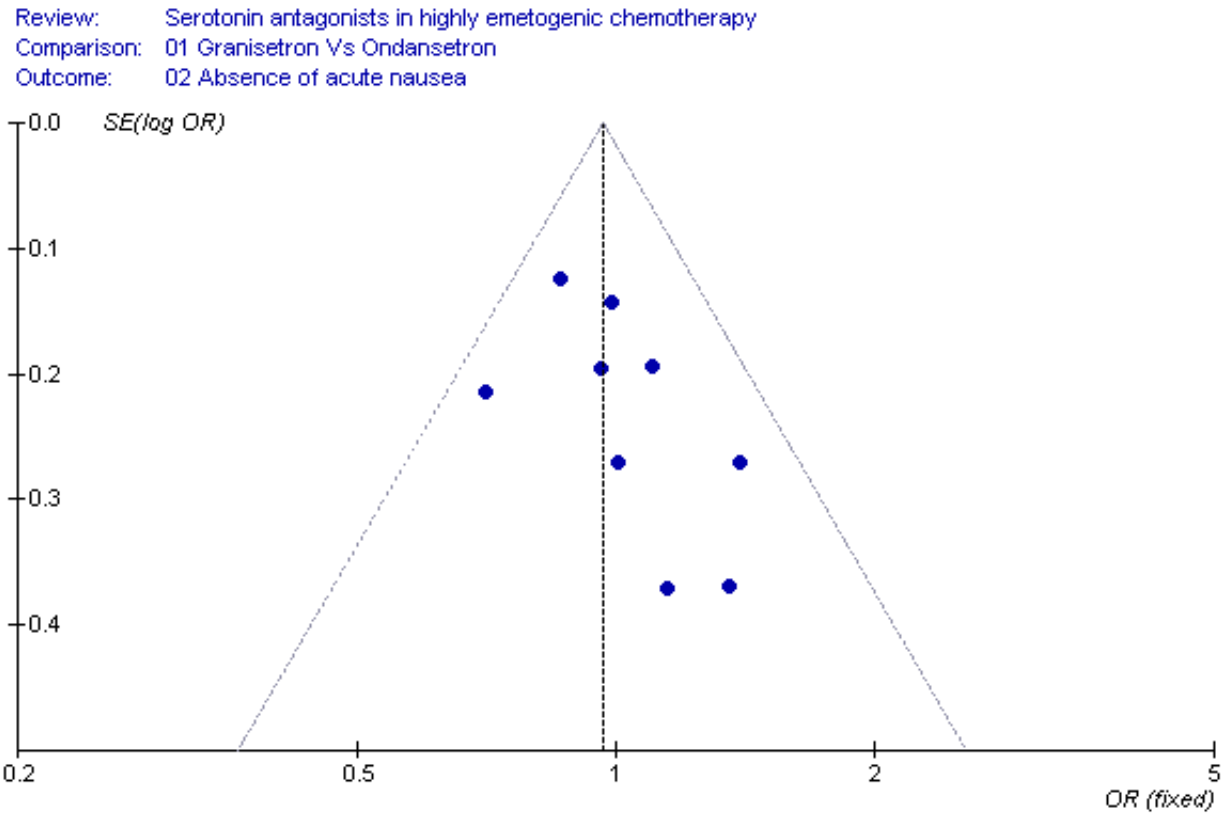


Figure 2.



Other potential sources of bias

In order to investigate the influence of the included trials we undertook clinical subgroup analyses. We investigated the following: use of discordant routes of administration for pairs of serotonin receptor antagonists, inclusion of mild nausea in the outcome, use of different routes of administration of 5-HT_3 RAs between the two groups and exclusion of previously chemotherapy-treated patients.

Effects of interventions

Primary outcome measures

Note: the trial comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone (Saito 2009) has been chosen as the one to emphasise from the single study comparisons because it is the only one showing superiority of one 5-HT_3 RA over the others. The data for this and the other single trials are available in the 'Data and analyses' section.

Acute vomiting

We combined the results of eight studies of granisetron versus ondansetron, including 4256 available participants with complete records, for the complete absence of acute vomiting (Del Favero 1995; Gebbia 1994; Gralla 1998; Martoni 1996; Navari 1995; Park 1997; Ruff 1994; Spector 1998).

The pooled OR was 0.89 (95% CI 0.78 to 1.02), favouring ondansetron. There was no statistical heterogeneity among the trials ($Chi^2 = 5.69$, df = 9, P = 0.77; $I^2 = 0\%$).

Sensitivity analysis resulted in favour of ondansetron in the following cases.

1. Based on five studies and excluding trials with participants previously treated with chemotherapy the pooled OR was 0.82 (95% CI of 0.70 to 0.96), favouring ondansetron in the control of acute vomiting.
2. Based on five studies and excluding non-blinded trials the pooled OR was 0.85 (95% CI of 0.74 to 0.98), favouring ondansetron in the control of acute vomiting.
3. In the best case ITT analysis ondansetron resulted in an OR of 0.87 (95% CI 0.76 to 0.99).

The sensitivity analysis did not show any significant difference with respect to different 5-HT_3 RA doses, concomitant corticosteroids, different doses of cisplatin, other ITT analysis with imputed data (worst case/best case scenario) or trials using discordant routes of administration for pairs of serotonin receptor antagonists.

In one study palonosetron plus dexamethasone and granisetron plus dexamethasone appeared similar and were not statistically different in controlling acute vomiting in 1114 participants (OR 1.06; 95% CI 0.80 to1.41) (Saito 2009).

Acute nausea

We combined and analysed seven studies of granisetron versus ondansetron, including 4160 available participants with complete records, for the complete absence of acute nausea (Del Favero 1995; Gebbia 1994; Gralla 1998; Martoni 1996; Navari 1995; Ruff 1994; Spector 1998).

The pooled OR was 0.97 (95% CI 0.85 to 1.10), favouring ondansetron. There was no statistical heterogeneity among the trials (Chi^2 = 6.47, df = 8, P = 0.60; I^2 = 0%).

The sensitivity analysis did not show any significant difference with respect to different 5-HT_3 RA doses, concomitant corticosteroids, different doses of cisplatin, intention-to-treat analysis with imputed data (worst case/best case scenario), trials including no chemotherapy-naive patients, trials using discordant routes of administration for pairs of serotonin receptor antagonists or trials incorporating mild nausea in the outcome.

In one study palonosetron plus dexamethasone and granisetron plus dexamethasone appeared similar and were not statistically different in controlling acute nausea in 1114 patients (OR 0.95; 95% CI 0.75 to 1.21) (Saito 2009).

Total control of acute nausea and vomiting

Note: this outcome refers to the absence of either nausea or vomiting in an individual participant.

We combined and analysed six studies of granisetron versus ondansetron, including 2809 available participants with complete records, for the complete absence of combined acute nausea and vomiting (Del Favero 1995; Gralla 1998; Mantovani 1996; Martoni 1996; Ruff 1994; Park 1997).

The pooled OR was 1.00 (95% CI 0.85 to 1.16). There was no statistical heterogeneity among the trials (Chi^2 = 3.91, df = 6, P = 0.69; I^2 = 0%).

The sensitivity analysis did not show any significant difference with respect to different 5-HT_3 RA doses, concomitant corticosteroids, different doses of cisplatin, ITT analysis with imputed data (worst case/best case scenario), trials including no chemotherapy-naive participants, trials using discordant routes of administration for pairs of serotonin receptor antagonists or trials incorporating mild nausea in the outcome.

In one study palonosetron plus dexamethasone and granisetron plus dexamethasone appeared similar and were not statistically different in complete response for acute nausea and vomiting in 1114 participants (OR 1.11; 95% CI 0.85 to 1.45) (Saito 2009).

Delayed vomiting

We combined and analysed three studies of granisetron versus ondansetron, including 1119 available participants with complete records, for the complete absence of delayed vomiting (Del Favero 1995; Gebbia 1994; Park 1997).

The pooled OR was 1.00 (95% CI 0.74 to 1.34). There was no statistical heterogeneity among the trials (Chi^2 = 0.17, df = 2, P = 0.92; I^2 = 0%).

The sensitivity analysis did not show any significant difference with respect to trials including ITT analysis with imputed data (worst case/best case scenario).

One study comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone showed superiority of palonosetron in controlling delayed vomiting in 1114 participants (OR 1.45; 95% CI 1.14 to 1.85). The proportion of participants experiencing complete control of delayed vomiting in the group with palonosetron was 351/555 (63.2%) versus 303/559 (54.2%) in the group with granisetron (Saito 2009).

Delayed nausea

We combined and analysed two studies, including 1024 available participants with complete records, for the complete absence of delayed nausea (Del Favero 1995; Gebbia 1994).

The pooled OR was 0.96 (95% CI 0.75 to 1.24) favouring ondansetron. There was no statistical heterogeneity among the trials (Chi^2 = 0.41, df = 1, P = 0.52; I^2 = 0%).

The sensitivity analysis did not show any significant difference with respect to trials including ITT analysis with imputed data (worst case/best case scenario).

One study comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone showed superiority of palonosetron in controlling delayed nausea in 1114 participants (OR 1.63; 95% CI 1.27 to 2.10). The proportion of participants experiencing complete control of delayed nausea in the group with palonosetron was 210/555 (37.8%) versus 152/559 (27.2%) in the group with granisetron (Saito 2009).

Total control of delayed nausea and vomiting

We combined and analysed two studies, including 1045 available participants with complete records, for the complete absence of combined delayed nausea and vomiting (Del Favero 1995; Park 1997).

The pooled OR was 1.00 (95% CI 0.78 to 1.28). There was no statistical heterogeneity among the trials (Chi^2 = 0.10, df = 1, P = 0.75; I^2 = 0%).

The sensitivity analysis did not show any significant difference with respect to trials including ITT analysis with imputed data (worst case/best case scenario).

One study comparing palonosetron plus dexamethasone versus granisetron plus dexamethasone showed superiority of palonosetron in complete response for delayed nausea and vomiting in 1114 participants (OR 1.63; 95% CI 1.29 to 2.07). The proportion of participants experiencing complete control of delayed nausea and vomiting in the group with palonosetron was 294/555 (53%) versus 237/559 (42.4%) in the group with granisetron (Saito 2009).

Adverse effects

Note: in this section only adverse effects related to the comparison ondansetron versus granisetron and palonosetron versus granisetron will be examined

We combined and analysed seven studies comparing ondansetron with granisetron, including 3383 evaluable participants with complete records, for the presence of headache (Del Favero 1995 ;Gebbia 1994; Gralla 1998; Martoni 1996; Park 1997; Ruff 1994; Spector 1998). The pooled OR was 1.05 (95% CI 0.82 to 1.34). There was no significant variability among the results of the trials (Chi^2 = 5.49, df = 7, P = 0.60; I^2 = 0%). We combined and analysed seven studies comparing ondansetron with granisetron and including 3383 evaluable participants with complete records for the presence of constipation (Del Favero 1995; Gebbia 1994; Gralla 1998; Martoni 1996; Park 1997; Ruff 1994; Spector 1998). The pooled OR was 0.71 (95% CI 0.52 to 0.96) favouring ondansetron. There was some variability among the trials (Chi^2 = 9.55, df = 7, P = 0.22; I^2 = 26.7%). We combined and analysed five studies, including 2242 evaluable participants with complete records, for the presence of diarrhoea (Gralla 1998; Martoni 1996; Park 1997; Ruff 1994; Spector 1998). The pooled OR was 1.01 (95% CI 0.70 to 1.45). There was some variability among the trials (Chi^2 = 6.16 df = 5, P = 0.29; I^2 = 18.9%). We combined and analysed five studies comparing ondansetron with granisetron, including 2242 evaluable participants with complete records, for the evaluation of cumulative adverse events (Gralla 1998; Martoni 1996; Park 1997; Ruff 1994; Spector 1998). The pooled OR was 0.87 (95% CI 0.74 to 1.06). There was some variability among the trials (Chi^2 = 7.21 df = 5, P = 0.21; I^2 = 30.7%).

The comparison of palonosetron plus dexamethasone versus granisetron plus dexamethasone showed no differences in the rate of cumulative treatment-related and severe adverse events (respectively OR 0.87; 95% CI 0.68 to 1.12 and OR 0.42; 95% CI 0.15 to 1.19) (Saito 2009)

DISCUSSION

This systematic review aimed to investigate differences between the effects of serotonin receptor antagonists (5-HT_3 RAs) when used with highly emetogenic chemotherapy in cancer patients. The small number of trials evaluating tropisetron, dolasetron, ramosetron and palonosetron, either in acute or delayed emesis, meant that we were not able to perform meta-analyses for those drugs and the only comparison for which we were able to combine the results of the trials was that between granisetron and ondansetron.

However, one study showed superiority of palonosetron plus dexamethasone versus granisetron plus dexamethasone in the control of delayed nausea and vomiting (Saito 2009). The remaining comparisons testing 5-HT_3 RAs other than granisetron versus ondansetron showed no superiority of one 5-HT_3 RA over another for the prevention of either acute or delayed emesis (Hesketh 1996; Kang 2002; Mantovani 1996; Marty 1995; Noda 2002).

Our meta-analyses of granisetron versus ondansetron found the following.

1. Granisetron and ondansetron showed similar treatment effects on the main outcomes of nausea and vomiting, either acute or delayed.
2. Granisetron and ondansetron showed similar effects on the incidence of the common side effects, such as headache and diarrhoea, with the possible exception of less constipation associated with ondansetron.
3. Sensitivity analyses confirmed the strength of these results, with the possible exception of ondansetron in trials excluding participants previously exposed to chemotherapy, in trials based on a blinded design and in worst case/best case scenarios.

When assessing the methodological quality of the studies in the review, the absence of an adequate description of allocation concealment for most of the trials, the lack of blinding in some trials and the low estimated risk of attrition means that there is a moderate risk of bias which could have affected the results.

The meta-analyses of adverse events, either evaluated as single or combined events, did not detect differences in the incidence of the common side effects, with the exception of less incidence of constipation associated with the use of ondansetron. However, given the presence of a certain degree of statistical heterogeneity in three of the four meta-analyses for adverse events, this interpretation requires great caution, and it is safest to say that we could not confirm or refute any differences.

The results are in line with two published systematic reviews on high-dose cisplatin (del Giglio 2000; Mendarte 2000) and one meta-analysis of acute emesis in cisplatin and non-cisplatin chemotherapy (Jordan 2007). However, unlike the latter (Jordan 2007) our review focused only on trials with highly emetogenic chemotherapy. This decision was based on the consideration that a difference among the 5-HT_3 RAs would be more easily detectable in the context of a homogenous, high-risk population.

Compared with the earlier meta-analyses on highly emetogenic chemotherapy (del Giglio 2000; Mendarte 2000), we evaluated a higher number of participants for each outcome and included different studies. This provides a more robust conclusion on the similarity of the effect of granisetron and ondansetron on acute nausea and vomiting. Our evaluation of the combined end point of acute nausea and vomiting was done with more than twice as many participants as the review of Mendarte 2000, and the review of del Giglio 2000 did not assess this combined outcome. Moreover, in contrast with these two meta-analyses, this Cochrane Review also included searches for unpublished trials and trials reported only in the grey literature, and also includes a formal quality evaluation of the selected studies in order to minimise bias.

Predictive factors associated with an increased risk of chemotherapy-induced emesis can be divided into those related to the chemotherapy agent and those related to the patient. Given that this systematic review was restricted to highly emetogenic chemotherapy, only patient-related factors, including female sex, prior chemotherapy, younger age (< 50 years), previous episodes of chemotherapy-associated emesis, and no alcohol consumption, need to be taken into account in terms of the increased risk of emesis. With the exception of one trial comprising an almost exclusively male population (Mantovani 1996), all trials were well-balanced regarding other patient factors associated with the risk of emesis.

Sensitivity analyses excluding trials with patients previously treated with chemotherapy, trials with non-blinded design and simulations of best case/worst case scenarios favoured ondansetron in the control of acute vomiting. Although these findings could be related to a better therapeutic efficacy of ondansetron for the prevention of acute vomiting, the results should be interpreted with great caution given the small number of studies and the upper limit of the 95% CI, which was always near to the point of no difference.

Different dose-intensity of cisplatin chemotherapy, different doses of 5-HT_3 receptor antagonists and the concomitant use of corticosteroids could have represented potential sources of clinical diversity among the different trials and were therefore analysed in three subgroup analyses. We dichotomised the dose-intensity of chemotherapy by an arbitrary cut-off of 70 mg/m^2 of cisplatin, whereas we respectively compared the ondansetron and granisetron doses at 8 mg versus > 8 mg/daily and at 1 mg versus 3 mg/daily. However, the four pooled odds ratios failed to demonstrate any significant difference in the treatment effect on acute vomiting, acute nausea and combined acute nausea and vomiting between these subgroups. By enhancing the efficacy of the anti-emetic treatment, the addition of corticosteroids could theoretically obviate the inferiority of one of the two comparators, producing an artificially equal treatment effect. Indeed it is worth considering that the two trials including corticosteroids in the anti-emetic protocol showed comparatively more control of emesis compared to trials based on a single 5-HT_3 receptor antagonist (Del Favero 1995; Gralla 1998).

The influence of corticosteroids on the meta-analysis was tested in a subgroup analysis in this review, which showed similar results for trials with and without corticosteroids.

Moreover, according to the view that different routes of administration of the 5-HT_3 receptor antagonists are currently regarded as equivalent (ASHP 1999; Gralla 1999), a sensitivity analysis considering only trials based on the intravenous route of administration yielded equivalence between the two anti-emetics.

We performed sensitivity analyses with imputed data according to best case/worst case scenario in order to assess the influence of missing data for excluded randomised patients from the meta-analyses. However, contrary to granisetron, when data were analysed by attributing to all missing patients in the ondansetron group the total control of emesis, the resulting pooled estimate of treatment effect regarding the control of acute vomiting favoured the latter drug, albeit with an upper confidence limit near to the point of no difference (OR 0.86; CI 0.76 to 0.98). It must be stressed that this should be interpreted cautiously as it was generated by an arbitrary decision of the imputing procedure. However, although different estimates of treatment effect obtained with the sensitivity analyses suggest that the lack of an ITT analysis in a trial could have resulted in attrition bias, the limited number of patients with missing data for acute vomiting (36/4292) and the borderline upper confidence limit of the estimate could be taken as arguments contrary to this interpretation.

Adverse effects are to be considered similar between ondansetron and granisetron, with the possible exception of constipation (OR 0.71; 95% CI 0.52 to 0.96). Considering that there was some variability among the trials (Chi^2 = 9.55, df = 7, P = 0.22; I^2 = 26.7%), this result should be taken cautiously.

A final comment about the relative value of the combination palonosetron plus dexamethasone in the setting of highly emetogenic chemotherapy is warranted. The superiority of palonosetron was indeed ascertained only with regard to delayed emesis according to a single, albeit large, trial in comparison with granisetron (Saito 2009). Although this result may well highlight the importance of the longer half-life of palonosetron in the setting of delayed emesis, it should be taken with a note of caution given the absence of benefit in another single trial comparing palonosetron with ondansetron (Aapro 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Regarding the question of whether there is one serotonin receptor antagonist (5-HT_3 RA) to be clearly preferred over the others in the prevention of emesis associated with highly emetogenic chemotherapy, the current answer according to this meta-analysis is no.

Ondansetron and granisetron can be reasonably regarded as equivalent drugs for the prevention of acute and delayed emesis when used with highly emetogenic chemotherapy. Moreover, current evidence does not suggest that any 5-HT_3 RAs could claim superiority over the others in the setting of acute vomiting and nausea.

According to this systematic review, a single study showed superiority of the combination of palonosetron and dexamethasone versus granisetron and dexamethasone in the control of delayed vomiting and nausea (Saito 2009).

Given the evidence favouring palonosetron plus dexamethasone for delayed nausea and vomiting control, palonosetron may possibly be considered the future candidate 5-HT_3 RA in the setting of highly emetogenic chemotherapy associated with substantial risk of delayed emesis. This suggestion nevertheless awaits more evidence before becoming a real recommendation.

The final choice of which 5-HT_3 RA to use for prevention of emesis associated with highly emetogenic chemotherapy will eventually depend on local considerations about drug availability and costs.

Implications for research

Further RCTs are warranted to compare the combination of palonosetron and dexamethasone in the setting of delayed nausea and vomiting associated with highly emetogenic chemotherapy.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aapro 2006

Methods	Phase III, multinational, randomised, double-blind, double-dummy, stratified, parallel group, active comparator
Participants	**Age:** > 18 years **Gender:** Palonosetron 0.25 mg iv female 115/223; males 108/223 Palonosetron 0.75 mg iv female 113/223; males 110/223 Ondansetron 32 mg iv female 113/223; males 110/221 **Type of CT:** cisplatin > 60 mg/sm or cyclophosphamide > 1500 mg/sm or carmustine (BCNU) > 250 mg/sm or dacarbazine (DTIC) or mechlorethamine **Setting:** outpatients **Country:** North America and Europe
Interventions	Palonosetron 0.25 mg iv versus palonosetron 0.75 mg ev versus ondansetron 32 mg iv Concurrent anti-emetics/corticosteroids: allowed
Outcomes	**Complete response:** no emetic episodes and no rescue medication use during the acute phase (0 to 24 hours post-chemotherapy) Mild nausea was allowed

Aapro 2006 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Not described Comment: probably done
Allocation concealment?	Unclear risk	Randomisation process not described Comment: probably done
Blinding? Assessor-reported outcomes	Unclear risk	"double-blind, double-dummy". No specification about the anti-emetics administration. No specifications about the outcomes assessors. Comment: probably done in a proper way
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Audhuy 1996

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Age:** > 18 years (mean 55) **Gender:** Dolasetron 1.8 mg/kg males:105/163; females 58/163 Dolasetron 2.4 mg/kg males:110/161; females 51/161 Granisetron: males: 100/150; females 50/150 **Type of CT:** cisplatin > 80 mg/sm **Setting:** hospitalised for 8 hours **Country:** France
Interventions	Dolasetron 1.8 mg/kg iv od versus dolasetron 2.4 mg/kg iv od versus granisetron 3 mg iv od Concurrent anti-emetics/corticosteroids: no

Audhuy 1996 *(Continued)*

Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea developing within 24 hours after starting CT. Intensity according to investigator's assessment based on a scale ranging from 0 (no nausea) to 3 (severe nausea). Mild nausea was not allowed for complete response. **Note:** participants were also evaluated for nausea according to a visual analogue scale (VAS) that ranged from "no nausea"(0 mm) to "nausea as bad it can be" (100 mm) within 24 hours after CT. Reported data on intensity of nausea are based on investigator's assessment.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Adequate
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Low risk	Adequate
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Del Favero 1995

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Age:** > 20 years (range 21 to 82; median age 61) **Gender:** Granisetron: males 317/483; females 166/483 Ondansetron: males 340/483; females 143/483 **Type of CT:** Cisplatin > 50 mg/sm **Setting:** mixed (outpatients + inpatients)

Del Favero 1995 *(Continued)*

	Country: Italy
Interventions	Granisetron 3 mg iv od versus ondansetron 8 mg iv od Concurrent anti-emetics/corticosteroids Dexamethasone 8 mg im was administered before cisplatin infusion to every participant; oral metoclopramide 20 mg iv qid and dexamethasone 8 mg im bid were administered from day 2 until day 4
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea within 24 hours after starting CT Intensity of nausea defined according to a graded scale of interference with normal daily life (grade a: no interference) Mild nausea was not allowed for complete response Delayed vomiting: as above but evaluated from day 2 to 6 Delayed nausea: as above but evaluated from day 2 to 6
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Adequate
Allocation concealment?	Low risk	Adequate
Blinding? Assessor-reported outcomes	Unclear risk	Unclear
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Gebbia 1994

Methods	Single centre, randomised, parallel, open trial
Participants	**Age:** range 25 to 75 years (mean 59)

Gebbia 1994 *(Continued)*

	Gender: Granisetron: males 48/82; females 34/82 Ondansetron: males 58/84; females 26/84 **Type of CT:** Cisplatin > 70 mg/sm Mean dose ondansetron 84 mg/sm; granisetron 83 mg/sm Concomitant CT: cyclophosphamide, epidoxorubicin, vinca alkaloids (moderate emetogenic) **Setting:** not stated **Country:** Italy
Interventions	Ondansetron 24 mg iv od versus granisetron 3 mg iv od Concomitant anti-emetic/corticosteroids: no
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea within 24 hours after starting CT Intensity of nausea defined according to a graded scale of interference with normal daily life (grade a: no interference) Mild nausea was allowed for complete response **Delayed vomiting:** as above but evaluated from day 2 to 5 **Delayed nausea:** as above but evaluated from day 2 to 5 Note: delayed nausea was evaluated in all participants receiving cisplatin on a single-day schedule
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	High risk	Not used
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Gebbia 1994 *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Gralla 1998

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Age:** >18 years (range 19 to 88; mean 61) **Gender:** Granisetron: males 346/534; females 188/534 Ondansetron: males 345/520; females 175/520 **Type of chemotherapy:** Cisplatin > 60 mg/sm **Setting:** hospitalised **Country:** USA
Interventions	Granisetron 2 mg po od versus ondansetron 32 mg iv od Concurrent anti-emetics/corticosteroids: yes
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea within 24 hours after starting CT as recorded by patients diary. No further details on assessment.
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Low risk	Adequate
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described

Gralla 1998 *(Continued)*

Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Hesketh 1996

Methods	Multi-centre, randomised, parallel, double-blind. Equivalence trial.
Participants	**Age:** range 20 to 85 years (median 62) **Gender:** Dolasetron 1.8 mg/kg: males 127/198; females 71/198 Dolasetron 2.4 mg/kg: males 129/205; females 76/205 Ondansetron: males:121/206, females 85/206 **Type of CT:** Group 1 cisplatin > 70 < 91 mg/sm Mean dose 75 mg/sm Group 2 cisplatin > 91 mg/sm **Setting:** in-patients and out-patients **Country:** USA
Interventions	Dolasetron 1.8 mg/kg iv od versus dolasetron 2.4 mg/kg iv od versus Ondansetron 32 mg iv od
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after CT **Acute nausea:** absence of nausea within 24 hours after starting of CT, recorded through patient's diary according to 100 mm VAS
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Adequate
Allocation concealment?	Low risk	Adequate
Blinding? Assessor-reported outcomes	Unclear risk	Unclear
Incomplete outcome data addressed?	Unclear risk	Not described

Hesketh 1996 *(Continued)*

acute vomiting		
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Kang 2002

Methods	Multi-centre, randomised, parallel, single-blind
Participants	**Age:** > 20 years (mean 54) **Gender:** Ramosetron: males 68/94; females 26/94 Granisetron: males 71/100; females 29/100 **Type of CT:** Cisplatin > 50 mg/sm **Setting:** not stated **Country:** South Korea
Interventions	Ramosetron 0.3 mg iv od versus granisetron 3 mg iv od Concurrent anti-emetics/corticosteroids: not stated
Outcomes	**Acute vomiting:** absence of vomiting within 24 hours after starting CT **Acute nausea:** absence of nausea within 24 hours after starting CT as recorded by patients diary according to a 0 (no nausea) to 4-point graded scale
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Adequate
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Low risk	Adequate

Kang 2002 *(Continued)*

Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Mantovani 1996

Methods	Single centre, randomised, parallel, open
Participants	**Age:** range 31 to 78 (mean 58) **Gender:** 113 males, 4 females (distribution among study drugs not stated) **Type of CT:** Cisplatin > 80 mg/sm **Setting:** hospitalised **Country:** Italy
Interventions	Granisetron 3 mg iv od versus ondansetron 24 mg iv od versus tropisetron 5 mg iv od Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting:** complete response defined as absence of vomiting within 24 hours after starting CT **Acute nausea:** complete response defined as no or only mild nausea within 24 hours after starting CT Absence of acute nausea and vomiting (combined outcome)
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	High risk	Not used
Incomplete outcome data addressed?	Unclear risk	Not described

Mantovani 1996 *(Continued)*

acute vomiting		
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	—

Martoni 1996

Methods	Single centre, randomised, cross-over, open
Participants	**Age:** range: 32 to 77 (median 62) **Gender:** Males: 93/124 Females: 21/124 **Type of CT:** Cisplatin > 50 mg/sm **Setting**: outpatients + inpatients **Country**: Italy
Interventions	Ondansetron 8 mg iv tid versus granisetron 3 mg iv od Ondansetron 8 mg po bid was administered on day 2 Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea**: absence of nausea within 24 hours after starting CT. No further details on assessment
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding?	High risk	Not used

Martoni 1996 *(Continued)*

Assessor-reported outcomes		
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Marty 1995

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Mean age**: tropisetron 56 years; ondansetron 58 years **Gender:** Tropisetron: males 83/117; females 34/117 Ondansetron: males 82/114; females 32/114 **Type of CT:** cisplatin > 50 mg/sm **Setting**: not stated **Country:** France
Interventions	Tropisetron 5 mg iv od versus ondansetron 32 mg iv od on day 1 Day 2 to 6: tropisetron 5 mg po od versus ondansetron 8 mg po tid Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea developing within 24 hours after starting CT recorded as duration of nausea in hours rounded to the nearest quarter. Total control of nausea defined as nausea lasting < 15 minutes
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Adequate
Allocation concealment?	Unclear risk	Not described

Marty 1995 *(Continued)*

Blinding? Assessor-reported outcomes	Low risk	Adequate
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Navari 1995

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Age:** > 18 years (range 23 to 86; mean 60) **Gender:** Granisetron 10 µg/kg: males 206/328; females 122/328 Granisetron 40 µg/kg: males 210/328 males; females 118/328 Ondansetron: males 211/331; females 120/331 **Type of CT:** Cisplatin > 60 mg/sm **Setting:** hospitalised for at least 8.30 hours **Country:** USA
Interventions	Granisetron 10 µg/kg iv od versus granisetron 40 µg/kg iv od versus ondansetron 0.15 mg/kg iv tid Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting**: absence of vomiting or retching within 24 hours after starting CT **Acute nausea**: absence of nausea within 24 hours after starting CT as assessed by patient's diary. No details on intensity scale.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Adequate

Navari 1995 *(Continued)*

Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Low risk	Adequate
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Noda 2002

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Age:** > 20 years (range 20 to 82) **Gender:** Ramosetron: 41 males 26/67; females /67 Ondansetron: males 35/69; females 34/69 **Type of CT:** Cisplatin > 50 mg/sm **Setting:** hospitalised **Country:** Japan
Interventions	Ramosetron 0.1 mg po od versus ondansetron 4 mg po od Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea within 24 hours after starting CT as recorded by patients diary according to 0 (no or only mild nausea) to 4-point graded scale
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Noda 2002 *(Continued)*

Adequate sequence generation?	Low risk	Adequate
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Low risk	Adequate
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Park 1997

Methods	Single centre, randomised, parallel, open
Participants	**Age:** 18 to 70 (median 51) **Gender:** Granisetron: males: 26/48 (ITT); 26/47 (efficacy analysis); females 22/48 (ITT); 22/47 (efficacy analysis) Ondansetron: males 25/49 (ITT); 25/48 (efficacy analysis); females 24/48 (ITT); 24/47 (efficacy analysis) **Type of CT:** Cisplatin > 80 mg/sm **Setting:** not reported **Country:** South Korea
Interventions	Granisetron 3 mg iv od versus ondansetron 8 mg iv tid followed by ondansetron 8 mg oral bid for 5 days Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting:** Absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** Absence of nausea developing within 24 hours after starting CT. Intensity evaluated according to the degree of interference with normal daily life scored by patients as none, mild, moderate and severe **Delayed vomiting:**

Park 1997 *(Continued)*

	As above but referred from day 2 to 7 **Delayed nausea:** As above but referred from day 2 to 7
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	High risk	Not used
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Ruff 1994

Methods	Multi-centre, randomised, parallel, double-blind
Participants	**Age:** > 18 years (mean 55) **Gender:** Ondansetron 8 mg: males 93/165; females 72/165 Ondansetron 32 mg: males 88/162; females 32 mg 74/162 Granisetron: males 98/169; females 71/169 **Type of CT:** Cisplatin > 50 mg/sm **Note:** a total of 68 participants received moderate emetogenic chemotherapy (cisplatin < 50 mg/sm). This population was equally distributed among the 3 comparison arms. **Setting:** not stated

Ruff 1994 *(Continued)*

	Country: Denmark, France, Germany, the Netherlands, South Africa, Switzerland, United Kingdom
Interventions	Ondansetron 8 mg iv od versus ondansetron 32 mg iv od versus Granisetron 3 mg iv od Concurrent anti-emetics/corticosteroids: not stated
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea**: absence of nausea within 24 hours after starting CT Intensity of nausea defined according to a graded scale of interference with normal daily life (grade a: no interference) Mild nausea was allowed for complete response
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Unclear risk	Unclear
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

Saito 2009

Methods	Multi-centre, phase III, randomised, double-blind, double dummy, stratified, parallel-group, active comparator trial
Participants	**Mean age:** palonosetron 58.4; granisetron 58.0 **Gender:** palonosetron: males 229/555 Granisetron: females 235/559 **Type of CT:** single dose of cisplatin > 50 mg/sm

Saito 2009 *(Continued)*

	Single dose of anthracycline and cyclophosphamide combination (AC/EC) **Setting:** not stated **Country:** Japan
Interventions	Palonosetron 0.75 mg + dexamethasone 16 mg iv on day 1 Granisetron 40 micrograms/Kg+dexamethasone 16 mg iv on day 1 Patients receiving cisplatin: dexamethasone 8 mg iv days 2,3 Patients receiving AC/EC: dexamethasone 4 mg orally days 2,3
Outcomes	Complete response (0 to 24 hours post-CT) Complete response (24 to 120 hours post CT) Acute vomiting Acute nausea Delayed vomiting (24 to 120 hours) Delayed nausea (24 to 120 hours)
Notes	Complete response: no emetic episodes and no use of rescue medication Hypothesis in primary analyses: • Complete response (0 to 24 hours): non-inferiority • Complete response (24 to 120 hours): superiority

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	A unique random sequence generated before the trial by an independent statistician
Allocation concealment?	Low risk	Randomisation was done centrally by computer by sequential application of the random sequence to each patient allocation
Blinding? Assessor-reported outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study
Incomplete outcome data addressed? acute vomiting	High risk	Not described
Incomplete outcome data addressed?	High risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	High risk	Not described

Spector 1998

Methods	Multi-centre, randomised, parallel, double-blind. Two identical studies.
Participants	**Age:** range 32 to 86; mean 64 **Gender:** Granisetron: males 101/187; females 86/187 Ondansetron: males 105/184; females 79/184 **Type of CT:** cisplatin > 50 mg/sm **Setting:** not stated **Country**: USA
Interventions	Granisetron: 10 µg/kg iv od versus ondansetron 24 mg po od Concurrent anti-emetics/corticosteroids: no
Outcomes	**Acute vomiting:** absence of vomiting or retching within 24 hours after starting CT **Acute nausea:** absence of nausea within 24 hours after starting CT according to patient's assessment based on an 11-point linear numerical scale ranging from no nausea (0) to nausea as bad as it could be (10)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Assessor-reported outcomes	Low risk	Adequate
Incomplete outcome data addressed? acute vomiting	Unclear risk	Not described
Incomplete outcome data addressed?	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described
Incomplete outcome data addressed? All outcomes	Unclear risk	Not described

bid = twice a day; CT = chemotherapy; im = intramuscular; ITT = intention-to-treat; iv = intravenous; od = once daily; po = orally; qid = four times a day; tid = three times a day

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barrajon 2000	Outcomes not evaluable
Bianchi 1996	Outcomes not evaluable
Chua 2000	Outcomes not evaluable
Forni 2000	Participants aged < 16 years
Koizumi 2003	Outcomes not evaluable
Nakamura 1999	Low quality (number of randomised patients not reported)
Raynov 2000	Protocol deviation
Tsukuda 1995	Full paper not available
Zhaocai 2008	Chemotherapy was not highly emetogenic (epirubicin 60 mg/sm was included)

DATA AND ANALYSES

Comparison 1. Granisetron versus ondansetron

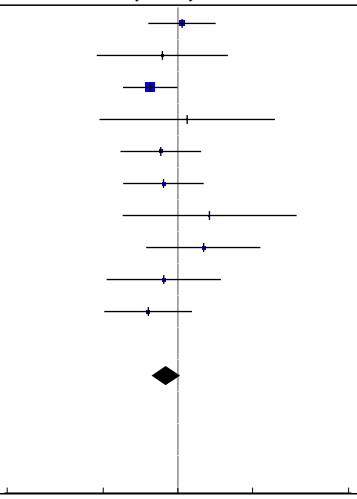
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting	8	4256	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.02]
2 Absence of acute nausea	7	4160	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.10]
3 Absence of delayed vomiting	3	1119	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.74, 1.34]
4 Absence of delayed nausea	2	1024	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.24]
5 Total control of acute nausea and vomiting	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.16]
6 Total control of delayed nausea and vomiting	2	1045	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.78, 1.28]
7 Absence of acute vomiting (ondansetron 8 mg vs > 8 mg)	8	4256	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.02]
7.1 Ondansetron 8 mg	2	1214	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.31]
7.2 Ondansetron > 8 mg	7	3042	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.74, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Absence of acute vomiting (excluding trials not blinded)	5	3871	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.98]
9 Absence of acute vomiting (concomitant corticosteroids)	7	3763	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.00]
9.1 Concomitant corticosteroids	2	2020	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.06]
9.2 No concomitant corticosteroids	5	1743	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.06]
10 Absence of acute nausea (Ondansetron 8 mg vs > 8 mg)	7	3915	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.08]
10.1 Ondansetron 8 mg	2	1215	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.27]
10.2 Ondansetron > 8 mg	5	2700	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.08]
11 Absence of acute vomiting (including only trials based on ITT analysis)	7	4090	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.02]
12 Absence of acute nausea (concomitant corticosteroids)	6	3666	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.08]
12.1 Concomitant corticosteroids	2	2020	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.76, 1.10]
12.2 No corticosteroids	4	1646	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.79, 1.19]
13 Absence of acute vomiting (including only trials enrolling CT naive patients)	5	2702	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.96]
14 Absence of acute nausea (excluding trials not blinded)	5	3870	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.08]
15 Total control of acute nausea and vomiting (excluding trials not blinded)	5	2714	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.15]
16 Total control of acute nausea and vomiting (including only trials with CT naive patients)	3	1255	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.13]
17 Total control of acute nausea and vomiting (including only trials with iv anti-emetic administration)	5	1755	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.90, 1.34]
18 Absence of acute nausea (including only ITT analysis based trials)	6	3994	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.09]
19 Total control of acute nausea and vomiting (ondansetron 8 mg vs > 8 mg)	6	2564	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.13]
19.1 Ondansetron 8 mg	3	1338	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]
19.2 Ondansetron > 8 mg	3	1226	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20 Total control of acute nausea and vomiting (concomitant corticosteroids)	5	2316	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
20.1 Concomitant corticosteroids	2	2020	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.12]
20.2 No concomitant corticosteroids	3	296	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.75, 2.00]
21 Total control of acute nausea and vomiting (including only ITT analysis)	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.16]

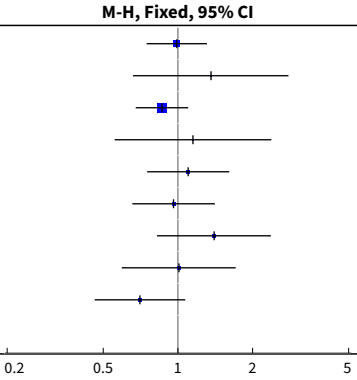
Analysis 1.1. Comparison 1 Granisetron versus ondansetron, Outcome 1 Absence of acute vomiting.

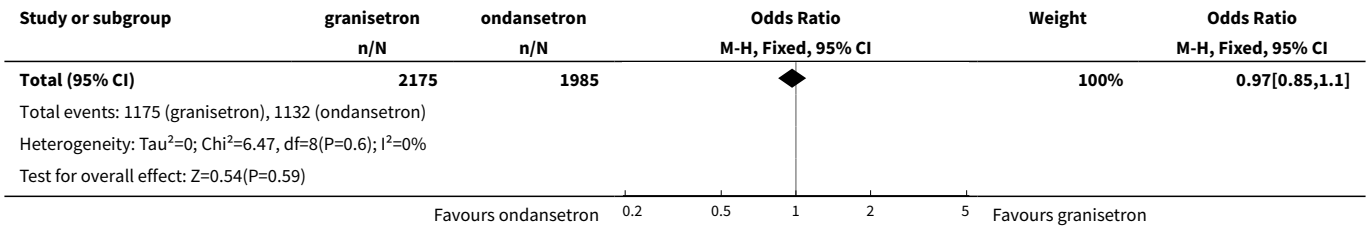
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	386/483	383/483		15.97%	1.04[0.76,1.42]
Gebbia 1994	40/82	44/84		4.62%	0.87[0.47,1.59]
Gralla 1998	327/534	349/520		28.46%	0.77[0.6,1]
Martoni 1996	50/66	43/58		2.3%	1.09[0.48,2.46]
Navari 1995	154/328	84/165		12.31%	0.85[0.59,1.24]
Navari 1995	157/328	85/166		12.22%	0.87[0.6,1.27]
Park 1997	25/47	22/48		2.12%	1.34[0.6,3.01]
Ruff 1994	48/85	81/160		5.08%	1.27[0.75,2.15]
Ruff 1994	47/84	97/164		6.01%	0.88[0.52,1.49]
Spector 1998	95/187	106/184		10.91%	0.76[0.5,1.14]
Total (95% CI)	**2224**	**2032**		**100%**	**0.89[0.78,1.02]**
Total events: 1329 (granisetron), 1294 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=5.69, df=9(P=0.77); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					



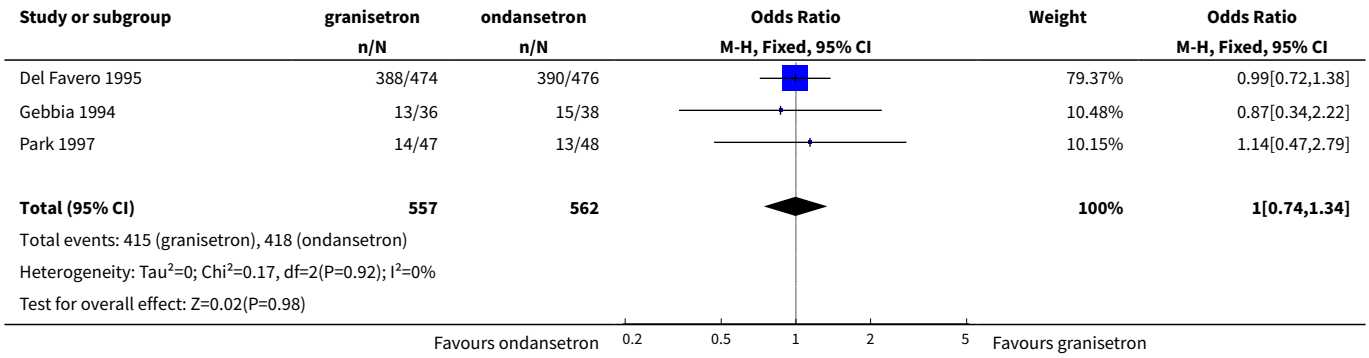
Analysis 1.2. Comparison 1 Granisetron versus ondansetron, Outcome 2 Absence of acute nausea.

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	347/483	348/483		20.87%	0.99[0.75,1.31]
Gebbia 1994	65/82	62/84		2.7%	1.36[0.66,2.79]
Gralla 1998	296/534	307/520		29.52%	0.86[0.68,1.1]
Martoni 1996	42/66	35/58		2.89%	1.15[0.56,2.38]
Navari 1995	138/328	66/166		10.81%	1.1[0.75,1.61]
Navari 1995	128/328	66/165		11.4%	0.96[0.65,1.41]
Ruff 1994	48/85	77/160		4.95%	1.4[0.82,2.37]
Ruff 1994	47/84	92/165		5.82%	1.01[0.59,1.71]
Spector 1998	64/185	79/184		11.03%	0.7[0.46,1.07]

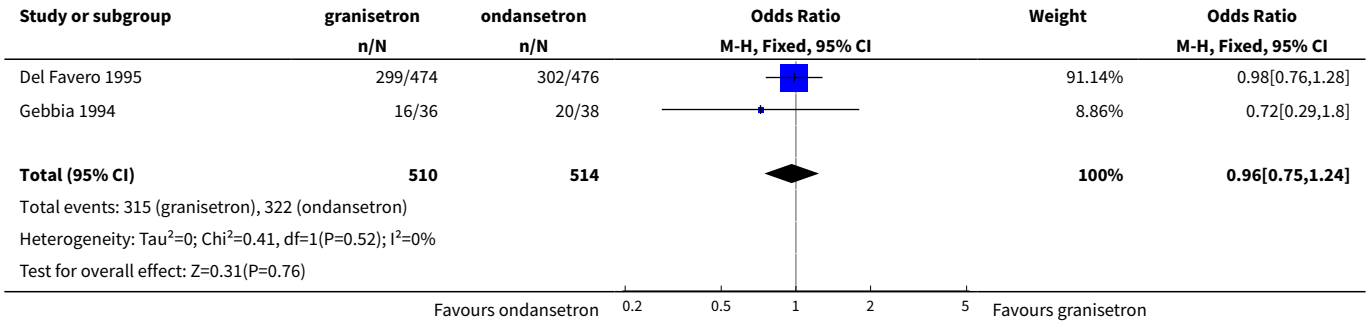




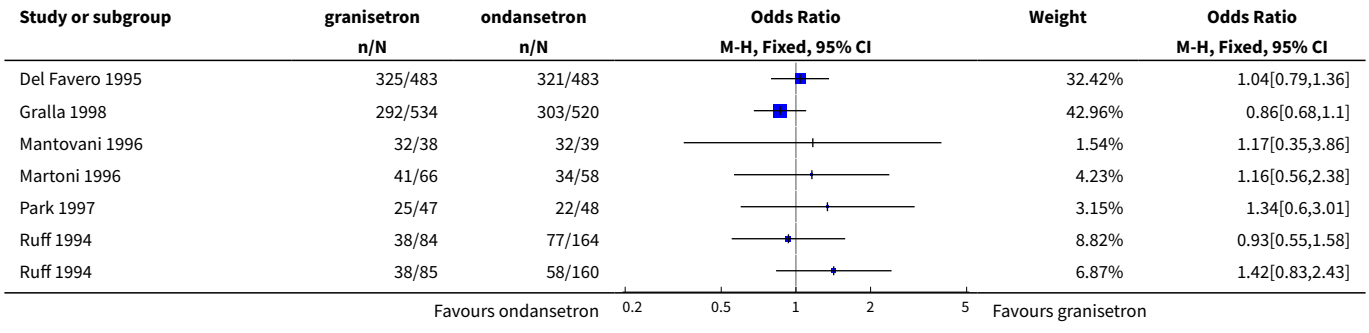
Analysis 1.3. Comparison 1 Granisetron versus ondansetron, Outcome 3 Absence of delayed vomiting.

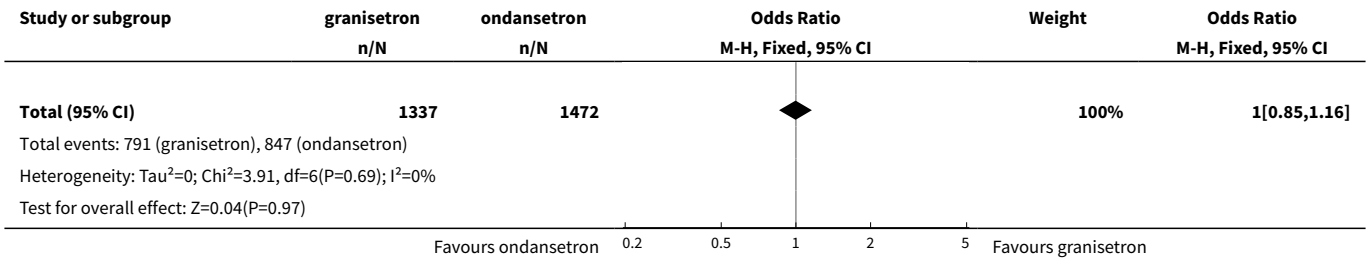


Analysis 1.4. Comparison 1 Granisetron versus ondansetron, Outcome 4 Absence of delayed nausea.

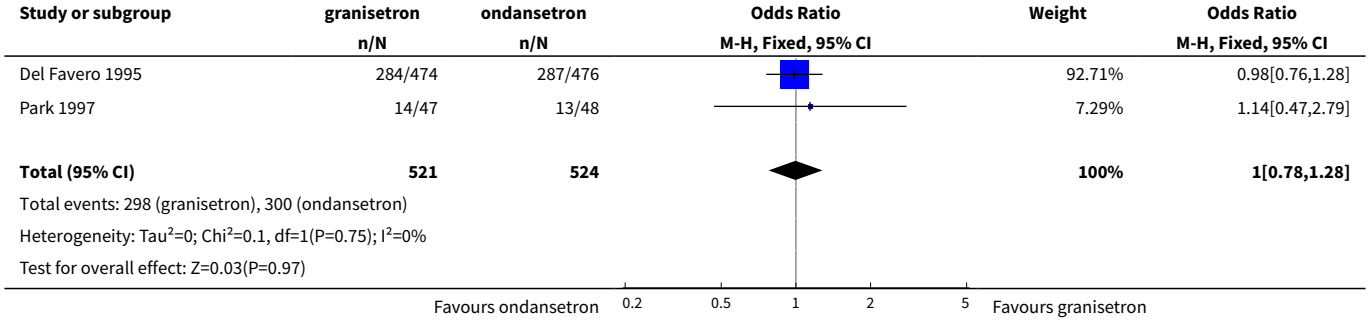


Analysis 1.5. Comparison 1 Granisetron versus ondansetron, Outcome 5 Total control of acute nausea and vomiting.

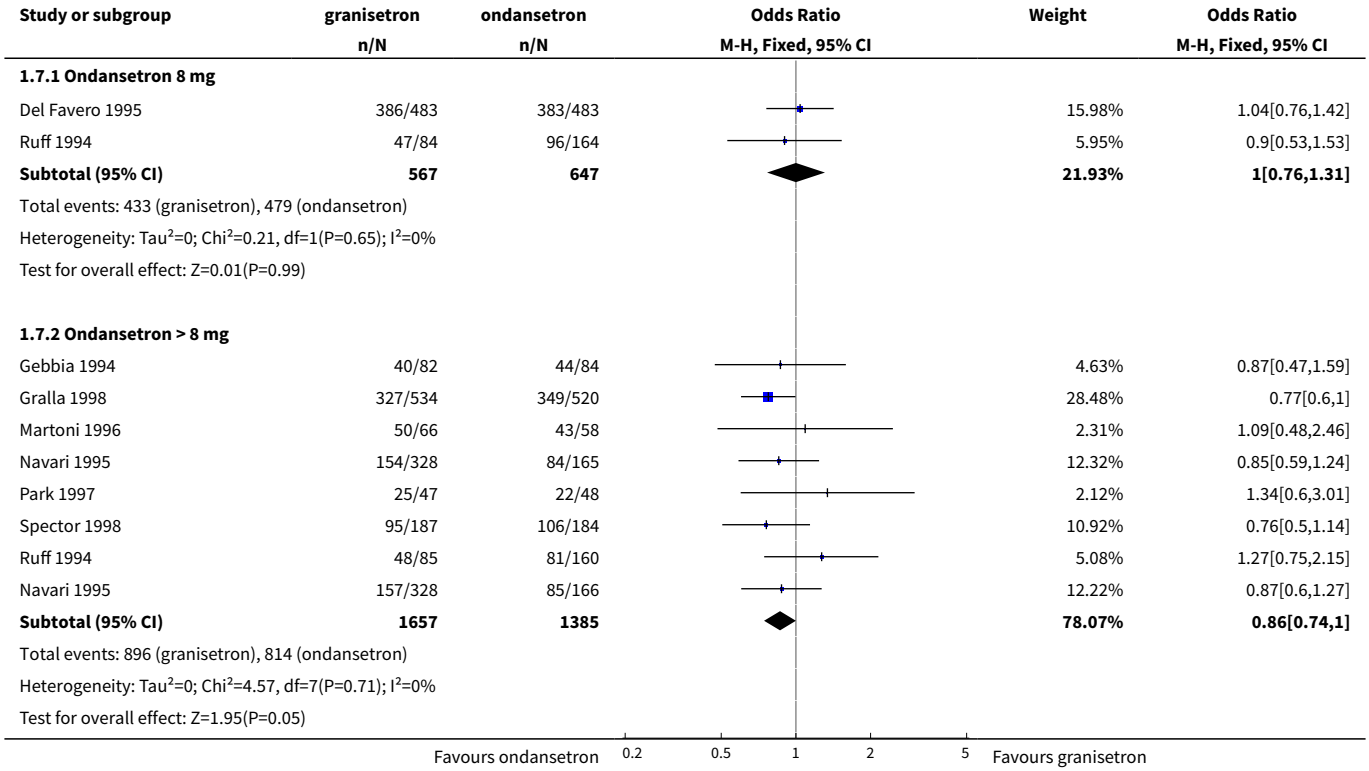


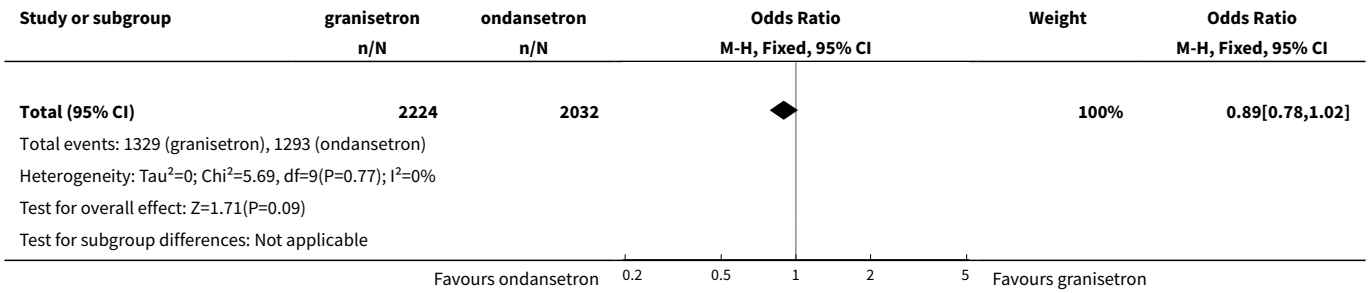


Analysis 1.6. Comparison 1 Granisetron versus ondansetron, Outcome 6 Total control of delayed nausea and vomiting.

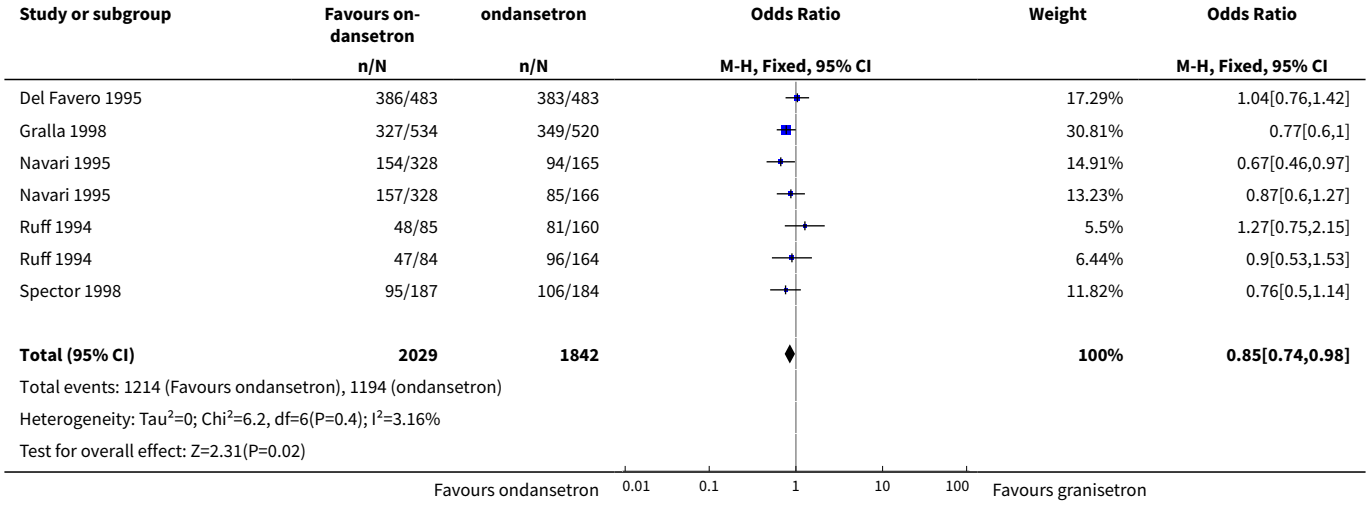


Analysis 1.7. Comparison 1 Granisetron versus ondansetron, Outcome 7 Absence of acute vomiting (ondansetron 8 mg vs > 8 mg).

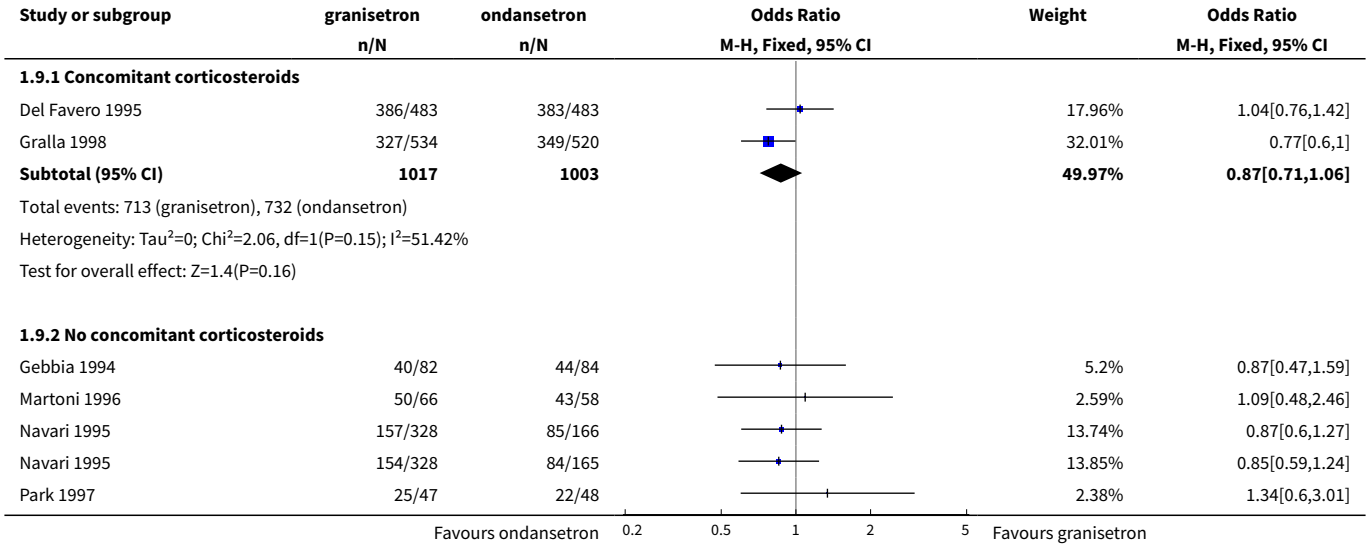


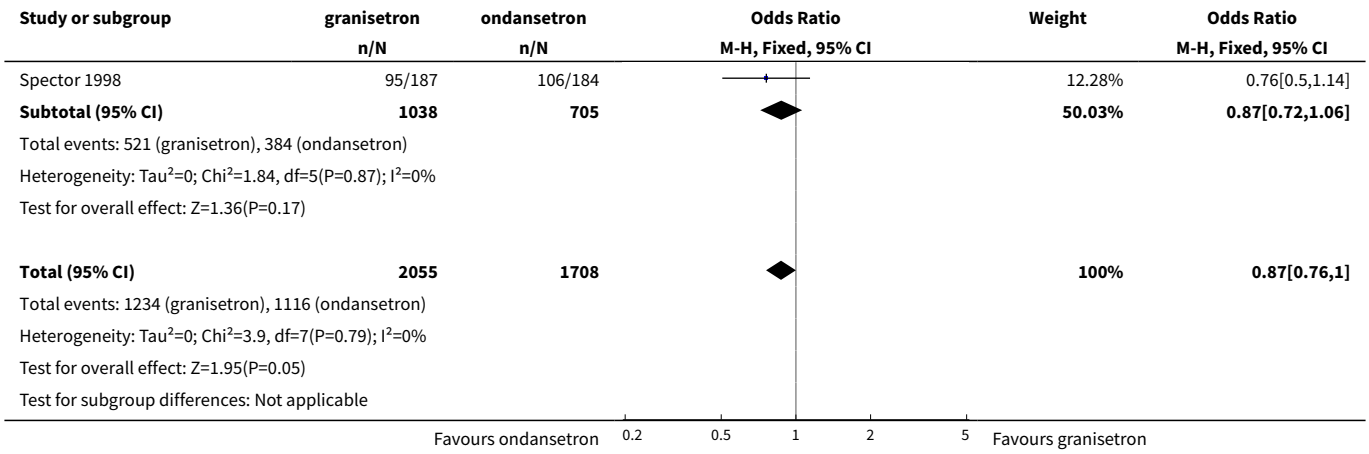


Analysis 1.8. Comparison 1 Granisetron versus ondansetron, Outcome 8 Absence of acute vomiting (excluding trials not blinded).

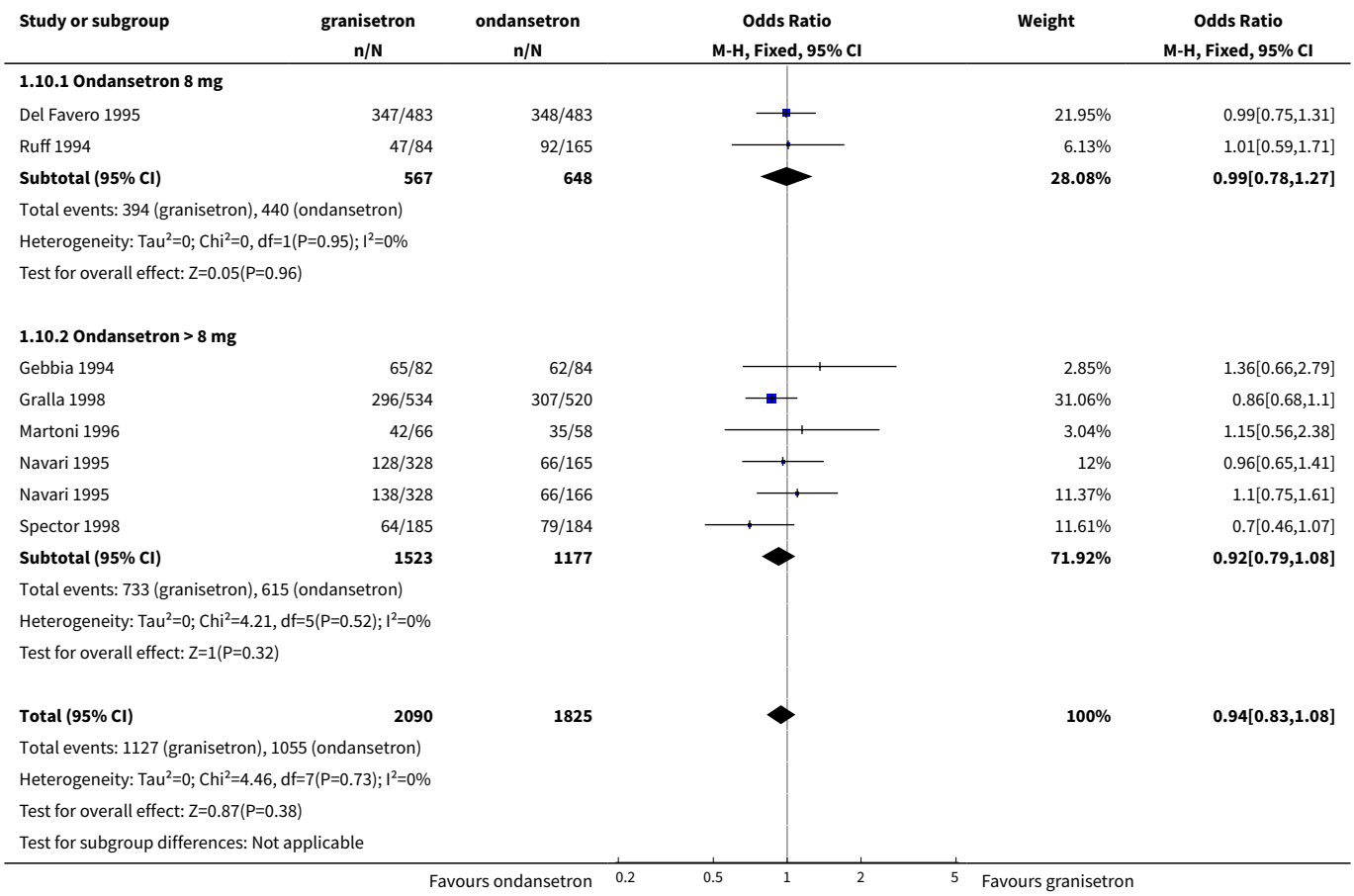


Analysis 1.9. Comparison 1 Granisetron versus ondansetron, Outcome 9 Absence of acute vomiting (concomitant corticosteroids).





Analysis 1.10. Comparison 1 Granisetron versus ondansetron, Outcome 10 Absence of acute nausea (Ondansetron 8 mg vs > 8 mg).



Analysis 1.11. Comparison 1 Granisetron versus ondansetron, Outcome 11 Absence of acute vomiting (including only trials based on ITT analysis).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	386/483	383/483		16.75%	1.04[0.76,1.42]
Gralla 1998	327/534	349/520		29.86%	0.77[0.6,1]
Martoni 1996	50/66	43/58		2.42%	1.09[0.48,2.46]
Navari 1995	154/328	84/165		12.92%	0.85[0.59,1.24]
Navari 1995	157/328	85/166		12.82%	0.87[0.6,1.27]
Park 1997	25/47	22/48		2.22%	1.34[0.6,3.01]
Ruff 1994	48/85	81/160		5.33%	1.27[0.75,2.15]
Ruff 1994	47/84	96/164		6.24%	0.9[0.53,1.53]
Spector 1998	95/187	106/184		11.45%	0.76[0.5,1.14]
Total (95% CI)	**2142**	**1948**		**100%**	**0.89[0.78,1.02]**
Total events: 1289 (granisetron), 1249 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=5.68$, df=8(P=0.68); $I^2=0\%$					
Test for overall effect: Z=1.65(P=0.1)					

Favours ondansetron — Favours granisetron

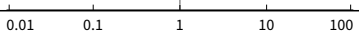
Analysis 1.12. Comparison 1 Granisetron versus ondansetron, Outcome 12 Absence of acute nausea (concomitant corticosteroids).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.12.1 Concomitant corticosteroids					
Del Favero 1995	347/483	348/483		23.39%	0.99[0.75,1.31]
Gralla 1998	296/534	307/520		33.09%	0.86[0.68,1.1]
Subtotal (95% CI)	**1017**	**1003**		**56.47%**	**0.92[0.76,1.1]**
Total events: 643 (granisetron), 655 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.52$, df=1(P=0.47); $I^2=0\%$					
Test for overall effect: Z=0.94(P=0.35)					
1.12.2 No corticosteroids					
Gebbia 1994	65/82	62/84		3.03%	1.36[0.66,2.79]
Martoni 1996	42/66	35/58		3.23%	1.15[0.56,2.38]
Navari 1995	128/328	66/165		12.78%	0.96[0.65,1.41]
Navari 1995	138/328	66/166		12.12%	1.1[0.75,1.61]
Spector 1998	64/185	79/184		12.36%	0.7[0.46,1.07]
Subtotal (95% CI)	**989**	**657**		**43.53%**	**0.97[0.79,1.19]**
Total events: 437 (granisetron), 308 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.71$, df=4(P=0.45); $I^2=0\%$					
Test for overall effect: Z=0.31(P=0.76)					
Total (95% CI)	**2006**	**1660**		**100%**	**0.94[0.82,1.08]**
Total events: 1080 (granisetron), 963 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=4.39$, df=6(P=0.62); $I^2=0\%$					
Test for overall effect: Z=0.91(P=0.36)					
Test for subgroup differences: Not applicable					

Favours ondansetron — Favours granisetron

Analysis 1.13. Comparison 1 Granisetron versus ondansetron, Outcome 13 Absence of acute vomiting (including only trials enrolling CT naive patients).

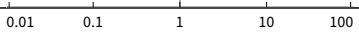
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Gebbia 1994	40/82	44/84		6.53%	0.87[0.47,1.59]
Gralla 1998	327/534	349/520		40.18%	0.77[0.6,1]
Martoni 1996	50/66	43/58		3.25%	1.09[0.48,2.46]
Navari 1995	154/328	84/165		17.38%	0.85[0.59,1.24]
Navari 1995	157/328	85/166		17.25%	0.87[0.6,1.27]
Spector 1998	95/187	106/184		15.41%	0.76[0.5,1.14]
Total (95% CI)	**1525**	**1177**		**100%**	**0.82[0.7,0.96]**
Total events: 823 (granisetron), 711 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=0.99, df=5(P=0.96); I^2=0%					
Test for overall effect: Z=2.48(P=0.01)					



Favours ondansetron — Favours granisetron

Analysis 1.14. Comparison 1 Granisetron versus ondansetron, Outcome 14 Absence of acute nausea (excluding trials not blinded).

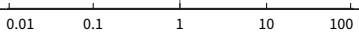
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	347/483	348/483		22.1%	0.99[0.75,1.31]
Gralla 1998	296/534	307/520		31.27%	0.86[0.68,1.1]
Navari 1995	138/328	66/166		11.45%	1.1[0.75,1.61]
Navari 1995	128/328	66/165		12.08%	0.96[0.65,1.41]
Ruff 1994	48/85	77/160		5.25%	1.4[0.82,2.37]
Ruff 1994	47/84	92/165		6.17%	1.01[0.59,1.71]
Spector 1998	64/185	79/184		11.69%	0.7[0.46,1.07]
Total (95% CI)	**2027**	**1843**		**100%**	**0.95[0.83,1.08]**
Total events: 1068 (granisetron), 1035 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=5.32, df=6(P=0.5); I^2=0%					
Test for overall effect: Z=0.78(P=0.43)					



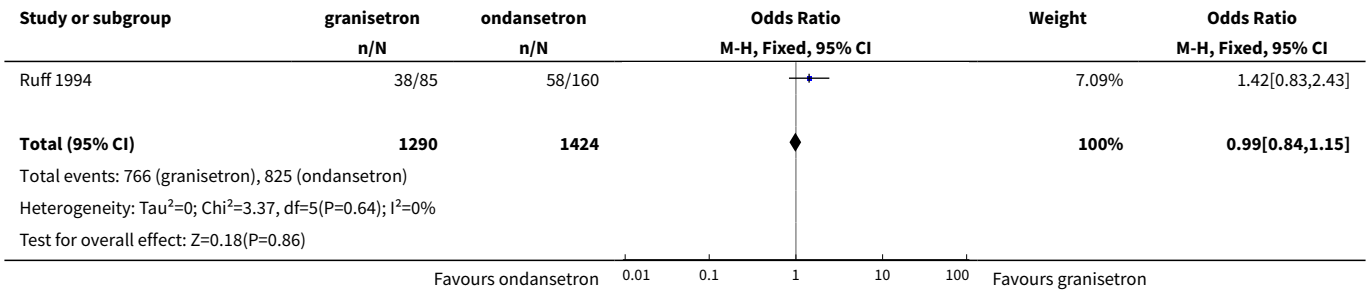
Favours ondansetron — Favours granisetron

Analysis 1.15. Comparison 1 Granisetron versus ondansetron, Outcome 15 Total control of acute nausea and vomiting (excluding trials not blinded).

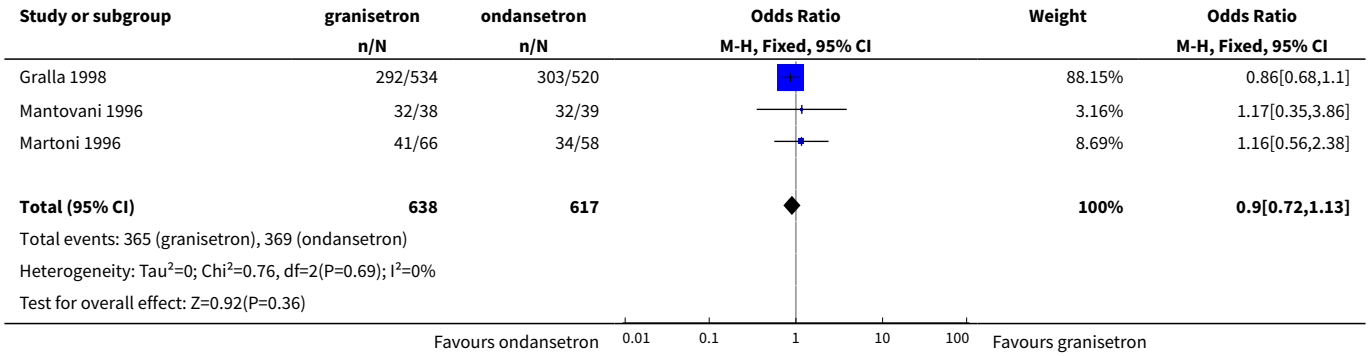
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	325/483	321/483		33.48%	1.04[0.79,1.36]
Gralla 1998	292/534	303/520		44.36%	0.86[0.68,1.1]
Mantovani 1996	32/38	32/39		1.59%	1.17[0.35,3.86]
Martoni 1996	41/66	34/58		4.37%	1.16[0.56,2.38]
Ruff 1994	38/84	77/164		9.11%	0.93[0.55,1.58]



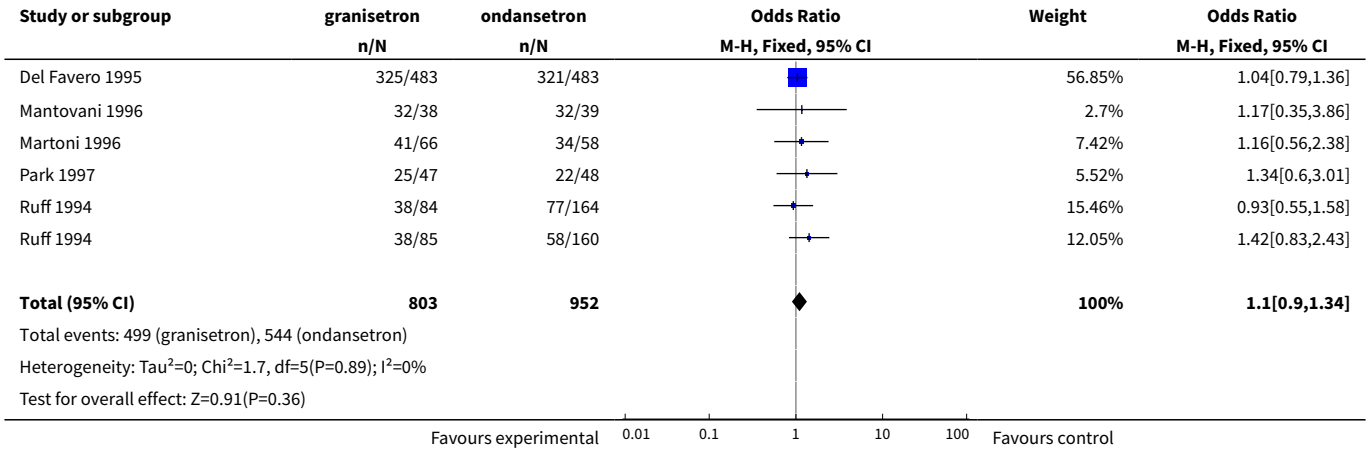
Favours ondansetron — Favours granisetron



Analysis 1.16. Comparison 1 Granisetron versus ondansetron, Outcome 16 Total control of acute nausea and vomiting (including only trials with CT naive patients).



Analysis 1.17. Comparison 1 Granisetron versus ondansetron, Outcome 17 Total control of acute nausea and vomiting (including only trials with iv anti-emetic administration).



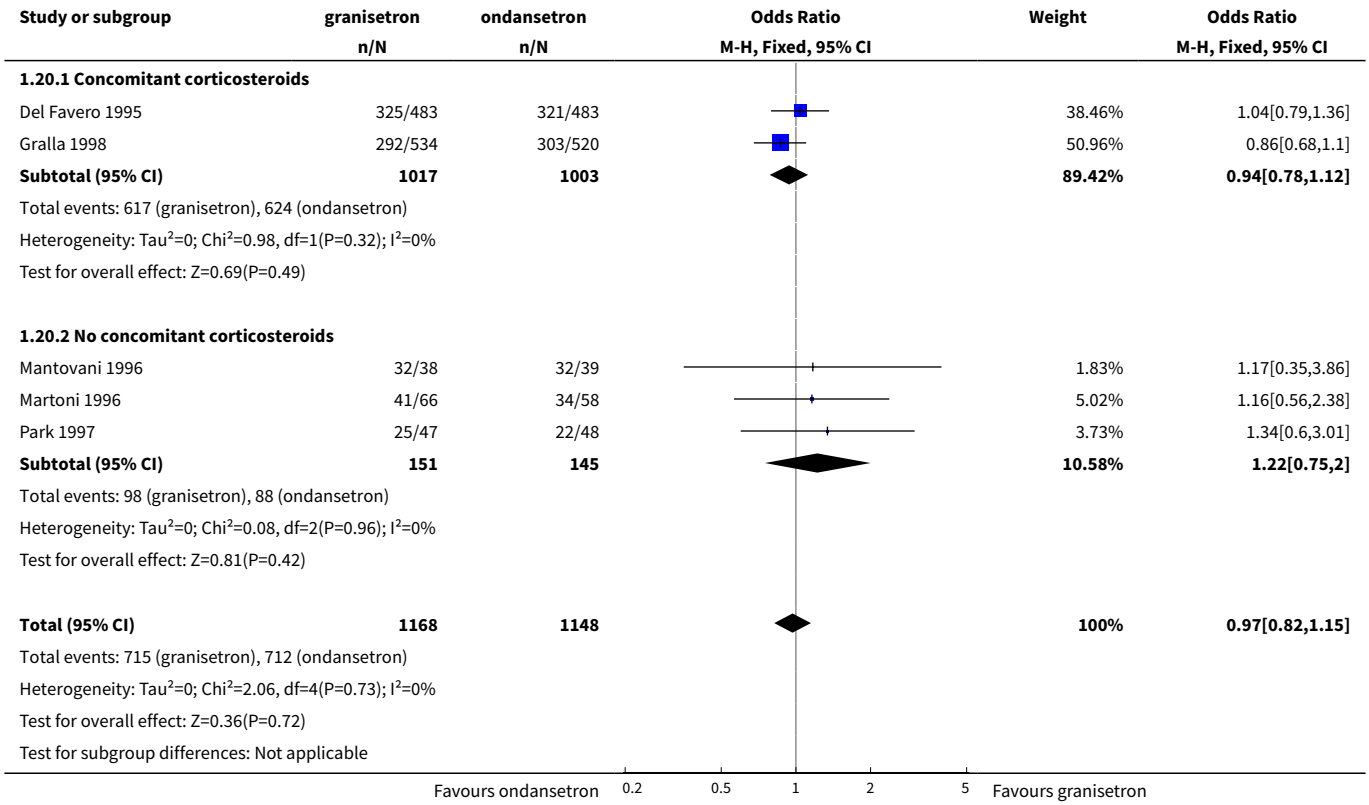
Analysis 1.18. Comparison 1 Granisetron versus ondansetron, Outcome 18 Absence of acute nausea (including only ITT analysis based trials).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	347/483	348/483		21.45%	0.99[0.75,1.31]
Gralla 1998	296/534	307/520		30.34%	0.86[0.68,1.1]
Martoni 1996	42/66	35/58		2.97%	1.15[0.56,2.38]
Navari 1995	138/328	66/166		11.11%	1.1[0.75,1.61]
Navari 1995	128/328	66/165		11.72%	0.96[0.65,1.41]
Ruff 1994	48/85	77/160		5.09%	1.4[0.82,2.37]
Ruff 1994	47/84	92/165		5.98%	1.01[0.59,1.71]
Spector 1998	64/185	79/184		11.34%	0.7[0.46,1.07]
Total (95% CI)	**2093**	**1901**		**100%**	**0.95[0.84,1.09]**
Total events: 1110 (granisetron), 1070 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=5.58, df=7(P=0.59); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					

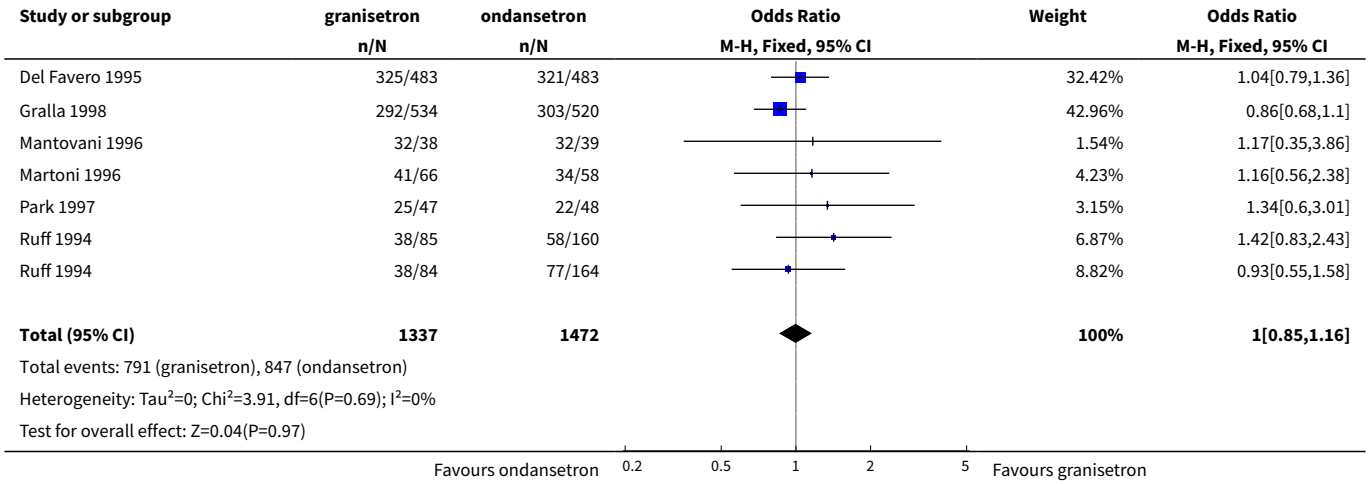
Analysis 1.19. Comparison 1 Granisetron versus ondansetron, Outcome 19 Total control of acute nausea and vomiting (ondansetron 8 mg vs > 8 mg).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.19.1 Ondansetron 8 mg					
Del Favero 1995	325/483	321/483		34.82%	1.04[0.79,1.36]
Martoni 1996	41/66	34/58		4.55%	1.16[0.56,2.38]
Ruff 1994	38/84	77/164		9.47%	0.93[0.55,1.58]
Subtotal (95% CI)	**633**	**705**		**48.83%**	**1.03[0.82,1.29]**
Total events: 404 (granisetron), 432 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=0.24, df=2(P=0.89); I^2=0%					
Test for overall effect: Z=0.25(P=0.81)					
1.19.2 Ondansetron > 8 mg					
Gralla 1998	292/534	303/520		46.13%	0.86[0.68,1.1]
Mantovani 1996	32/38	32/39		1.65%	1.17[0.35,3.86]
Park 1997	25/47	22/48		3.38%	1.34[0.6,3.01]
Subtotal (95% CI)	**619**	**607**		**51.17%**	**0.91[0.72,1.14]**
Total events: 349 (granisetron), 357 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=1.23, df=2(P=0.54); I^2=0%					
Test for overall effect: Z=0.85(P=0.4)					
Total (95% CI)	**1252**	**1312**		**100%**	**0.97[0.82,1.13]**
Total events: 753 (granisetron), 789 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=2.07, df=5(P=0.84); I^2=0%					
Test for overall effect: Z=0.42(P=0.67)					
Test for subgroup differences: Not applicable					

Analysis 1.20. Comparison 1 Granisetron versus ondansetron, Outcome 20 Total control of acute nausea and vomiting (concomitant corticosteroids).



Analysis 1.21. Comparison 1 Granisetron versus ondansetron, Outcome 21 Total control of acute nausea and vomiting (including only ITT analysis).



Comparison 2. Granisetron versus ondansetron

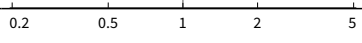
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting (cisplatin dose)	8	4256	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.02]
1.1 Cisplatin > 70 mg/m2	3	1315	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.03]
1.2 Cisplatin < 70 mg/m2	5	2941	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
2 Absence of acute nausea (cisplatin > 70 mg/m2 vs < 70 mg/m2)	7	4160	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.10]
2.1 Cisplatin > 70 mg/m2	2	1220	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.72, 1.14]
2.2 Cisplatin < 70 mg/m2	5	2940	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.85, 1.16]
3 Absence of delayed vomiting (cisplatin > 70 mg/m2 vs < 70 mg/m2)	3	1119	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.74, 1.34]
3.1 Cisplatin > 70 mg/m2	2	169	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.52, 1.91]
3.2 Cisplatin < 70 mg/m2	1	950	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.72, 1.38]
4 Absence of delayed nausea (cisplatin dose)	2	1024	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.24]
4.1 Cisplatin > 70 mg/m2	1	74	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.29, 1.80]
4.2 Cisplatin < 70 mg/m2	1	950	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.28]
5 Total control of acute nausea and vomiting (cisplatin > 70 mg/m2 vs < 70 mg/m2)	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.16]
5.1 Cisplatin > 70 mg/m2	3	1226	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.14]
5.2 Cisplatin < 70 mg/m2	3	1583	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.88, 1.33]
6 Absence of delayed nausea and vomiting (cisplatin > 70 mg/m2 vs < 70 mg/m2)	2	1045	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.78, 1.28]
6.1 Cisplatin > 70 mg/m2	1	95	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.47, 2.79]
6.2 Cisplatin < 70 mg/m2	1	950	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.76, 1.28]
7 Absence of acute nausea (excluding trials allowing mild nausea)	5	3500	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.06]
8 Absence of delayed vomiting (best case ondansetron)	3	1160	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.60, 1.06]
9 Absence of delayed nausea (best case ondansetron)	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.64, 1.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Total control of delayed nausea and vomiting (best case ondansetron)	2	1057	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.23]
11 Absence of acute nausea (including only trials with iv anti-emetic administration)	5	2737	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
12 Absence of delayed vomiting (best case granisetron)	3	1160	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.92, 1.63]
13 Total control of acute nausea and vomiting (excluding trials allowing mild nausea)	5	2316	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
14 Absence of acute vomiting (including only trials with iv anti-emetic administration)	6	2831	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.15]
15 Absence of acute vomiting (best case ondansetron)	8	4285	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 0.99]
16 Absence of acute nausea (best case ondansetron)	7	4186	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.07]
17 Absence of delayed nausea (best case granisetron)	2	1063	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.88, 1.44]
18 Total control of delayed nausea and vomiting (best case granisetron)	2	1070	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.40]
19 Total control of acute nausea and vomiting (best case granisetron)	6	2819	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.18]
20 Absence of acute vomiting (best case granisetron)	8	3546	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.05]
21 Absence of acute nausea (best case granisetron)	7	3447	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.10]
22 Absence of acute vomiting (granisetron dose)	8	3517	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 1.01]
22.1 Granisetron 1 mg	2	864	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.61, 1.07]
22.2 Granisetron 3 mg	6	2653	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.76, 1.06]
23 Total control of acute nausea and vomiting (best case ondansetron)	6	2574	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.12]
24 Absence of acute nausea (granisetron dose)	7	3421	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.80, 1.06]
24.1 Granisetron 1 mg	2	862	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.63, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 Granisetron 3 mg	5	2559	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.81, 1.13]
25 Headache	7	3135	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.82, 1.34]
26 Constipation	7	3283	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.52, 0.96]
27 Diarrhoea	5	1994	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.70, 1.45]
28 Cumulative adverse events	5	1994	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.06]

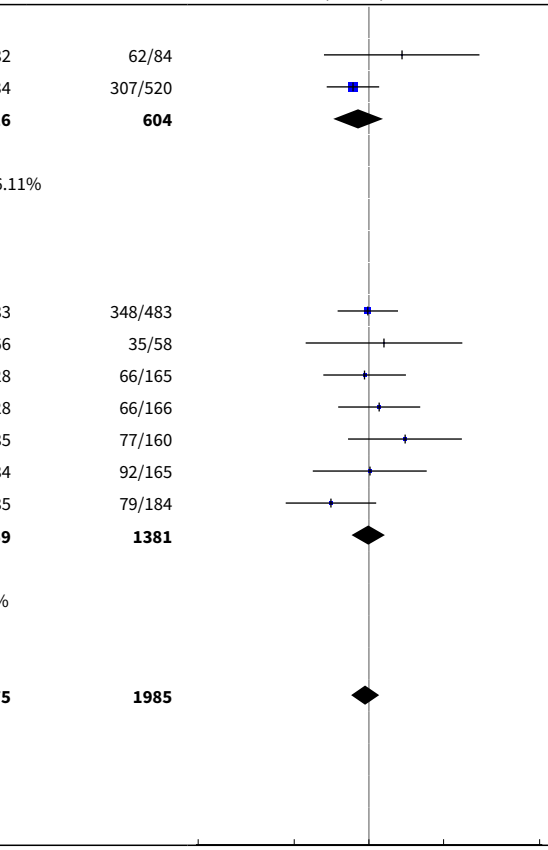
Analysis 2.1. Comparison 2 Granisetron versus ondansetron, Outcome 1 Absence of acute vomiting (cisplatin dose).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Cisplatin > 70 mg/m2					
Gebbia 1994	40/82	44/84		4.63%	0.87[0.47,1.59]
Gralla 1998	327/534	349/520		28.48%	0.77[0.6,1]
Park 1997	25/47	22/48		2.12%	1.34[0.6,3.01]
Subtotal (95% CI)	**663**	**652**		**35.22%**	**0.82[0.66,1.03]**
Total events: 392 (granisetron), 415 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=1.67, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=1.74(P=0.08)					
2.1.2 Cisplatin < 70 mg/m2					
Del Favero 1995	386/483	383/483		15.98%	1.04[0.76,1.42]
Martoni 1996	50/66	43/58		2.31%	1.09[0.48,2.46]
Navari 1995	154/328	84/165		12.32%	0.85[0.59,1.24]
Ruff 1994	47/84	96/164		5.95%	0.9[0.53,1.53]
Spector 1998	95/187	106/184		10.92%	0.76[0.5,1.14]
Ruff 1994	48/85	81/160		5.08%	1.27[0.75,2.15]
Navari 1995	157/328	85/166		12.22%	0.87[0.6,1.27]
Subtotal (95% CI)	**1561**	**1380**		**64.78%**	**0.93[0.79,1.09]**
Total events: 937 (granisetron), 878 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=3.18, df=6(P=0.79); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	**2224**	**2032**		**100%**	**0.89[0.78,1.02]**
Total events: 1329 (granisetron), 1293 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=5.69, df=9(P=0.77); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					
Test for subgroup differences: Not applicable					



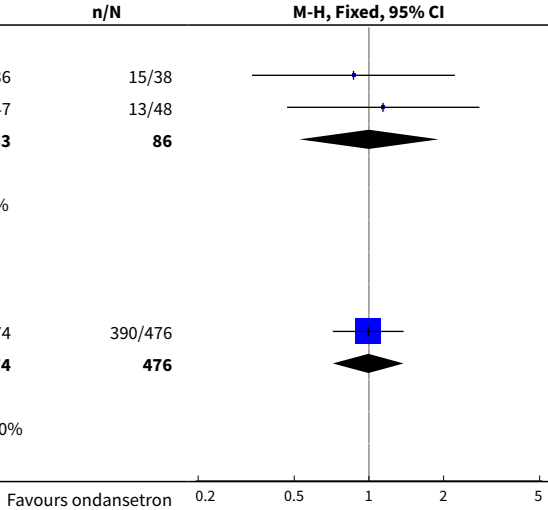
Analysis 2.2. Comparison 2 Granisetron versus ondansetron, Outcome 2 Absence of acute nausea (cisplatin > 70 mg/m2 vs < 70 mg/m2).

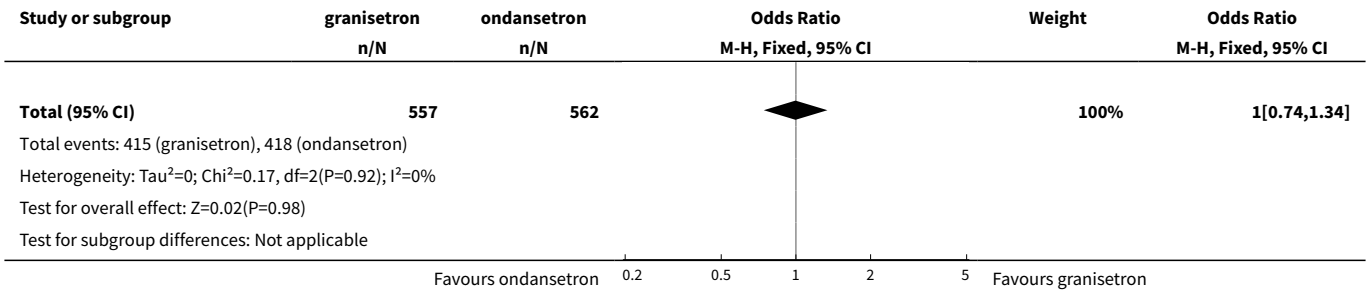
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Cisplatin > 70 mg/m2					
Gebbia 1994	65/82	62/84		2.7%	1.36[0.66,2.79]
Gralla 1998	296/534	307/520		29.52%	0.86[0.68,1.1]
Subtotal (95% CI)	**616**	**604**		**32.23%**	**0.9[0.72,1.14]**
Total events: 361 (granisetron), 369 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=1.35, df=1(P=0.24); I^2=26.11%					
Test for overall effect: Z=0.85(P=0.39)					
2.2.2 Cisplatin < 70 mg/m2					
Del Favero 1995	347/483	348/483		20.87%	0.99[0.75,1.31]
Martoni 1996	42/66	35/58		2.89%	1.15[0.56,2.38]
Navari 1995	128/328	66/165		11.4%	0.96[0.65,1.41]
Navari 1995	138/328	66/166		10.81%	1.1[0.75,1.61]
Ruff 1994	48/85	77/160		4.95%	1.4[0.82,2.37]
Ruff 1994	47/84	92/165		5.82%	1.01[0.59,1.71]
Spector 1998	64/185	79/184		11.03%	0.7[0.46,1.07]
Subtotal (95% CI)	**1559**	**1381**		**67.77%**	**0.99[0.85,1.16]**
Total events: 814 (granisetron), 763 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=4.67, df=6(P=0.59); I^2=0%					
Test for overall effect: Z=0.08(P=0.94)					
Total (95% CI)	**2175**	**1985**		**100%**	**0.97[0.85,1.1]**
Total events: 1175 (granisetron), 1132 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=6.47, df=8(P=0.6); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Not applicable					



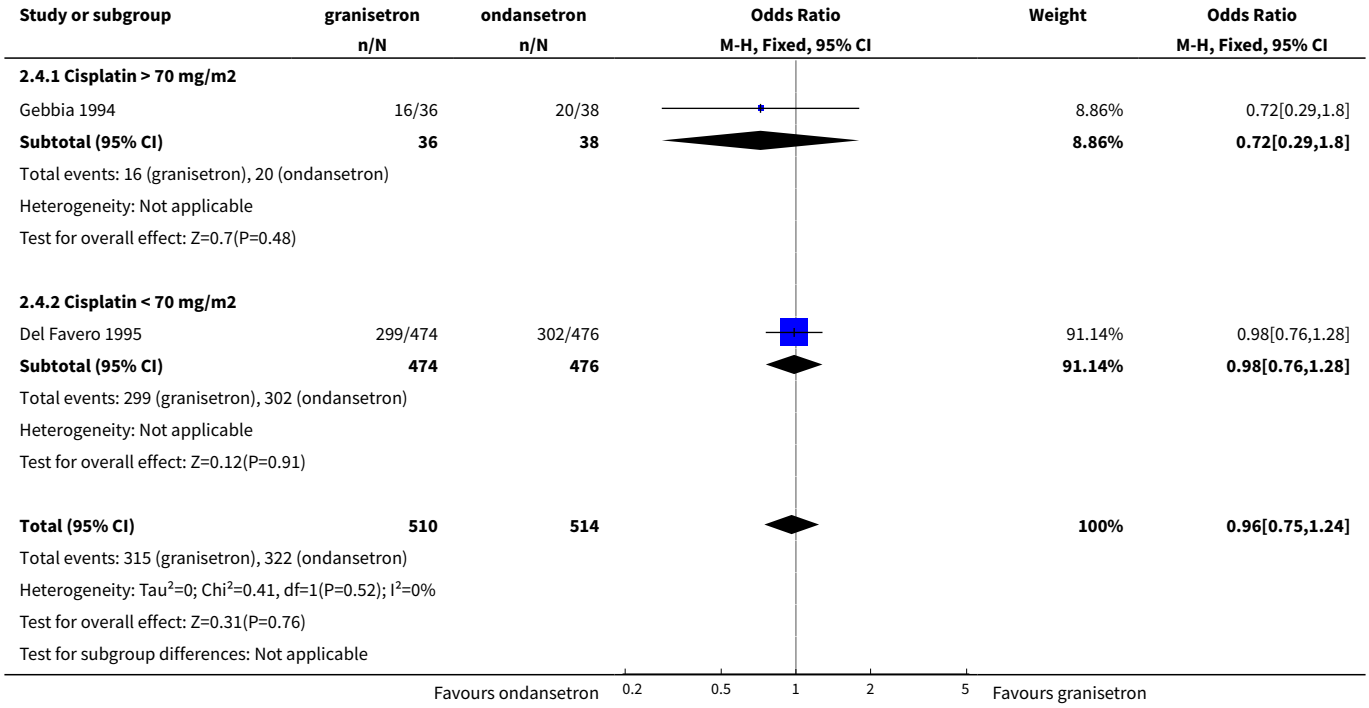
Analysis 2.3. Comparison 2 Granisetron versus ondansetron, Outcome 3 Absence of delayed vomiting (cisplatin > 70 mg/m2 vs < 70 mg/m2).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Cisplatin > 70 mg/m2					
Gebbia 1994	13/36	15/38		10.48%	0.87[0.34,2.22]
Park 1997	14/47	13/48		10.15%	1.14[0.47,2.79]
Subtotal (95% CI)	**83**	**86**		**20.63%**	**1[0.52,1.91]**
Total events: 27 (granisetron), 28 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					
2.3.2 Cisplatin < 70 mg/m2					
Del Favero 1995	388/474	390/476		79.37%	0.99[0.72,1.38]
Subtotal (95% CI)	**474**	**476**		**79.37%**	**0.99[0.72,1.38]**
Total events: 388 (granisetron), 390 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.03(P=0.98)					

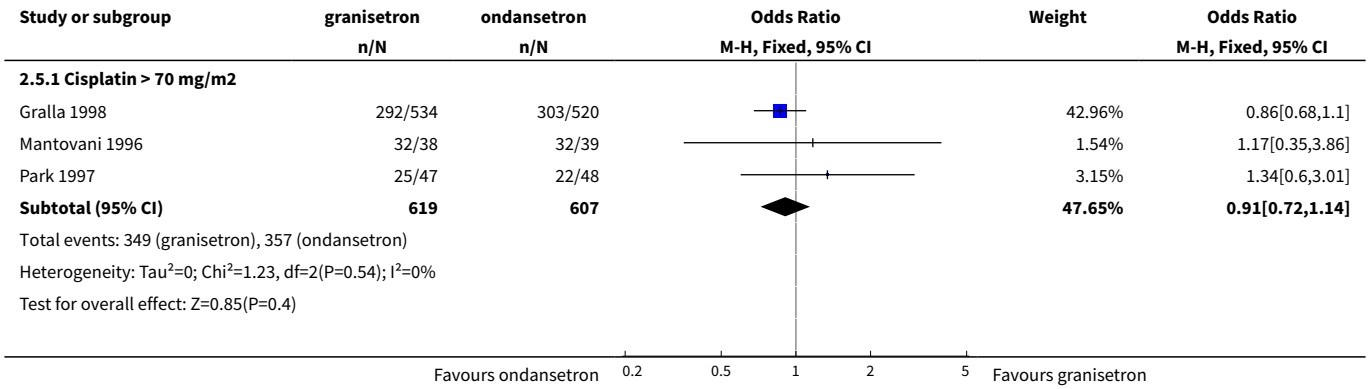


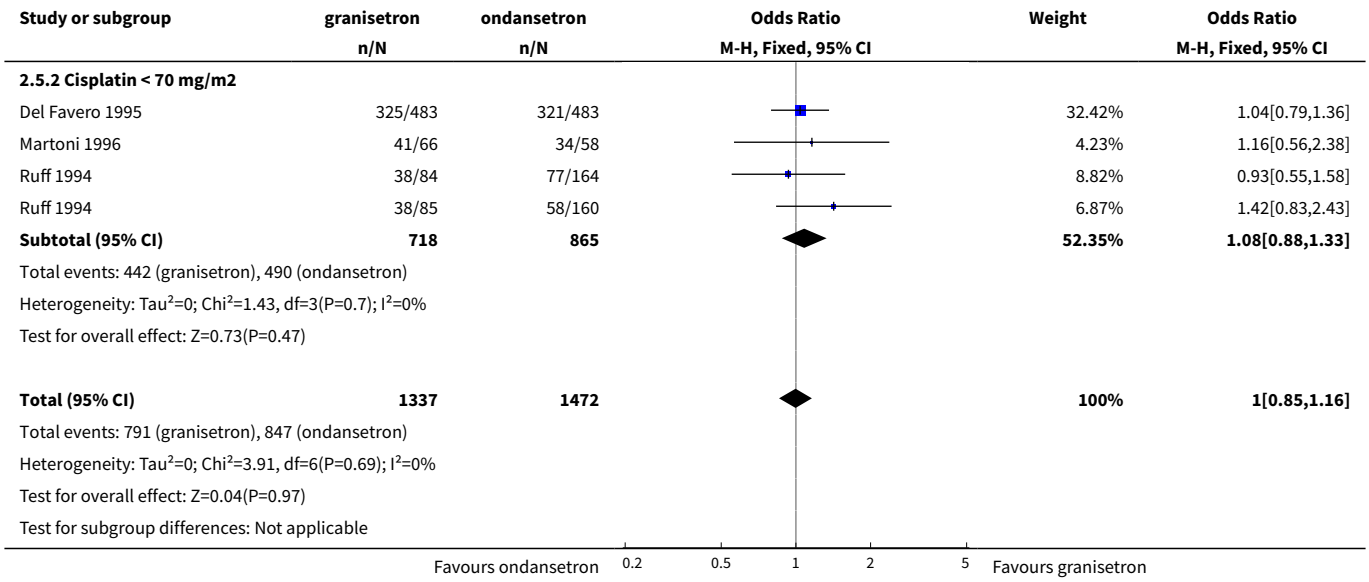


Analysis 2.4. Comparison 2 Granisetron versus ondansetron, Outcome 4 Absence of delayed nausea (cisplatin dose).

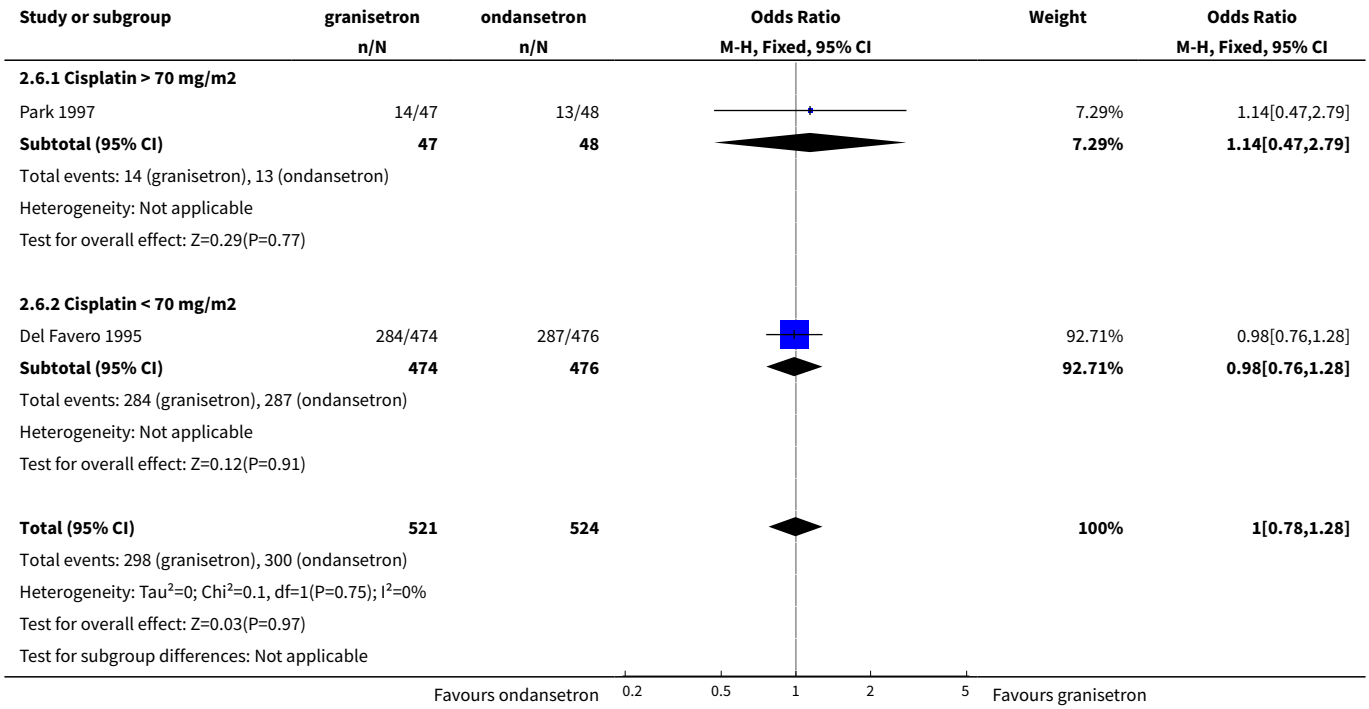


Analysis 2.5. Comparison 2 Granisetron versus ondansetron, Outcome 5 Total control of acute nausea and vomiting (cisplatin > 70 mg/m2 vs < 70 mg/m2).



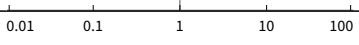


Analysis 2.6. Comparison 2 Granisetron versus ondansetron, Outcome 6 Absence of delayed nausea and vomiting (cisplatin > 70 mg/m2 vs < 70 mg/m2).



Analysis 2.7. Comparison 2 Granisetron versus ondansetron, Outcome 7 Absence of acute nausea (excluding trials allowing mild nausea).

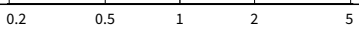
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	347/483	348/483		24.12%	0.99[0.75,1.31]
Gralla 1998	296/534	307/520		34.12%	0.86[0.68,1.1]
Martoni 1996	42/66	35/58		3.33%	1.15[0.56,2.38]
Navari 1995	138/328	66/166		12.5%	1.1[0.75,1.61]
Navari 1995	128/328	66/165		13.18%	0.96[0.65,1.41]
Spector 1998	64/185	79/184		12.75%	0.7[0.46,1.07]
Total (95% CI)	**1924**	**1576**		**100%**	**0.93[0.8,1.06]**
Total events: 1015 (granisetron), 901 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.35$, df=5(P=0.65); $I^2=0\%$					
Test for overall effect: Z=1.09(P=0.28)					



Favours ondansetron — Favours granisetron

Analysis 2.8. Comparison 2 Granisetron versus ondansetron, Outcome 8 Absence of delayed vomiting (best case ondansetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	388/487	400/486		76.03%	0.84[0.61,1.16]
Gebbia 1994	13/44	23/46		14.8%	0.42[0.18,1]
Park 1997	14/48	14/49		9.17%	1.03[0.43,2.48]
Total (95% CI)	**579**	**581**		**100%**	**0.8[0.6,1.06]**
Total events: 415 (granisetron), 437 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=2.54$, df=2(P=0.28); $I^2=21.38\%$					
Test for overall effect: Z=1.57(P=0.12)					



Favours ondansetron — Favours granisetron

Analysis 2.9. Comparison 2 Granisetron versus ondansetron, Outcome 9 Absence of delayed nausea (best case ondansetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	299/487	312/486		87.37%	0.89[0.68,1.15]
Gebbia 1994	16/44	28/46		12.63%	0.37[0.16,0.86]
Total (95% CI)	**531**	**532**		**100%**	**0.82[0.64,1.05]**
Total events: 315 (granisetron), 340 (ondansetron)					
Heterogeneity: $Tau^2=0$; $Chi^2=3.75$, df=1(P=0.05); $I^2=73.35\%$					
Test for overall effect: Z=1.56(P=0.12)					

Favours ondansetron — Favours granisetron

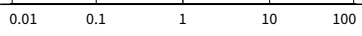
Analysis 2.10. Comparison 2 Granisetron versus ondansetron, Outcome 10 Total control of delayed nausea and vomiting (best case ondansetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	284/474	297/486		92.29%	0.95[0.73,1.23]
Park 1997	14/48	14/49		7.71%	1.03[0.43,2.48]
Total (95% CI)	**522**	**535**		**100%**	**0.96[0.75,1.23]**
Total events: 298 (granisetron), 311 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					

Favours ondansetron — Favours granisetron

Analysis 2.11. Comparison 2 Granisetron versus ondansetron, Outcome 11 Absence of acute nausea (including only trials with iv anti-emetic administration).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	347/483	348/483		35.06%	0.99[0.75,1.31]
Gebbia 1994	65/82	62/84		4.54%	1.36[0.66,2.79]
Martoni 1996	42/66	35/58		4.85%	1.15[0.56,2.38]
Navari 1995	138/328	66/166		18.17%	1.1[0.75,1.61]
Navari 1995	128/328	66/165		19.16%	0.96[0.65,1.41]
Ruff 1994	48/85	77/160		8.32%	1.4[0.82,2.37]
Ruff 1994	47/84	93/165		9.89%	0.98[0.58,1.67]
Total (95% CI)	**1456**	**1281**		**100%**	**1.06[0.9,1.25]**
Total events: 815 (granisetron), 747 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=2.15, df=6(P=0.91); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					



Favours ondansetron — Favours granisetron

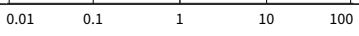
Analysis 2.12. Comparison 2 Granisetron versus ondansetron, Outcome 12 Absence of delayed vomiting (best case granisetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	401/487	390/486		80.68%	1.15[0.83,1.58]
Gebbia 1994	21/44	15/46		8.97%	1.89[0.8,4.43]
Park 1997	15/48	13/49		10.35%	1.26[0.52,3.04]
Total (95% CI)	**579**	**581**		**100%**	**1.23[0.92,1.63]**
Total events: 437 (granisetron), 418 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=2(P=0.56); I^2=0%					
Test for overall effect: Z=1.4(P=0.16)					

Favours ondansetron — Favours granisetron

Analysis 2.13. Comparison 2 Granisetron versus ondansetron, Outcome 13 Total control of acute nausea and vomiting (excluding trials allowing mild nausea).

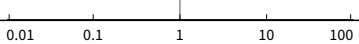
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	325/483	321/483		38.46%	1.04[0.79,1.36]
Gralla 1998	292/534	303/520		50.96%	0.86[0.68,1.1]
Mantovani 1996	32/38	32/39		1.83%	1.17[0.35,3.86]
Martoni 1996	41/66	34/58		5.02%	1.16[0.56,2.38]
Park 1997	25/47	22/48		3.73%	1.34[0.6,3.01]
Total (95% CI)	**1168**	**1148**		**100%**	**0.97[0.82,1.15]**
Total events: 715 (granisetron), 712 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=2.06, df=4(P=0.73); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					



Favours ondansetron — Favours granisetron

Analysis 2.14. Comparison 2 Granisetron versus ondansetron, Outcome 14 Absence of acute vomiting (including only trials with iv anti-emetic administration).

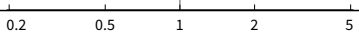
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	386/483	383/483		26.37%	1.04[0.76,1.42]
Gebbia 1994	40/82	44/84		7.63%	0.87[0.47,1.59]
Martoni 1996	50/66	43/58		3.8%	1.09[0.48,2.46]
Navari 1995	157/328	85/166		20.17%	0.87[0.6,1.27]
Navari 1995	154/328	84/165		20.33%	0.85[0.59,1.24]
Park 1997	25/47	22/48		3.49%	1.34[0.6,3.01]
Ruff 1994	48/85	81/160		8.39%	1.27[0.75,2.15]
Ruff 1994	47/84	96/164		9.82%	0.9[0.53,1.53]
Total (95% CI)	**1503**	**1328**		**100%**	**0.97[0.83,1.15]**
Total events: 907 (granisetron), 838 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=2.81, df=7(P=0.9); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					



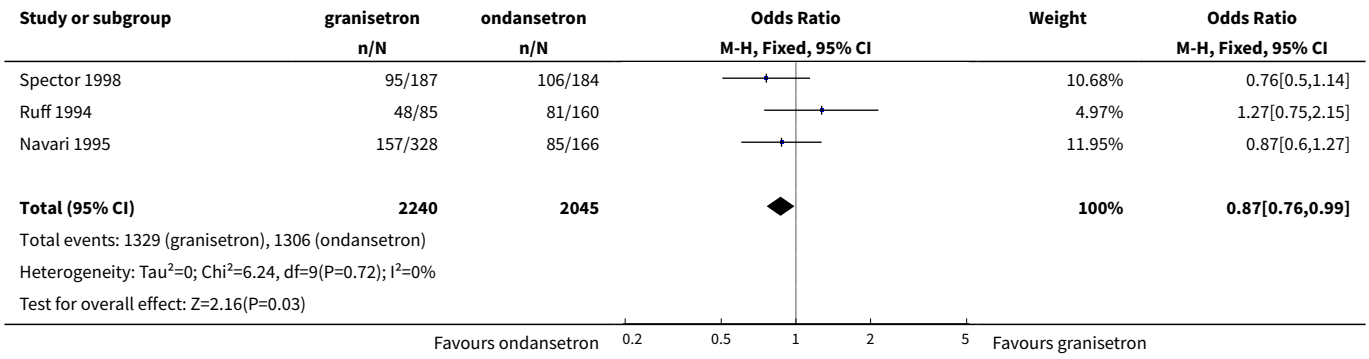
Favours ondansetron — Favours granisetron

Analysis 2.15. Comparison 2 Granisetron versus ondansetron, Outcome 15 Absence of acute vomiting (best case ondansetron).

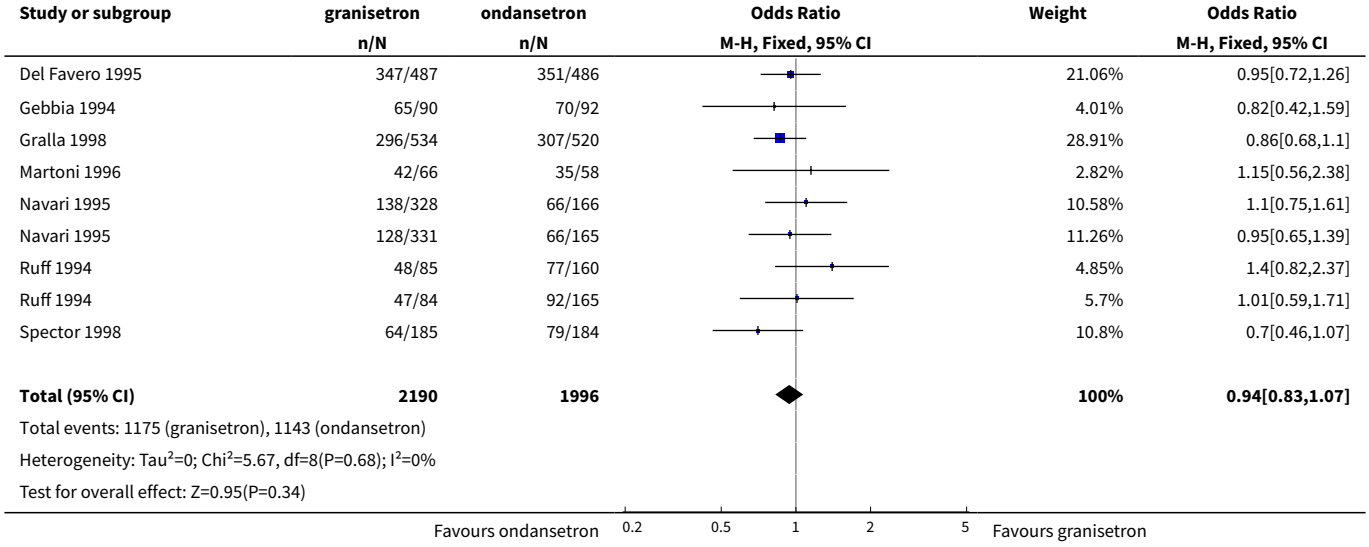
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	386/487	386/486		16.27%	0.99[0.73,1.35]
Gebbia 1994	40/90	52/92		5.8%	0.62[0.34,1.11]
Gralla 1998	327/534	349/520		27.84%	0.77[0.6,1]
Martoni 1996	50/66	43/58		2.25%	1.09[0.48,2.46]
Navari 1995	154/331	84/165		12.17%	0.84[0.58,1.22]
Park 1997	25/48	23/49		2.21%	1.23[0.55,2.73]
Ruff 1994	47/84	97/165		5.85%	0.89[0.52,1.51]



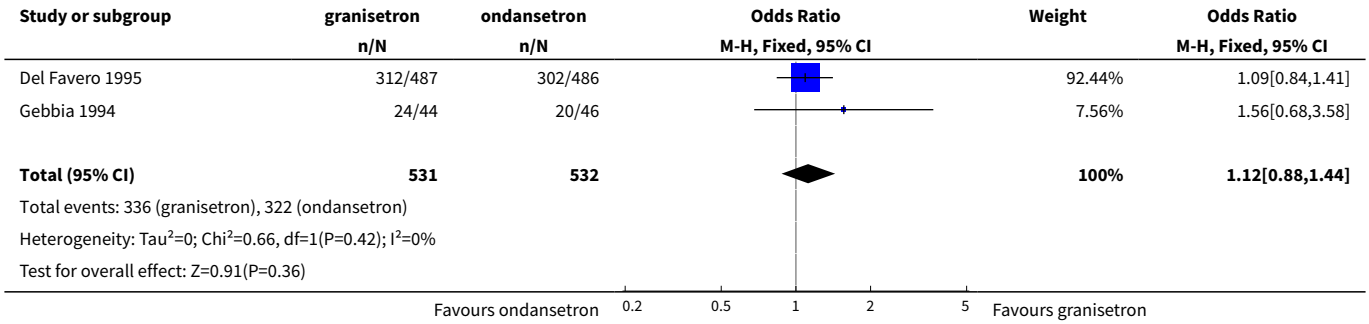
Favours ondansetron — Favours granisetron



Analysis 2.16. Comparison 2 Granisetron versus ondansetron, Outcome 16 Absence of acute nausea (best case ondansetron).



Analysis 2.17. Comparison 2 Granisetron versus ondansetron, Outcome 17 Absence of delayed nausea (best case granisetron).



Analysis 2.18. Comparison 2 Granisetron versus ondansetron, Outcome 18 Total control of delayed nausea and vomiting (best case granisetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	297/487	287/486		92.69%	1.08[0.84,1.4]
Park 1997	15/48	13/49		7.31%	1.26[0.52,3.04]
Total (95% CI)	**535**	**535**		**100%**	**1.1[0.86,1.4]**
Total events: 312 (granisetron), 300 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%					
Test for overall effect: Z=0.73(P=0.46)					

Favours ondansetron — Favours granisetron

Analysis 2.19. Comparison 2 Granisetron versus ondansetron, Outcome 19 Total control of acute nausea and vomiting (best case granisetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	329/487	321/486		32.3%	1.07[0.82,1.4]
Gralla 1998	292/534	303/520		43.11%	0.86[0.68,1.1]
Mantovani 1996	32/38	32/39		1.55%	1.17[0.35,3.86]
Martoni 1996	41/66	34/58		4.25%	1.16[0.56,2.38]
Park 1997	26/48	22/49		3.09%	1.45[0.65,3.23]
Ruff 1994	38/85	58/160		6.89%	1.42[0.83,2.43]
Ruff 1994	38/84	77/165		8.81%	0.94[0.56,1.6]
Total (95% CI)	**1342**	**1477**		**100%**	**1.01[0.87,1.18]**
Total events: 796 (granisetron), 847 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=4.36, df=6(P=0.63); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					

Favours ondansetron — Favours granisetron

Analysis 2.20. Comparison 2 Granisetron versus ondansetron, Outcome 20 Absence of acute vomiting (best case granisetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	390/487	383/486		19.34%	1.08[0.79,1.48]
Gebbia 1994	48/90	44/92		5.14%	1.25[0.7,2.23]
Gralla 1998	327/534	349/520		34.72%	0.77[0.6,1]
Martoni 1996	50/66	43/58		2.81%	1.09[0.48,2.46]
Navari 1995	157/331	84/165		14.93%	0.87[0.6,1.26]
Park 1997	26/48	22/49		2.53%	1.45[0.65,3.23]
Ruff 1994	47/84	96/165		7.23%	0.91[0.54,1.55]
Spector 1998	95/187	106/184		13.31%	0.76[0.5,1.14]
Total (95% CI)	**1827**	**1719**		**100%**	**0.91[0.79,1.05]**
Total events: 1140 (granisetron), 1127 (ondansetron)					

Favours ondansetron — Favours granisetron

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=6.17, df=7(P=0.52); I²=0%					
Test for overall effect: Z=1.35(P=0.18)					

Favours ondansetron 0.2 0.5 1 2 5 Favours granisetron

Analysis 2.21. Comparison 2 Granisetron versus ondansetron, Outcome 21 Absence of acute nausea (best case granisetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	351/487	348/486		24.73%	1.02[0.77,1.35]
Gebbia 1994	73/90	62/92		2.94%	2.08[1.05,4.12]
Gralla 1998	296/534	307/520		35.24%	0.86[0.68,1.1]
Martoni 1996	42/66	35/58		3.44%	1.15[0.56,2.38]
Navari 1995	131/331	66/165		13.53%	0.98[0.67,1.44]
Ruff 1994	47/84	92/165		6.95%	1.01[0.59,1.71]
Spector 1998	64/185	79/184		13.17%	0.7[0.46,1.07]
Total (95% CI)	**1777**	**1670**		**100%**	**0.95[0.83,1.1]**
Total events: 1004 (granisetron), 989 (ondansetron)					
Heterogeneity: Tau²=0; Chi²=8.2, df=6(P=0.22); I²=26.83%					
Test for overall effect: Z=0.66(P=0.51)					

Favours ondansetron 0.2 0.5 1 2 5 Favours granisetron

Analysis 2.22. Comparison 2 Granisetron versus ondansetron, Outcome 22 Absence of acute vomiting (granisetron dose).

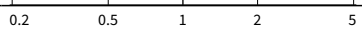
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.22.1 Granisetron 1 mg					
Navari 1995	154/328	84/165		14.9%	0.85[0.59,1.24]
Spector 1998	95/187	106/184		13.21%	0.76[0.5,1.14]
Subtotal (95% CI)	**515**	**349**		**28.1%**	**0.81[0.61,1.07]**
Total events: 249 (granisetron), 190 (ondansetron)					
Heterogeneity: Tau²=0; Chi²=0.17, df=1(P=0.68); I²=0%					
Test for overall effect: Z=1.5(P=0.13)					
2.22.2 Granisetron 3 mg					
Del Favero 1995	386/483	383/483		19.32%	1.04[0.76,1.42]
Gebbia 1994	40/82	44/84		5.59%	0.87[0.47,1.59]
Gralla 1998	327/534	349/520		34.44%	0.77[0.6,1]
Martoni 1996	50/66	43/58		2.79%	1.09[0.48,2.46]
Park 1997	25/47	22/48		2.56%	1.34[0.6,3.01]
Ruff 1994	47/84	96/164		7.2%	0.9[0.53,1.53]
Subtotal (95% CI)	**1296**	**1357**		**71.9%**	**0.9[0.76,1.06]**
Total events: 875 (granisetron), 937 (ondansetron)					
Heterogeneity: Tau²=0; Chi²=3.35, df=5(P=0.65); I²=0%					
Test for overall effect: Z=1.26(P=0.21)					

Favours ondansetron 0.2 0.5 1 2 5 Favours granisetron

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total (95% CI)	**1811**	**1706**		**100%**	**0.87[0.76,1.01]**
Total events: 1124 (granisetron), 1127 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=3.91, df=7(P=0.79); I^2=0%					
Test for overall effect: Z=1.86(P=0.06)					
Test for subgroup differences: Not applicable					

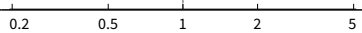
Analysis 2.23. Comparison 2 Granisetron versus ondansetron, Outcome 23 Total control of acute nausea and vomiting (best case ondansetron).

Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	325/487	324/486		35.32%	1[0.77,1.31]
Gralla 1998	292/534	303/520		45.55%	0.86[0.68,1.1]
Mantovani 1996	32/38	32/39		1.63%	1.17[0.35,3.86]
Martoni 1996	41/66	34/58		4.49%	1.16[0.56,2.38]
Park 1997	25/48	23/49		3.57%	1.23[0.55,2.73]
Ruff 1994	38/84	78/165		9.44%	0.92[0.54,1.56]
Total (95% CI)	**1257**	**1317**		**100%**	**0.95[0.81,1.12]**
Total events: 753 (granisetron), 794 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=5(P=0.91); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					



Analysis 2.24. Comparison 2 Granisetron versus ondansetron, Outcome 24 Absence of acute nausea (granisetron dose).

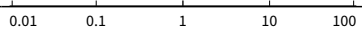
Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.24.1 Granisetron 1 mg					
Navari 1995	128/328	66/165		13.54%	0.96[0.65,1.41]
Spector 1998	64/185	79/184		13.1%	0.7[0.46,1.07]
Subtotal (95% CI)	**513**	**349**		**26.63%**	**0.83[0.63,1.11]**
Total events: 192 (granisetron), 145 (ondansetron)					
Heterogeneity: Tau^2=0; Chi^2=1.15, df=1(P=0.28); I^2=13.33%					
Test for overall effect: Z=1.26(P=0.21)					
2.24.2 Granisetron 3 mg					
Del Favero 1995	347/483	348/483		24.77%	0.99[0.75,1.31]
Gebbia 1994	65/82	62/84		3.21%	1.36[0.66,2.79]
Gralla 1998	296/534	307/520		35.05%	0.86[0.68,1.1]
Martoni 1996	42/66	35/58		3.42%	1.15[0.56,2.38]
Ruff 1994	47/84	92/165		6.91%	1.01[0.59,1.71]
Subtotal (95% CI)	**1249**	**1310**		**73.37%**	**0.95[0.81,1.13]**
Total events: 797 (granisetron), 844 (ondansetron)					



Study or subgroup	granisetron n/N	ondansetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.92, df=4(P=0.75); I²=0%					
Test for overall effect: Z=0.56(P=0.58)					
Total (95% CI)	**1762**	**1659**		**100%**	**0.92[0.8,1.06]**
Total events: 989 (granisetron), 989 (ondansetron)					
Heterogeneity: Tau²=0; Chi²=3.73, df=6(P=0.71); I²=0%					
Test for overall effect: Z=1.12(P=0.26)					
Test for subgroup differences: Not applicable					

Analysis 2.25. Comparison 2 Granisetron versus ondansetron, Outcome 25 Headache.

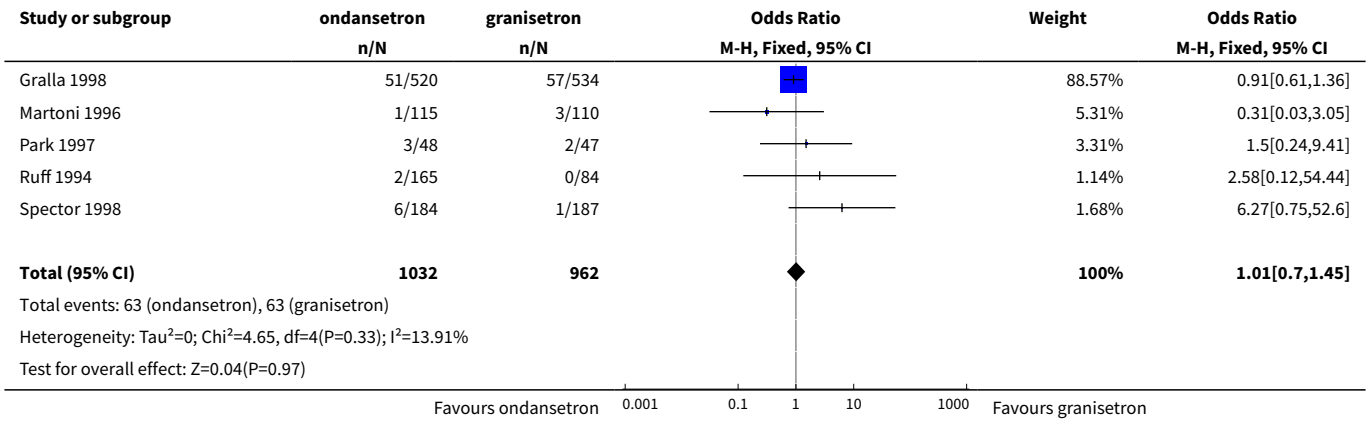
Study or subgroup	ondansetron n/N	granisetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	15/483	15/484		11.82%	1[0.48,2.07]
Gebbia 1994	3/38	1/36		0.77%	3[0.3,30.26]
Gralla 1998	73/520	83/534		57.3%	0.89[0.63,1.25]
Martoni 1996	21/115	14/110		9.52%	1.53[0.74,3.19]
Park 1997	4/48	3/47		2.26%	1.33[0.28,6.31]
Ruff 1994	20/165	5/84		4.74%	2.18[0.79,6.03]
Spector 1998	13/184	23/287		13.59%	0.87[0.43,1.77]
Total (95% CI)	**1553**	**1582**		**100%**	**1.05[0.82,1.34]**
Total events: 149 (ondansetron), 144 (granisetron)					
Heterogeneity: Tau²=0; Chi²=5.09, df=6(P=0.53); I²=0%					
Test for overall effect: Z=0.37(P=0.71)					



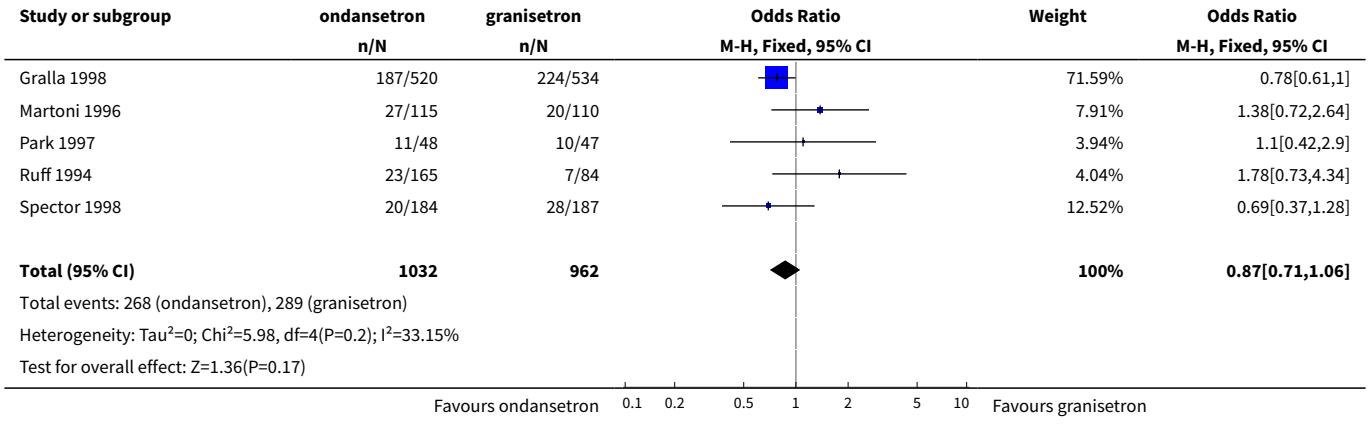
Analysis 2.26. Comparison 2 Granisetron versus ondansetron, Outcome 26 Constipation.

Study or subgroup	ondansetron n/N	granisetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Del Favero 1995	2/483	3/484		2.95%	0.67[0.11,4.01]
Gebbia 1994	6/38	3/36		2.57%	2.06[0.47,8.96]
Gralla 1998	63/520	84/534		72.06%	0.74[0.52,1.05]
Martoni 1996	5/115	3/110		2.9%	1.62[0.38,6.95]
Park 1997	4/48	5/47		4.58%	0.76[0.19,3.04]
Ruff 1994	1/165	4/84		5.21%	0.12[0.01,1.11]
Ruff 1994	0/163	4/85		5.82%	0.06[0,1.04]
Spector 1998	1/184	4/187		3.9%	0.25[0.03,2.26]
Total (95% CI)	**1716**	**1567**		**100%**	**0.71[0.52,0.96]**
Total events: 82 (ondansetron), 110 (granisetron)					
Heterogeneity: Tau²=0; Chi²=9.55, df=7(P=0.22); I²=26.74%					
Test for overall effect: Z=2.26(P=0.02)					

Analysis 2.27. Comparison 2 Granisetron versus ondansetron, Outcome 27 Diarrhoea.



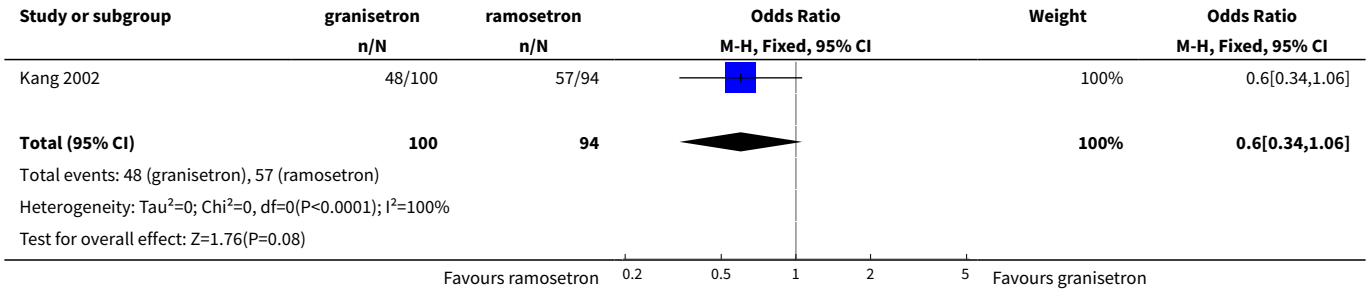
Analysis 2.28. Comparison 2 Granisetron versus ondansetron, Outcome 28 Cumulative adverse events.



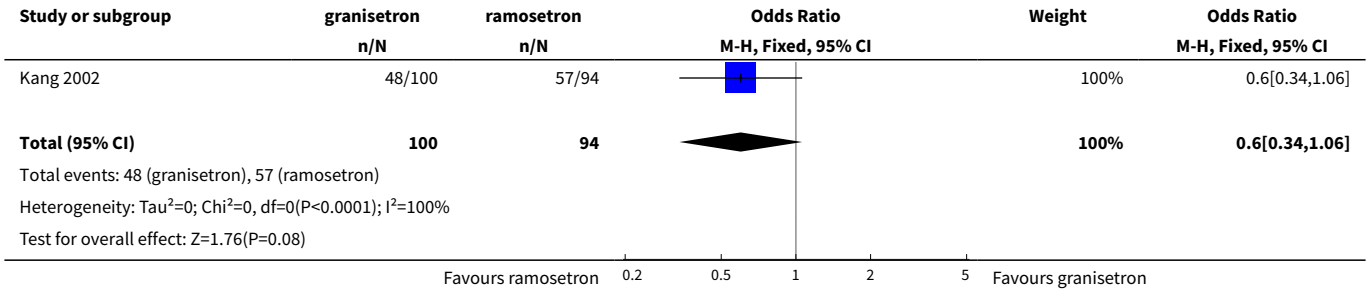
Comparison 3. Granisetron versus ramosetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting	1	194	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.34, 1.06]
2 Absence of acute nausea	1	194	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.34, 1.06]

Analysis 3.1. Comparison 3 Granisetron versus ramosetron, Outcome 1 Absence of acute vomiting.



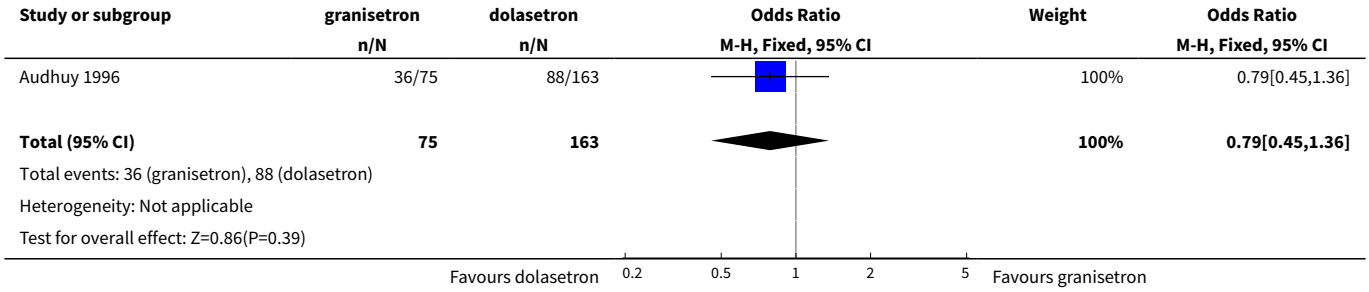
Analysis 3.2. Comparison 3 Granisetron versus ramosetron, Outcome 2 Absence of acute nausea.



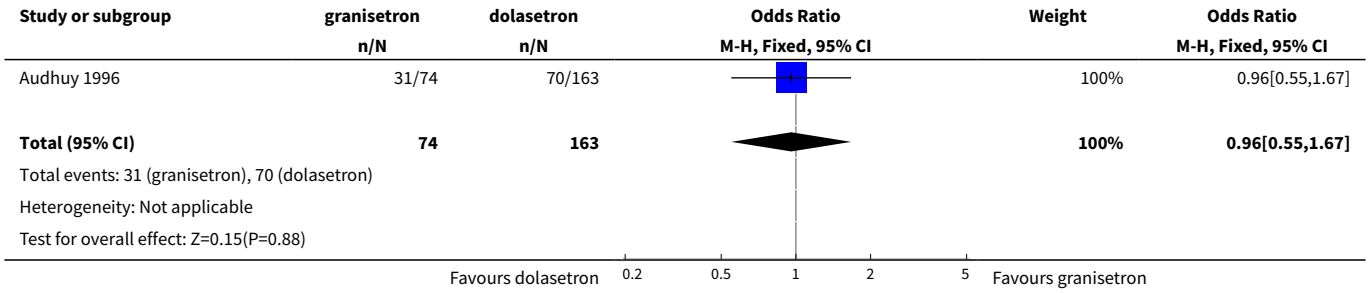
Comparison 4. Granisetron vs dolasetron

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Absence of acute vomiting	1	238	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.45, 1.36]
2 Absence of acute nausea	1	237	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.55, 1.67]

Analysis 4.1. Comparison 4 Granisetron vs dolasetron, Outcome 1 Absence of acute vomiting.



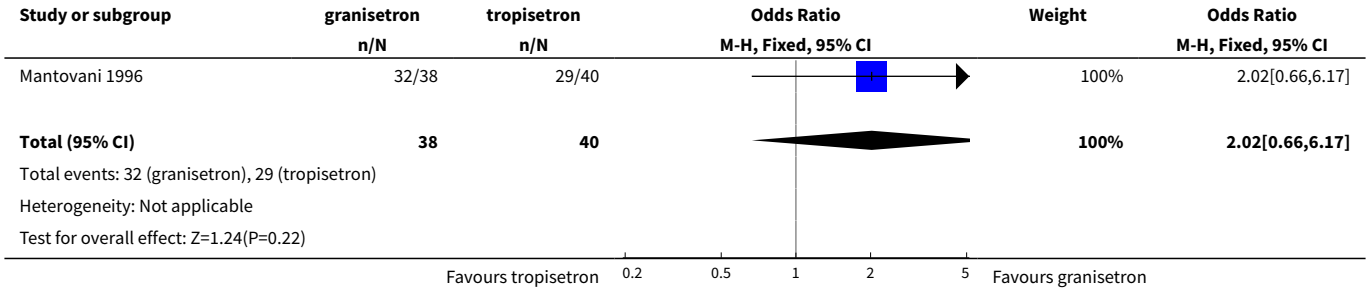
Analysis 4.2. Comparison 4 Granisetron vs dolasetron, Outcome 2 Absence of acute nausea.



Comparison 5. Granisetron versus tropisetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute nausea and vomiting	1	78	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.66, 6.17]

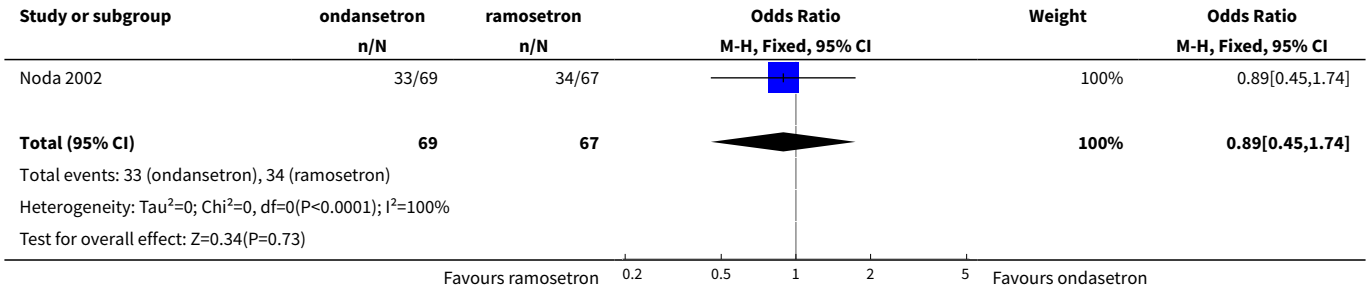
Analysis 5.1. Comparison 5 Granisetron versus tropisetron, Outcome 1 Absence of acute nausea and vomiting.



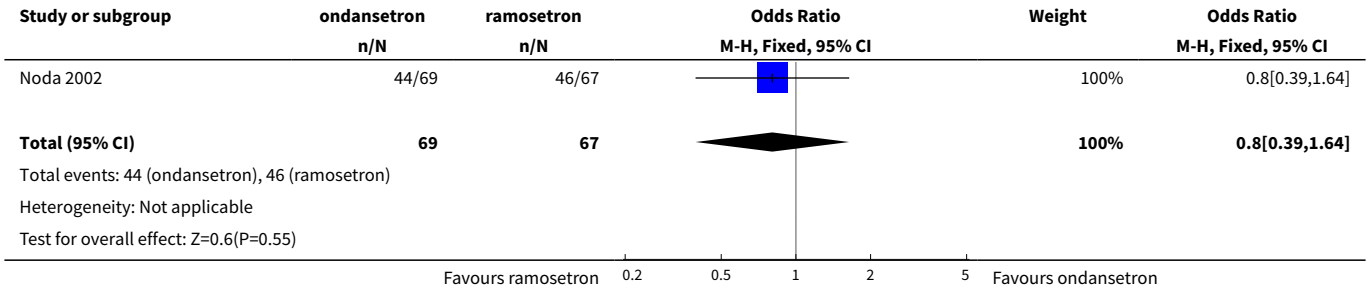
Comparison 6. Ondansetron versus ramosetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting	1	136	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.45, 1.74]
2 Absence of acute nausea	1	136	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.64]

Analysis 6.1. Comparison 6 Ondansetron versus ramosetron, Outcome 1 Absence of acute vomiting.



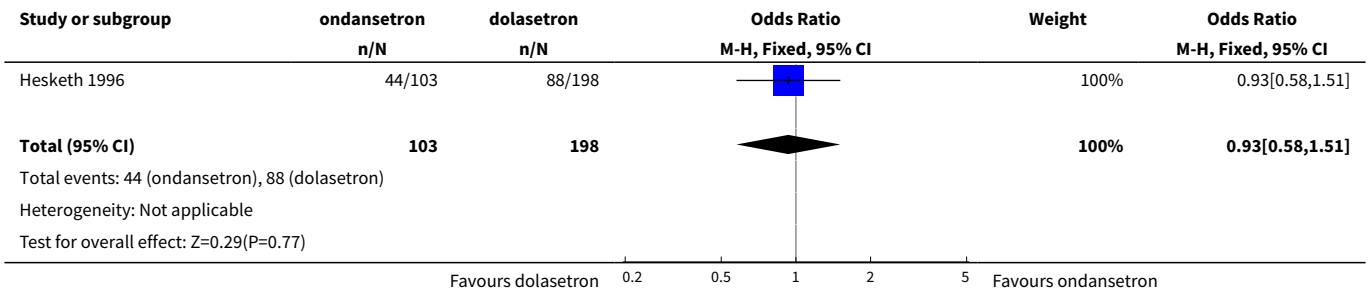
Analysis 6.2. Comparison 6 Ondansetron versus ramosetron, Outcome 2 Absence of acute nausea.



Comparison 7. Ondansetron versus dolasetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting	1	301	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.51]

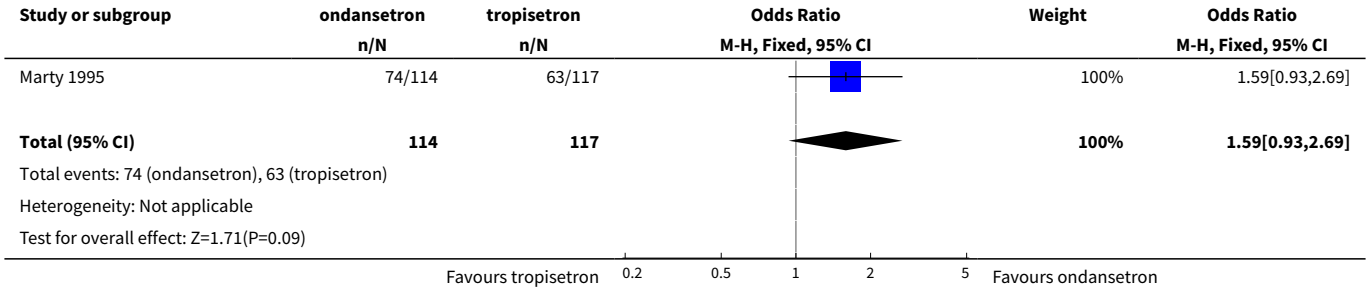
Analysis 7.1. Comparison 7 Ondansetron versus dolasetron, Outcome 1 Absence of acute vomiting.



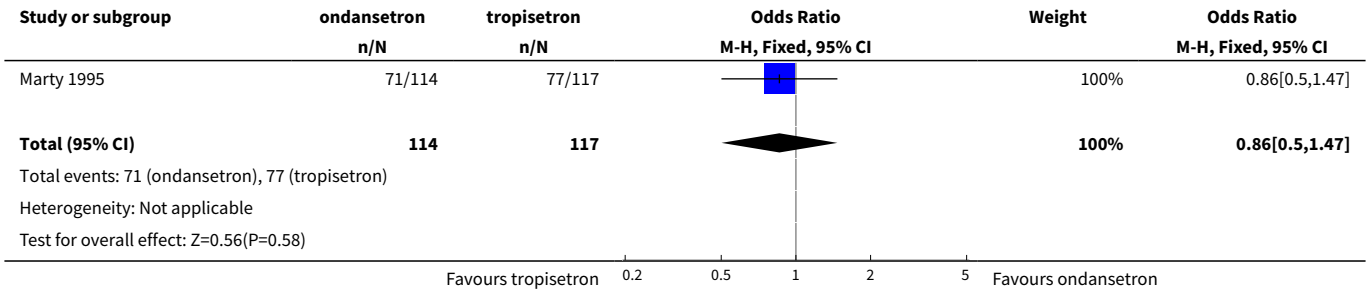
Comparison 8. Ondansetron versus tropisetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting	1	231	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.93, 2.69]
2 Absence of acute nausea	1	231	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.50, 1.47]
3 Absence of delayed vomiting	1	231	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.48]
4 Absence of delayed nausea	1	231	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.39, 1.09]
5 Absence of acute and delayed vomiting	1	231	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.79, 2.31]
6 Absence of acute and delayed vomiting and nausea (days 1 to 6)	1	231	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.59, 2.01]
7 Absence of combined acute and delayed nausea	1	231	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.38]
8 Absence of acute vomiting and nausea	1	79	Odds Ratio (M-H, Fixed, 95% CI)	1.73 [0.59, 5.07]

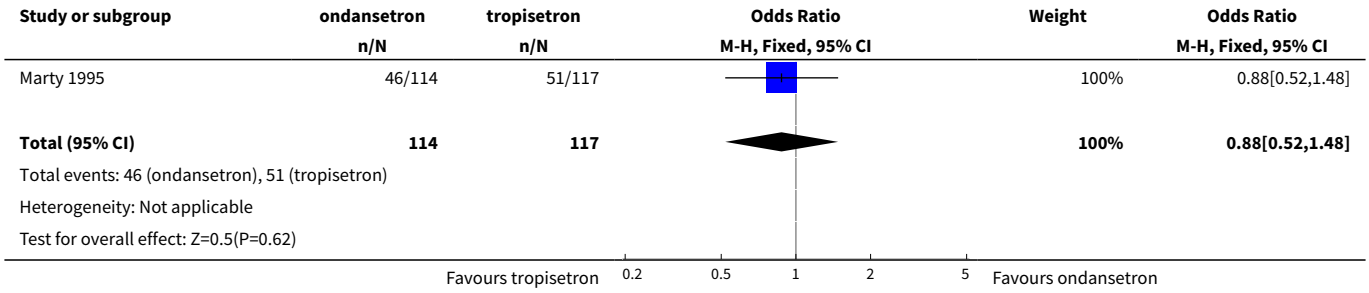
Analysis 8.1. Comparison 8 Ondansetron versus tropisetron, Outcome 1 Absence of acute vomiting.



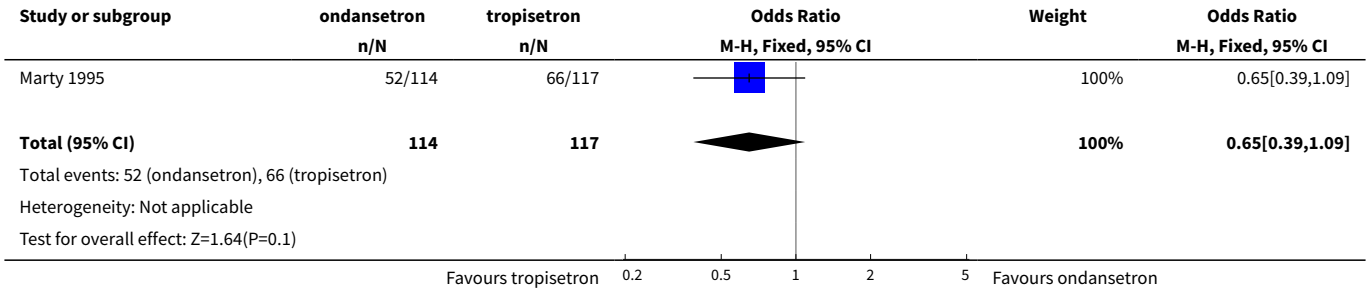
Analysis 8.2. Comparison 8 Ondansetron versus tropisetron, Outcome 2 Absence of acute nausea.



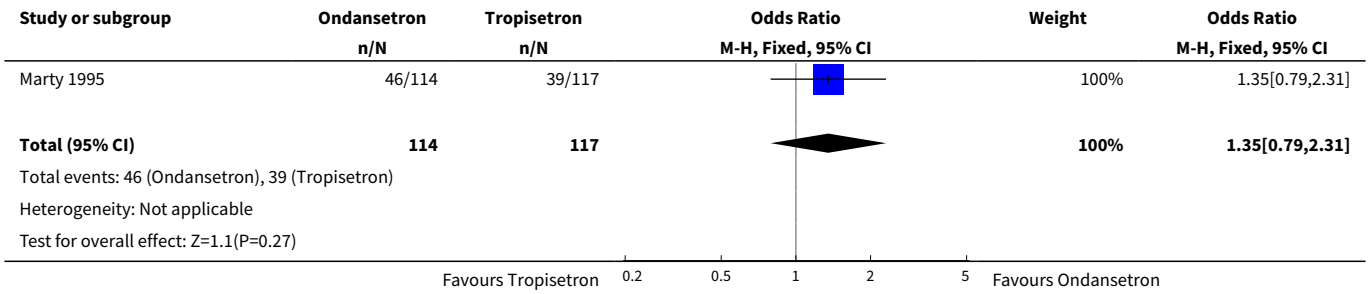
Analysis 8.3. Comparison 8 Ondansetron versus tropisetron, Outcome 3 Absence of delayed vomiting.



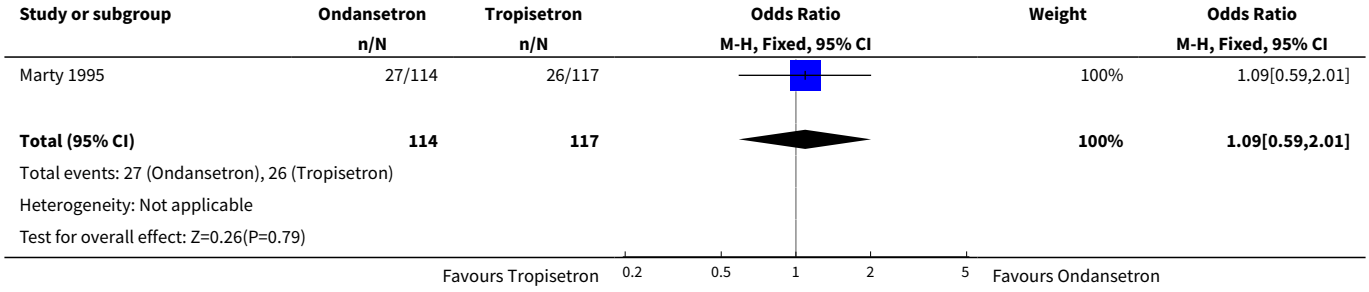
Analysis 8.4. Comparison 8 Ondansetron versus tropisetron, Outcome 4 Absence of delayed nausea.



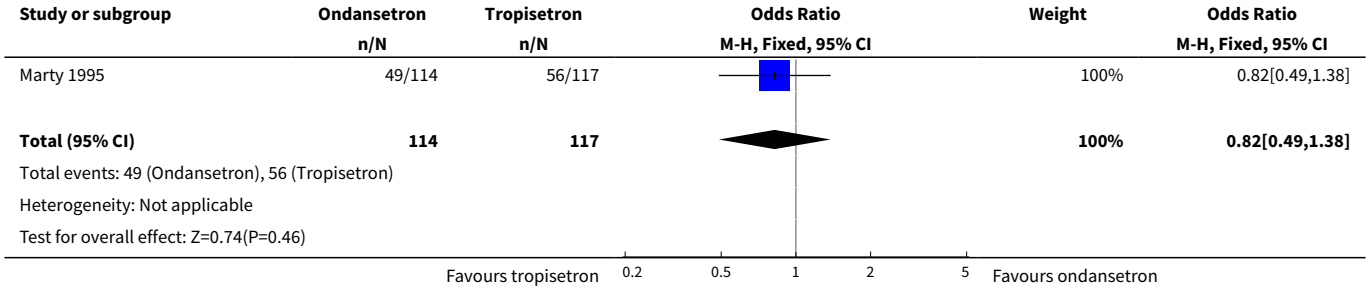
Analysis 8.5. Comparison 8 Ondansetron versus tropisetron, Outcome 5 Absence of acute and delayed vomiting.



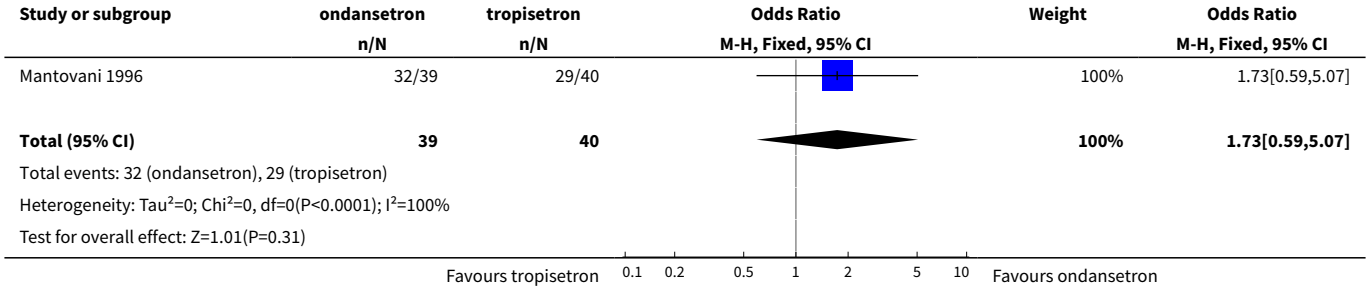
Analysis 8.6. Comparison 8 Ondansetron versus tropisetron, Outcome 6 Absence of acute and delayed vomiting and nausea (days 1 to 6).



Analysis 8.7. Comparison 8 Ondansetron versus tropisetron, Outcome 7 Absence of combined acute and delayed nausea.



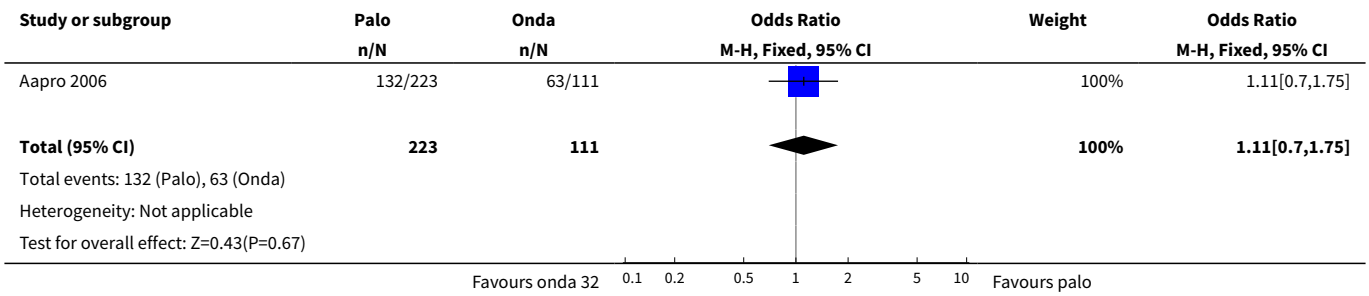
Analysis 8.8. Comparison 8 Ondansetron versus tropisetron, Outcome 8 Absence of acute vomiting and nausea.



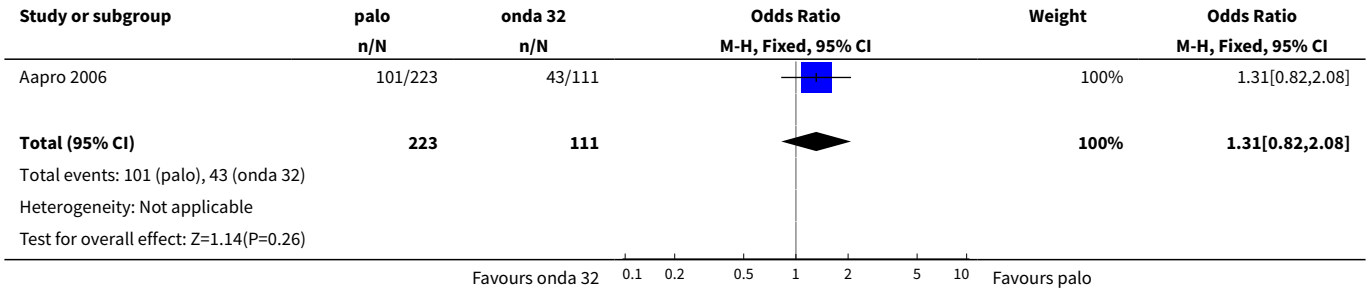
Comparison 9. Ondansetron versus palonosetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Absence of acute vomiting	1	334	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.70, 1.75]
2 Absence of delayed vomiting	1	334	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.82, 2.08]

Analysis 9.1. Comparison 9 Ondansetron versus palonosetron, Outcome 1 Absence of acute vomiting.



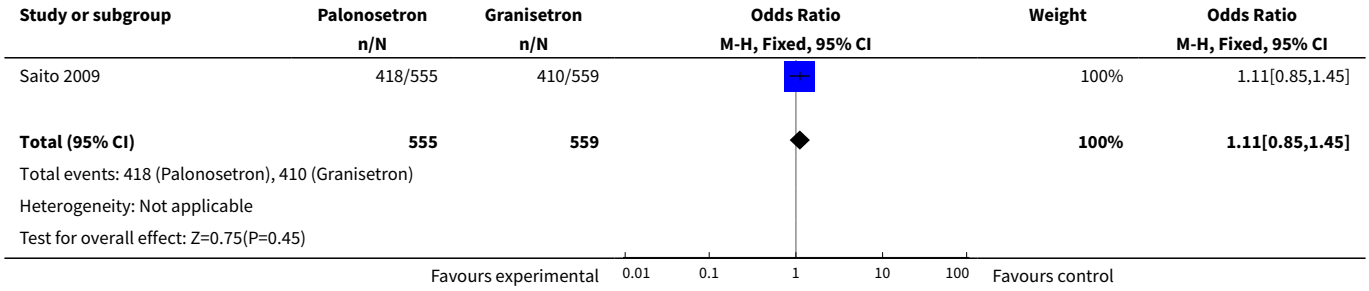
Analysis 9.2. Comparison 9 Ondansetron versus palonosetron, Outcome 2 Absence of delayed vomiting.



Comparison 10. Granisetron plus dexamethasone versus palonosetron plus dexamethasone

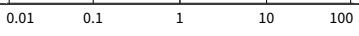
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Complete response (0 to 24 hours)	1	1114	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.85, 1.45]
2 Complete response (24 to 120 hours)	1	1114	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [1.29, 2.07]
3 Absence of acute vomiting	1	1114	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.41]
4 Absence of acute nausea	1	1114	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.21]
5 Absence of delayed vomiting	1	1114	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [1.14, 1.85]
6 Absence of delayed nausea	1	1114	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [1.27, 2.10]
7 Treatment-related adverse events	1	1119	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.68, 1.12]
8 Severe adverse events	1	1119	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.15, 1.19]

Analysis 10.1. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 1 Complete response (0 to 24 hours).



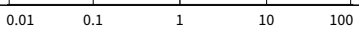
Analysis 10.2. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 2 Complete response (24 to 120 hours).

Study or subgroup	Palonosetron n/N	Granisetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Saito 2009	315/555	249/559		100%	1.63[1.29,2.07]
Total (95% CI)	**555**	**559**		**100%**	**1.63[1.29,2.07]**
Total events: 315 (Palonosetron), 249 (Granisetron)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.07(P<0.0001)					



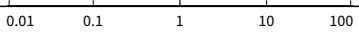
Analysis 10.3. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 3 Absence of acute vomiting.

Study or subgroup	Palonosetron n/N	Granisetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Saito 2009	430/555	427/559		100%	1.06[0.8,1.41]
Total (95% CI)	**555**	**559**		**100%**	**1.06[0.8,1.41]**
Total events: 430 (Palonosetron), 427 (Granisetron)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.67)					



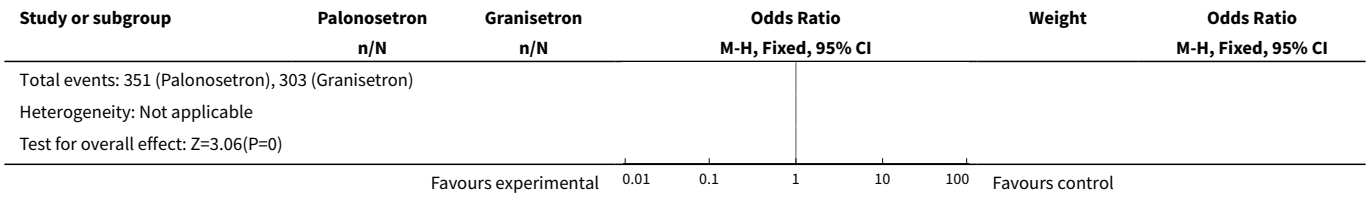
Analysis 10.4. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 4 Absence of acute nausea.

Study or subgroup	Palonosetron n/N	Granisetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Saito 2009	326/555	335/559		100%	0.95[0.75,1.21]
Total (95% CI)	**555**	**559**		**100%**	**0.95[0.75,1.21]**
Total events: 326 (Palonosetron), 335 (Granisetron)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.4(P=0.69)					

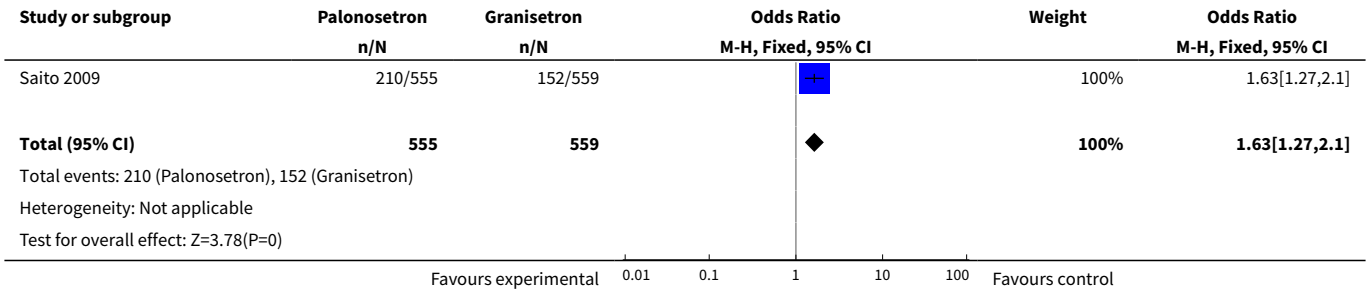


Analysis 10.5. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 5 Absence of delayed vomiting.

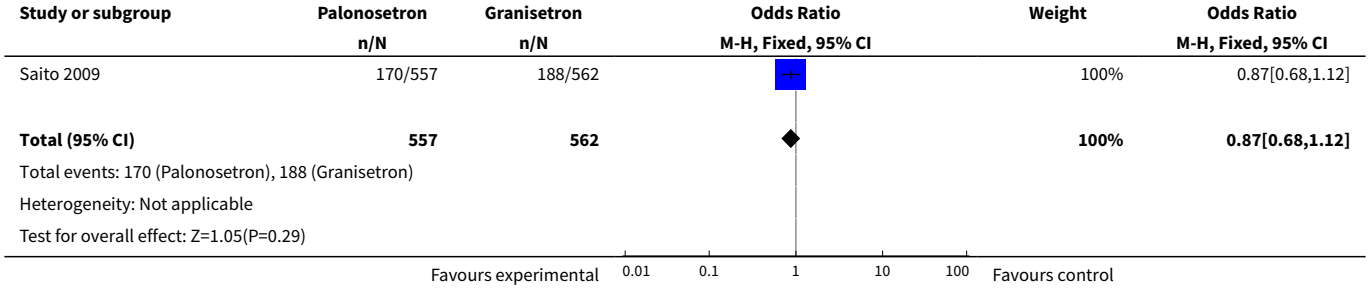
Study or subgroup	Palonosetron n/N	Granisetron n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Saito 2009	351/555	303/559		100%	1.45[1.14,1.85]
Total (95% CI)	**555**	**559**		**100%**	**1.45[1.14,1.85]**



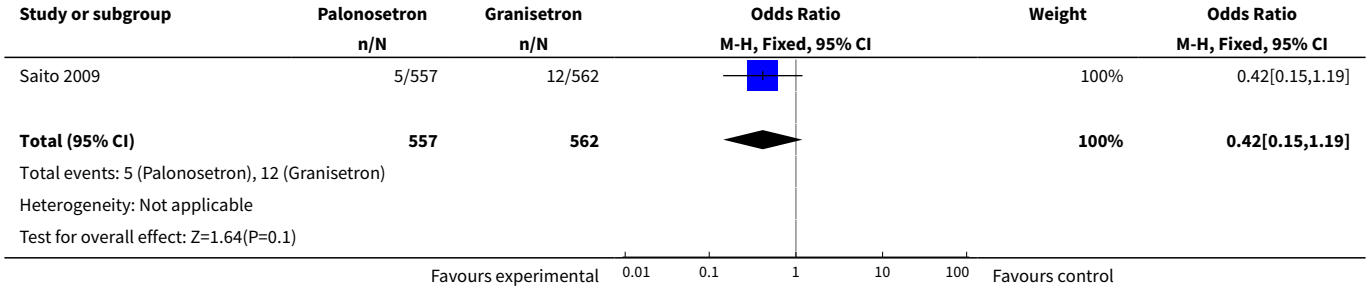
Analysis 10.6. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 6 Absence of delayed nausea.



Analysis 10.7. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 7 Treatment-related adverse events.



Analysis 10.8. Comparison 10 Granisetron plus dexamethasone versus palonosetron plus dexamethasone, Outcome 8 Severe adverse events.



APPENDICES

Appendix 1. MEDLINE search strategy

#1 the highly sensitive strategy for identifying reports of RCTs (Dickersin 1994)
#2 Granisetron [MeSH]
#3 Ondansetron [MeSH]
#4 Tropisetron [tw]
#5 Dolasetron [tw]
#6 Ramosetron [tw]
#7 Palonosetron [tw]
#8 Azasetron [tw]
#9 (#2 AND #3) OR (#2 AND #4) OR (#2 AND #5) OR (#2 AND #6) OR (#2 AND #7) OR (#2 AND #8) OR (#3 AND #4) OR (#3 AND #5) OR (#3 AND #6) OR (#3 AND #7) OR (#3 AND #8) OR (#4 AND #5) OR (#4 AND #6) OR (#4 AND #7) OR (#4 AND #8) OR (#5 AND #6) OR (#5 AND #7) OR (#5 AND #8) OR (#6 AND #7) OR (#6 AND #8) OR (#7 AND #8)
#10 Chemotherapy,adjuvant [mh]
#11 Chemotherapy (tw)
#12 Antineoplastic agents [mh]
#13 Antineoplastic protocols [mh]
#14 Cisplatin
#15(#10 OR #11 OR #12 OR #13 OR #14)
#16 (#1 AND #9 AND #15)

CONTRIBUTIONS OF AUTHORS

AB: protocol writing, literature search, data extraction, review writing, review updating.

EM: data extraction, data analysis.

MC: revision of manuscript.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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- National Institute for Health Research, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

Dexamethasone [adverse effects] [therapeutic use]; Granisetron [adverse effects] [therapeutic use]; Isoquinolines [adverse effects] [therapeutic use]; Nausea [chemically induced] [*drug therapy]; Ondansetron [adverse effects] [therapeutic use]; Quinuclidines [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Serotonin 5-HT3 Receptor Antagonists [*therapeutic use]; Vomiting [chemically induced] [*drug therapy]

MeSH check words

Adult; Humans