Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents (Review)

Fedorowicz Z, Jagannath VA, Carter B

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[Intervention Review]

Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Zbys Fedorowicz[1], Vanitha A Jagannath[2], Ben Carter[3]

[1]UKCC (Bahrain Branch), Ministry of Health, Bahrain, Awali, Bahrain. [2]Department of Paediatrics, American Mission Hospital, Manama, Bahrain. [3]North Wales Clinical School, Department of Primary Care & Public Health, School of Medicine, Cardiff University, Wrexham, UK

Contact address: Zbys Fedorowicz, UKCC (Bahrain Branch), Ministry of Health, Bahrain, Box 25438, Awali, Bahrain. zbysfedo@batelco.com.bh. zbysfedorowicz@gmail.com.

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ABSTRACT

Background

Vomiting is a common manifestation of acute gastroenteritis in children and adolescents. When untreated it can be a hindrance to oral rehydration therapy, which is the cornerstone in the management of acute gastroenteritis. Evidence is needed concerning the safety and efficacy of antiemetic use for vomiting in acute gastroenteritis in children.

Objectives

To assess the safety and effectiveness of antiemetics on gastroenteritis induced vomiting in children and adolescents.

Search methods

We searched the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register comprising references identified from comprehensive electronic database searches and hand searches of relevant journals and abstract books of conferences.The search was re-run and is up to date as on 20 July 2010.

Selection criteria

Randomized controlled trials comparing antiemetics with placebo or no treatment, in children and adolescents under the age of 18, for vomiting due to gastroenteritis.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

We included seven trials involving 1,020 participants. Mean time to cessation of vomiting in one study was 0.34 days less with dimenhydrinate suppository compared to placebo (P value = 0.036). Pooled data from three studies comparing oral ondansetron with placebo showed: a reduction in the immediate hospital admission rate (RR 0.40, NNT 17, 95% CI 10 to 100) but no difference between the hospitalization rates at 72 hours after discharge from the Emergency Department (ED); a reduction in IV rehydration rates both during the ED stay (RR 0.41, NNT 5, 95% CI 4 to 8), and in follow-up to 72 hours after discharge from the ED stay

(worst-best scenario for ondansetron RR 0.57, NNT 6, 95% CI 4 to 13) and an increase in the proportion of patients with cessation of vomiting (RR 1.34, NNT 5, 95% CI 3 to 7)). No significant difference was noted in the revisit rates or adverse events, although diarrhea was reported as a side effect in four of the five ondansetron studies. In one study the proportion of patients with cessation of vomiting in 24 hours was (58%) with IV ondansetron, (17%) placebo and (33%) in the metoclopramide group (P value = 0.039).

Authors' conclusions

Oral ondansetron increased the proportion of patients who had ceased vomiting and reduced the number needing intravenous rehydration and immediate hospital admission. Intravenous ondansetron and metoclopramide reduced the number of episodes of vomiting and hospital admission, and dimenhydrinate as a suppository reduced the duration of vomiting.

PLAIN LANGUAGE SUMMARY

Anti-sickness medication for vomiting in acute stomach upsets in children

Vomiting caused by acute gastroenteritis is very common in children and adolescents. Treatment of vomiting in children with acute gastroenteritis can be problematic and there is lack of agreement among clinicians on the indications for the use of antiemetics. There have also been concerns expressed about apparently unacceptable levels of side effects with some of the older generation of antiemetics. The small number of included trials provided evidence which appeared to favour the use of antiemetics over placebo to reduce the number of episodes of vomiting due to gastroenteritis in children. A single oral dose of ondansetron given to children with mild to moderate dehydration can control vomiting, avoid hospitalization and intravenous fluid administration which would otherwise be needed. There were no major side effects other than a few reports of increased frequency of diarrhea.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Oral ondansetron (weight based) compared to placebo for vomiting related to acute gastroenteritis in children

Patient or population: patients with vomiting related to acute gastroenteritis with mild to moderate dehydration
Settings: emergency paediatric department
Intervention: oral ondansetron (weight based)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oral ondansetron (weight based)				
Rate of admission during ED stay	Study population		RR 0.40 (0.19 to 0.83)	465 (3 studies)	⊕⊕⊕◯ **moderate**[1]	Ondansetron reduced the immediate hospital admission rate during the ED stay
	99 per 1000	40 per 1000 (19 to 82)				
Rate of admission 72 hrs follow-up after ED discharge (best-worst scenario)	Study population		RR 0.6 (0.34 to 1.04)	461 (3 studies)	⊕⊕◯◯ **low**[1,2]	
	131 per 1000	79 per 1000 (45 to 136)				
Rate of admission in 72 hrs follow-up after ED discharge (worst-best scenario)	Study population		RR 0.73 (0.43 to 1.22)	461 (3 studies)	⊕⊕◯◯ **low**[1,2]	
	131 per 1000	96 per 1000 (56 to 160)				
Time to cessation of vomiting	Study population		Not estimable	0 (0)		Not reported
	See comment	See comment				

Rate of intravenous rehydration during ED stay	**Study population**		**RR 0.41** (0.29 to 0.59)	465 (3 studies)	⊕⊕⊕○ **moderate**[1]	Ondansetron reduced the intravenous rehydration rate during the ED stay
	339 per 1000	**139 per 1000** (98 to 200)				
Rate of intravenous rehydration up to 72 hrs following discharge from ED (best - worst scenario)	**Study population**		**RR 0.52** (0.38 to 0.1)	461 (3 studies)	⊕⊕○○ **low**[1,2]	
	376 per 1000	**196 per 1000** (143 to 38)				
Rate of intravenous rehydration up to 72 hrs following discharge from ED (worst - best scenario)	**Study population**		**RR 0.57** (0.42 to 0.76)	461 (3 studies)	⊕⊕○○ **low**[1,2]	
	376 per 1000	**214 per 1000** (158 to 286)				
	Medium risk population					
Proportion of patients with cessation of vomiting	**Study population**		**RR 1.33** (1.19 to 1.49)	465 (3 studies)	⊕⊕⊕○ **moderate**[1]	Ondansetron increases the chance of cessation of vomiting
	639 per 1000	**853 per 1000** (760 to 952)				
Revisit rate	**Study population**		**RR 1.09** (0.66 to 1.79)	460 (3 studies)	⊕⊕○○ **low**[1,2]	The medication does not reduce the revisit rate
	104 per 1000	**113 per 1000** (69 to 186)				
Adverse events	**Study population**		Not estimable	465 (3 studies)		Diarrhea was reported as a side effect in all the studies
	See comment	See comment				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] Design limitation (risk of bias)
[2] Inconsistency due to possible change of effect of intervention over time and inconsistent follow up

BACKGROUND

Description of the condition

Epidemiology

Acute gastroenteritis is the leading cause of vomiting in children under three years of age and is a very common reason for children and adolescents attending emergency departments. Although vomiting is a fairly frequent occurrence in the younger child, it tends to be less prevalent in older children (Taylor 1999). Vomiting is usually accompanied by diarrhea, and each year in the United States more than 200,000 children aged less than five years require admission for treatment of dehydration secondary to gastroenteritis (Herikstad 2002). There is a similar pattern in the UK, with acute gastroenteritis in children under five years accounting for 20% of general practitioner consultations and resulting in 24,000 hospital admissions annually (Flake 2004).

Vomiting is usually defined as a violent expulsion of gastric contents through the mouth. The act of vomiting requires the coordinated contractions of the abdominal muscles, coupled with a diminished esophageal sphincter pressure and esophageal dilatation, with the stomach itself playing a somewhat passive role.

Dehydration, which is the decrease in total body water through a reduction in both the intracellular and extracellular fluid volumes, is an important cause of morbidity in children with vomiting (AAP1996). The clinical manifestations of dehydration are closely related to intravascular volume depletion, which may lead to complications including irreversible shock, intractable seizures and renal failure.

Starvation caused by reduced caloric intake in children with vomiting can lead to ketonemia, which in turn may lead to further dehydration.

Aetiology

Gastroenteritis attributable to viruses or bacteria occurs in the UK at a rate of 1.2 infections per person per year and is most common in the autumn and winter (Taylor 1999). The incidence in other developed countries is likely to be similar but may possibly be even higher in developing countries. The rotavirus, calcivirus, astrovirus, reoviruses and adenoviruses are most commonly implicated. Bacterial causes may include *Staphylococcus aureus*, *Salmonella*, *Bacillus cereus*, or *Clostridium perfringens*. However, in developing countries, the rotavirus remains the most common cause of vomiting in children under three years of age (Doan 2003).

Intestinal irritation caused by gastroenteritis appears to be the main stimulus for vomiting. As the virus invades the mucosal cells of the upper gastrointestinal tract, it disrupts the normal sodium and osmotic intracellular balance and intracellular fluids are lost, producing cellular fluid depletion. Paralysis of the bowel develops with resultant abdominal distension, which induces further vomiting.

Vomiting, from whatever cause, occurs because of the stimulation of the two centers located in the brain, the chemoreceptor trigger zone and the vomiting center. The vomiting center, which controls and integrates the act of vomiting, is located close to other centers which regulate respiration, vasomotor and other autonomic functions, and that may play an additional role in vomiting.

Stimuli are received by the vomiting centre from the gastrointestinal tract, from other parts of the body and the chemoreceptor trigger zone (Feldman 1989). In turn, the vomiting centre stimulates the salivation center, respiratory center and the pharyngeal, gastrointestinal and abdominal muscles, which then leads to vomiting (Friedman 1998).

The chemoreceptor trigger zone (CTZ) may receive stimuli from bacterial toxins or from metabolic abnormalities that occur with uremia, but it cannot independently mediate the act of vomiting (Brunton 1996). Instead impulses from the CTZ are relayed to the vomiting center, which coordinates the various physiological functions involved in vomiting.

Description of the intervention

Vomiting associated with acute gastroenteritis is a distressing symptom for children and their parents. When faced with distraught parents, pediatricians may find themselves compelled to administer medication to stop children from vomiting. Treatment of vomiting in children is a controversial issue. Although the American Academy of Pediatrics stated in its position statement on the management of acute gastroenteritis in young children that it did not specifically evaluate the use of antiemetic drugs, it did confirm that there was a consensus of opinion that antiemetic drugs are not recommended and that physicians should be aware of their potential side effects (AAP1996).

Antiemetic medications are known to alleviate vomiting by inhibiting the body's chemoreceptor trigger zone (CTZ) or by a more direct action on the brain's vomiting centre.

A wide range of medicines in oral and intravenous format have been used as antiemetics in children. These medications include: dopamine (D2) antagonists, serotonin or 5-hydroxytryptamine (5-HT3) antagonists, anticholinergic agents, antihistamines, benzodiazepines, corticosteroids, and cannabinoids (Brunton 1996). Promethazine was the most commonly prescribed antiemetic agent for children, with metoclopramide and prochlorperazine prescribed less frequently because of important side effects such as sedation and extra pyramidal reactions (Taylor 1999). 5-Hydroxytryptamine antagonists, such as ondansetron, are a class of antiemetic drugs that have few adverse effects and that have been safely used in children. Choosing between these therapeutic agents involves the careful consideration of a number of factors, including their effectiveness, their side effect profiles and cost.

Why it is important to do this review

Physicians who provide care to paediatric patients in the emergency department (ED) usually prescribe intravenous fluid therapy (IVT) for mild or moderate dehydration when vomiting is the major symptom. Additional symptomatic treatment of vomiting with antiemetics could lead to an important reduction in the use of intravenous rehydration as well as hospitalization, and a resumption of oral rehydration therapy (ORT). Concerns have also been expressed about the side effects of some antiemetics.
A number of randomized control trials have investigated the effectiveness of different antiemetics, some of which have been assessed in several recent non-Cochrane systematic reviews.

OBJECTIVES

The objective of this review was to provide reliable evidence regarding the clinical effectiveness and safety of antiemetics prescribed for vomiting due to gastroenteritis by comparing clinical outcomes expressed as cessation of vomiting, reduction in the need for intravenous rehydration or hospitalization and the eventual resumption of oral rehydration therapy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomized controlled clinical trials in this review.

Types of participants

Studies which had recruited children and adolescents who were under the age of 18 and who presented with vomiting and a confirmed clinical diagnosis of gastroenteritis.
We excluded any studies in which patients were vomiting as a result of general anaesthesia or due to chemotherapy. In addition, we excluded studies in which patients were suffering from surgical conditions (for example, acute appendicitis/pelvic abscess, inflammatory bowel disease), or systemic infections (such as urinary tract infections, pneumonia, meningitis), or metabolic conditions (diabetes mellitus or any other previously diagnosed disorders, including immunodeficiency).

Types of interventions

Active interventions

We considered any antiemetics administered orally, intravenously or as suppositories at any dosage, prescribed to terminate or reduce vomiting.

Control

Administration of placebo, vehicle or nothing prescribed to terminate vomiting. We included studies which compared different antiemetics.

Types of outcome measures

Primary outcomes

Time taken from the first administration of the treatment until cessation of vomiting.

Secondary outcomes

We also considered the following secondary outcomes for this review.

- Parental satisfaction as assessed by questionnaire or interview
- Number of participants who required hospitalization: during the ED stay; and up to 72 hours following discharge from the ED stay
- Number of participants who required intravenous rehydration during the ED stay; and up to 72 hours following discharge from the ED stay
- Mean number of episodes of vomiting
- Proportion of participants with cessation of vomiting
- Number of participants who revisited
- Number of participants who resumed oral rehydration

Adverse events

- Any clinically documented or patient reported adverse events.

Search methods for identification of studies

Electronic searches

We conducted searches on 28th July 2005, and have updated these subsequently (July 2006, June 2008, and July 2010), to identify all published and unpublished randomized controlled trials. There were no language or date restrictions in the electronic searches.

We constructed the search strategy for this review using a combination of MESH subject headings and text words relating to the use of antiemetics for the treatment of gastroenteritis in children. We identified trials by searching the following electronic databases:

- The Cochrane Central Register of Controlled Trials - CENTRAL (which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register) (*The Cochrane Library* 2010, Issue 2);
- MEDLINE (1966 to July 2010); and
- EMBASE (1980 to July 2010).

To identify randomized controlled trials, we combined the search strategy in Appendix 1 with the Cochrane Highly Sensitive Search Strategy phases one, two and three, as contained in the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 6.4.11.1 (Higgins 2011). We re-ran this search on 12 July 2006 and found one new trial. We made amendments and additions were made to earlier search strategies and the updated searches were re-run in June 2008, finding two new trials (Appendix 2), and most recently in 2010 (Appendix 3, Appendix 4, Appendix 5), finding three additional trials.

Searching other resources

We handsearched reference lists from trials selected by electronic searching to identify further relevant trials. We also handsearched published abstracts from conference proceedings from the United European Gastroenterology Week (published in Gut) and Digestive Disease Week (published in Gastroenterology).

In addition we contacted members of the Cochrane UGPD Group and experts in the field and asked them to provide details of any ongoing clinical trials and any relevant unpublished materials. We also corresponded with and sought clarification of study details from the investigators of several of the included trials.

Data collection and analysis

Selection of studies

Two review authors (DAH/SF) independently assessed the abstracts of studies resulting from the searches and excluded all irrelevant studies. We obtained full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision. We excluded studies not matching our inclusion criteria and noted their details and reasons for exclusion in 'Characteristics of excluded studies'.

Data extraction and management

We entered study details into the 'Characteristics of included studies' table in Review Manager (RevMan) 5 (RevMan 2011). We collected outcomes data using a pre-determined form and entered them into RevMan 5 (RevMan 2011). We included data only if we reached consensus independently. We discussed all disagreements and resolved them by consulting with a third review author Hakima Alhashimi (HAH).

We extracted the following details.

1. Study methods: method of allocation, masking of participants and outcomes, exclusion of participants after randomization and proportion of losses to follow-up.
2. Participants: country of origin, sample size, age, sex, inclusion and exclusion criteria.
3. Intervention: type of antiemetic; dose, frequency and route.
4. Control: placebo, vehicle or nil.
5. Outcomes: any primary and secondary outcomes which had been specified *a priori* in the 'Types of outcomes measures' section of the protocol.
6. Adverse effects: we noted any adverse effects related to any clinically diagnosed hypersensitivity or other adverse reactions or side effects to the antiemetics. We used this information to help us assess heterogeneity and the external validity of the trials.

Assessment of risk of bias in included studies

Two review authors (ZF, DAH) independently assessed risk of bias using The Cochrane Collaboration's tool for assessing risk of bias as described in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We compared the gradings and discussed and resolved any inconsistencies in the assessments.

We assessed the following domains as 'low risk of bias', 'unclear' (uncertain risk of bias) or 'high risk of bias':

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel;
4. blinding of outcomes assessment;
5. incomplete outcome data;
6. selective outcome reporting;
7. other bias.

We have reported these assessments for each individual study in the 'Risk of bias in included studies' table.

We also categorized and reported the overall risk of bias of each of the included studies according to the following categories.

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
- Unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear.
- High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

We have presented dichotomous outcomes data as risk ratios (RR). We have reported all outcomes data with their associated 95%

confidence intervals (CI) and P values (where possible). Where we have pooled dichotomous data and the RR suggested does not straddle the position of null effect, we have calculated the number needed to treat (NNT) and the associated 95% CI.
We did not enter other data into the RevMan analysis, but in future updates if data for continuous outcomes are available, we will report the mean difference (MD) or, the standardized mean difference (SMD) if different scales are used.

Unit of analysis issues

Cluster randomized trials

We identified no cluster randomized trials for inclusion in this review. If in future updates we identify cluster randomized trials (i.e. groups of individuals randomized to intervention or control) in the searches, we will check these for unit of analysis errors based on the advice provided in section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We were able to contact the investigators in a number of the trials, to clarify inconsistencies and to obtain some missing data (Freedman 2006; Roslund 2008; Yilmaz 2010). We reanalyzed data according to a treatment by allocation principle whenever possible (Section 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2011). If data were not reported and authors had conducted a per-protocol analysis we inspected the degree of imbalance in the dropout between the trial arms to determine the potential impact of bias. In the absence of a treatment by allocation population, we have used an available case population and reported this accordingly.
We have included studies within a data synthesis if they had a minimum of an 80% response at follow-up of the total number of participants randomized. If data were missing or unavailable and we were unable to clarify inconsistencies in the studies, we carried out and have reported sensitivity analyses using best-worst, and worst-best case scenarios (Gamble 2005; Higgins 2011).

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the characteristics of the eligible studies; the similarities and differences among the types of participants, interventions and outcome measures are as specified in the 'Criteria for considering studies for this review'.

Assessment of reporting biases

The low number of studies evaluating similar interventions and comparisons did not permit an assessment of publication bias. In future updates, if we identify a sufficient number of trials assessing similar interventions for inclusion in this review, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry as described in Section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we identify asymmetry, we will try to assess other possible causes and explore these in the discussion if appropriate.

Data synthesis

Review authors (ZF, BC) carried out the data synthesis in RevMan (RevMan 2011) and reported each outcome as specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We have carried out data synthesis only if a sufficient number of studies (N > 2) investigating similar treatments in similar populations and route of administration were included and only if they provided data which could be pooled (Treadwell 2006). We used a fixed-effect model to combine the results of individual studies in this review and, as a post- hoc sensitivity analysis, we have also run the analyses with the random-effects model to assess the robustness of the results.
Due to the clinical heterogeneity between the studies and the paucity of data that were suitable for pooling, we were only able to carry out a meta-analysis for four outcomes in the comparison of oral ondansetron versus placebo, and have provided a descriptive narrative of outcomes for the other comparisons.

Subgroup analysis and investigation of heterogeneity

The clinical diversity between the studies in this review as well as the limited number of studies that could be combined for each intervention allowed us to make assessments of heterogeneity between the studies for only four outcomes in one of the comparisons. We reported heterogeneity as important when it was at least moderate to substantial by using I^2 statistic > 60% (Higgins 2011).

Sensitivity analysis

Where possible we have imputed participants with incomplete data and included these in a sensitivity analysis. We have carried out a best-worst scenario and worst-best scenario analysis to test the effect of the missing data as defined below:
• best-worst case scenario: best-case scenario for ondansetron and worst-case scenario for placebo;
• worst-best case scenario: worst-case scenario for ondansetron and best-case scenario for placebo.
If we had defined a sufficient number of studies as a 'low risk' of bias, we would have carried out a sensitivity analysis on these studies.
To assess the potential impact of heterogeneity, we have reanalyzed all meta-analyses using a random-effects model. We have not conducted any other sensitivity analyses, although we will re-evaluate this in future updates.

RESULTS

Description of studies

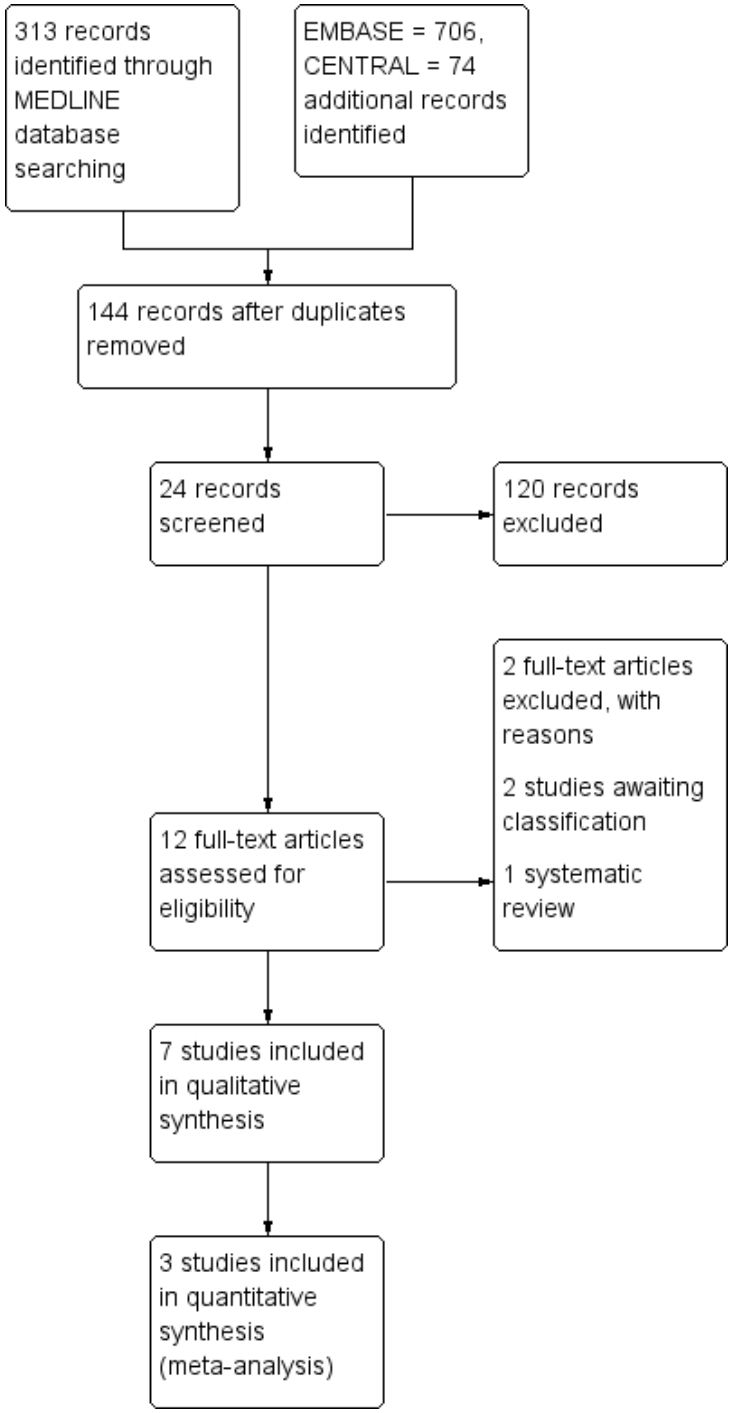
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

The initial search strategy identified 2,443 references (the Cochrane Library = 644, MEDLINE = 628, EMBASE = 1,171). After examination of the titles and abstracts of these references, we excluded all but seven studies from further review. We obtained full text copies of the seven remaining studies and subjected these to further evaluation.

A search conducted in July 2006 for new trials identified one prospective double blind randomized trial comparing ondansetron and placebo to control vomiting among children six months to 10 years (Freedman 2006). In June 2008, we carried out updated searches and identified a further trial, Roslund 2008. We found this study to have several errata in the text; one of the review authors (ZF) wrote to the journal editors, who provided clarification, and an erratum has since been published. The updated searches in July 2010 identified two additional studies for inclusion (Uhlig 2009; Yilmaz 2010) and a further study (Stork 2006) which had been identified in a non-Cochrane systematic review (DeCamp 2008). The number of participants enrolled in Yilmaz 2010 was inconsistently reported; two authors (BC, ZF) wrote to the investigators, who provided clarification. This has also resulted in an erratum being submitted for this study. For further details see 'Study Flow Diagram' (Figure 1).

Figure 1. Study flow diagram (PRISMA).



Included studies

We have included seven trials (Cubeddu 1997; Freedman 2006; Ramsook 2002; Roslund 2008; Stork 2006; Uhlig 2009; Yilmaz 2010). Further details of these are available in the Characteristics of included studies tables. Even though not all of the included studies fully addressed the primary or secondary outcomes specified in the protocol for this review, it was considered that their inclusion and the reporting of their results will help provide additional evidence for the use of antiemetics in this population. There were several differences between the studies, and we summarize these differences and the main study characteristics below. For further details please see Characteristics of included studies.

Methods

All seven trials were randomized, double blind, placebo-controlled. The total sample size comprised 1,020 children: Cubeddu 1997 (36); Freedman 2006 (215); Ramsook 2002 (145); Roslund 2008 (106); Stork 2006 (166); Uhlig 2009 (243); Yilmaz 2010 (109).

Participants and setting

Six of the trials were conducted in the emergency departments of children's hospitals in the USA, Canada, Turkey and Venezuela; the remaining study (Uhlig 2009) was carried out in Germany and enrolled children from six pediatric practices.The age of the participants ranged from five months to 12 years and the inclusion criteria for enrolment were similar for all seven studies.

The trials were conducted over different time periods. In the Ramsook 2002 study, the children were discharged to home care after the initial observation period in the emergency department and were followed up for up to 48 hours, whereas the Cubeddu 1997 study was completed in 24 hours, after which all the participants were discharged and received no further care. In Roslund 2008 discharge was dependent on oral rehydration levels and daily follow-up continued until symptoms had resolved. Participants in Freedman 2006 were only followed up on days three and seven after randomization. In Stork 2006 participants who were able to tolerate oral hydration were discharged from the emergency department and followed up over a 72-hour period; only those unable to tolerate oral hydration continued to receive IV therapy and were re-evaluated at four-hourly intervals. Follow-up and assessment in Uhlig 2009 was at 18 to 24 hours and seven to 14 days after enrolment.

The participants in Yilmaz 2010 were kept under observation in hospital for an eight-hour period; if they became dehydrated, refused oral rehydration, had excessive vomiting or failed to gain weight during this time, they were admitted and the study protocol was discontinued. Participants who had been discharged were followed up by telephone interview within 16 hours.

In the Cubeddu 1997 study, a diagnosis of either bacterial or viral gastroenteritis was confirmed by stool analysis, whereas the diagnosis in Ramsook 2002 and Roslund 2008 was less clear, with a clinical definition of gastroenteritis described as "the presence of vomiting with or without diarrhea". The cause of gastroenteritis was not investigated in the Freedman 2006 study but "all children with symptoms consistent with gastroenteritis" were considered eligible for screening. A diagnosis of acute gastritis or gastroenteritis determined by the pediatric emergency physician was a pre-requisite for enrolment in Stork 2006. The participants in Uhlig 2009 comprised children with "suspected infectious gastroenteritis" but those with moderate to severe gastroenteritis were excluded from the study. The participants in Yilmaz 2010 had "symptoms consistent with acute gastroenteritis", albeit of unspecified aetiology, which had been assessed by a paediatrician.

Intervention

In four of the trials (Freedman 2006; Ramsook 2002; Roslund 2008; Yilmaz 2010), participants received a weight- or age-dependent dose of orally dissolving tablets of ondansetron or placebo, whereas participants in Cubeddu 1997 received either ondansetron hydrochloride dihydrate 0.3 mg/kg, metoclopramide hydrochloride 0.3 mg/kg, or sterile saline solution (placebo) administered as a single intravenous dose. Dexamethasone, ondansetron or placebo (normal saline) was infused intravenously over a 10-minute period in Stork 2006. A single oral dose of ondansetron was administered in Freedman 2006 and Roslund 2008, while in Ramsook 2002 participants received six doses over 48 hours and in Yilmaz 2010 three oral doses were administered over 24 hours. In Uhlig 2009 a suppository of dimenhydrinate or placebo was administered in the emergency department and the caregivers were instructed to administer further suppositories (weight-dependent up to a maximum of three), only if there was persistent vomiting or excretion of the suppository after insertion.

Rehydration therapy

In Freedman 2006 intensive ORT was instituted one hour after the intervention and discharge was at the discretion of the treating physician. Participants in Roslund 2008 underwent an oral challenge 30 minutes after the intervention and if they failed this, they then received intravenous rehydration; powdered oral rehydration solution together, with instructions on how it should be used was provided for home care in Uhlig 2009.

Only in Cubeddu 1997 and Yilmaz 2010 did investigators use the WHO standard formulation for oral rehydration fluid. The

participants in Freedman 2006 and Ramsook 2002 received a reduced osmolality formula i.e. Pedialyte and Enfalyte, respectively, and a reconstituted solution of glucose, sodium and potassium was used in Uhlig 2009. In Yilmaz 2010 oral rehydration therapy was started 30 minutes after the intervention and the success of ORT was re-evaluated periodically.

All of the participants in Cubeddu 1997 were hospitalized for a minimum of 24 hours; they were orally rehydrated and none received any intravenous fluids. In all of the studies, with the exception of Cubeddu 1997, if any of the participants failed oral rehydration or continued to vomit, they were admitted and intravenous rehydration was instituted. All of the participants in Stork 2006 received intravenous rehydration therapy of 0.9% sodium chloride solution as part of the study protocol; discharge was based on the ability to tolerate oral rehydration, but no details were reported about the type of ORT.

Treatment failures

Discharge from the emergency department was dependent on oral rehydration status in the included studies. Participants in all of the studies, with the exception of Cubeddu 1997, who received intravenous rehydration or were admitted were considered treatment failures and took no further part in the study. In the Yilmaz 2010 study, participants who received insufficient oral rehydration were admitted to the emergency department observation unit but continued with the study. The protocol was only discontinued and the participant admitted to the ward if vomiting occurred more than three times, if oral intake was refused three times consecutively or if there was weight loss at the end of the first eight-hour period. It was unclear in Uhlig 2009 if participants who were hospitalized or lost to follow-up at 18-24 hours were considered treatment failures.

Outcomes

The primary outcome for this review, the time taken from the first administration of the treatment measure until cessation of vomiting, was reported in only one of the included studies (Uhlig 2009). All of the remaining studies (Cubeddu 1997; Freedman 2006; Roslund 2008; Stork 2006; Uhlig 2009; Yilmaz 2010) partially addressed our secondary outcomes.

Data for the secondary outcomes of rates of rehydration either oral and/or intravenous and hospitalization were reported in six of the trials (Freedman 2006; Ramsook 2002; Roslund 2008; Stork 2006; Uhlig 2009; Yilmaz 2010). While hospitalization of all the participants in the Cubeddu 1997 study ensured they were more closely observed and that data collection was more likely to be complete, greater reliance was placed on the participants and their carers in the remaining studies. Thus in Ramsook 2002, the carers were asked to complete a diary recording the number of episodes of vomiting in the 24-hour follow-up period and, although they were contacted by telephone 24 and 48 hours after discharge, compliance with medication, oral rehydration and the BRAT diet guidelines could not be assured. The completed diaries were to be mailed by the carers to the investigators, which would enable them to confirm the data which had previously been obtained over the telephone, but losses to telephone follow-up and mail-in diary amounted to 10% to 15% of participants in this study.

The carers in the Freedman 2006 study were interviewed on the third and seventh day by a research assistant and asked whether the child had returned to the emergency department, had been admitted to hospital or had received intravenous rehydration. In Roslund 2008, revisits by participants were recorded up to 72 hours following discharge in addition to the number of participants who were subsequently admitted to hospital or had received intravenous rehydration.

Standardized daily symptom diaries were provided for parents or guardians of all of the participants in Roslund 2008 and follow-up consisted of daily telephone interviews until symptoms had resolved. These symptom diaries and telephone interviews recorded the number of episodes of vomiting per day. However only 10% of the symptom diaries were returned, whereas 94% (ondansetron group) and 88% (placebo group) of the carers participated in the telephone interviews. In Yilmaz 2010, the participants' carers were contacted over the 24-hour period following discharge and questioned about the "general condition of the patient", which included the number of episodes of emesis, timing of administration of study medication and whether there had been any side effects to the intervention. A follow-up assessment was scheduled for 18 to 24 hours after randomization in Uhlig 2009, and this was followed by a telephone interview seven to 14 days after enrolment which enquired about the time to cessation of vomiting and parental satisfaction with treatment success, which was rated on a scale: 1 = best, 6 = worst.

Parental satisfaction with "the medicine their child received" was evaluated, by telephone interview, in Roslund 2008 but no data were reported by the investigators.

Excluded studies

We excluded two studies; see Characteristics of excluded studies for details. The Ginsburg study was a non-randomized controlled trial and it was withdrawn from further review (Ginsburg 1980). The Van Eygen trial did not include any of our primary or secondary outcomes and was therefore excluded from further assessment (Van Eygen 1979).

Studies awaiting assessment

We translated the Debray trial from the French into the English language and then assessed it against the inclusion criteria specified for this review (Debray 1990). The participants in this trial included children and infants vomiting from either bacterial or viral infectious diseases, of which less than half (49%) had vomiting

attributable to gastroenteritis, whereas the remaining participants were vomiting due to bronchitis or 'other'. As more than half of the participants in this study were not suffering with gastroenteritis and the authors did not report separate data for those children with vomiting induced by gastroenteritis, this study is awaiting further assessment. We have written to the authors to try to obtain the missing data and, on the basis of any additional information we receive, will update this review accordingly.

The inclusion criteria in our protocol specified that the participants should be children and adolescents up to the age of 18 years. Although the mean age of participants in the Reeves trial was 5.3 years, this trial did include patients up to the age of 22 years, which we considered neither children nor adolescents (Reeves 2002). As it was not clear from the text how many of the participants were over the age of 18 years, we have written to the trialists asking for clarification as to how many of the participants fall outside our inclusion criteria of 18 years of age. This trial is awaiting further assessment pending a reply from the trialists.

Full trial details of a study, which was identified when we carried out updated searches in June 2008, were eventually published as Yilmaz 2010 which we have included in this current update.

Risk of bias in included studies

We assessed each of the included studies for risk of bias and have reported the judgements for each of the individual domains in the Assessment of risk of bias in included studies; we have also presented information in the Risk of Bias graph in (Figure 2) and the Risk of Bias summary in (Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

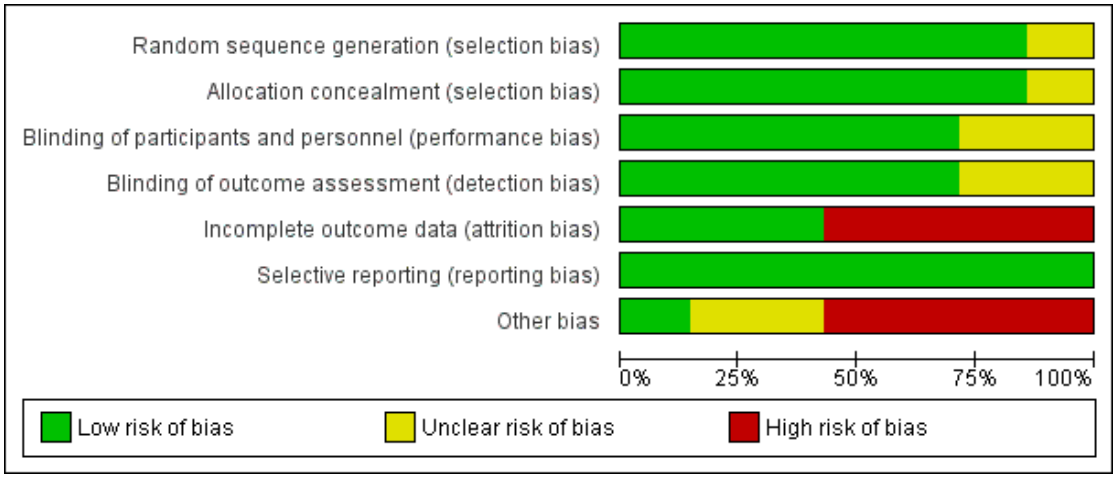
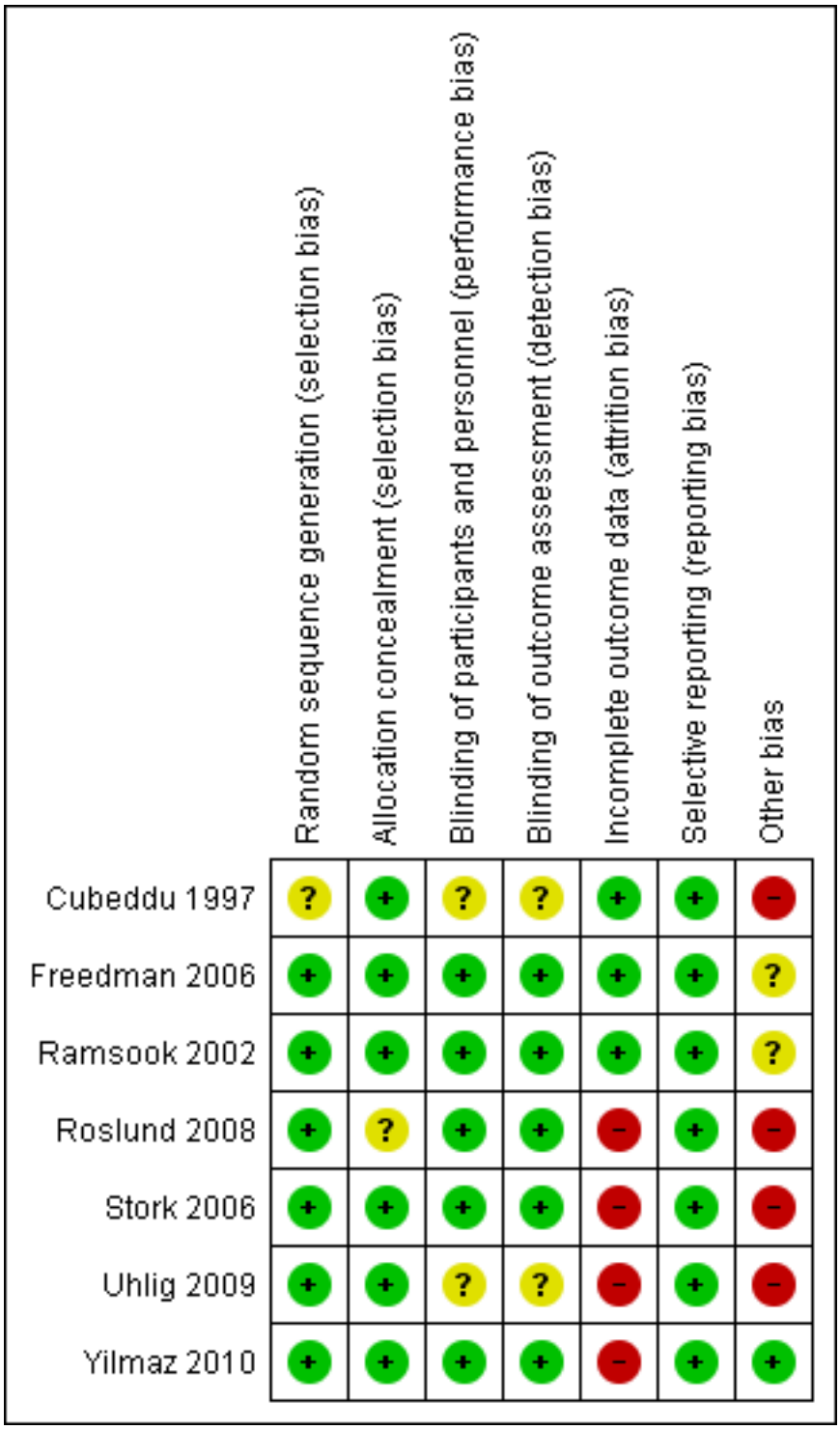


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



We assessed the overall risk of bias in each study, and have categorized two of the studies (Freedman 2006 and Ramsook 2002) included in this review as 'unclear risk of bias' (plausible bias that raises some doubt about the results) because one or more criteria were assessed as unclear. We have rated the remaining five studies as 'high risk of bias' (plausible bias that seriously weakens confidence in the results) because one or more domain received a judgement of 'high risk'.

Allocation

Randomization

In Cubeddu 1997, the investigators stated that the participants were randomly assigned to interventions and control, but the method used to achieve randomization was not explicit; thus we have judged this domain as 'unclear risk of bias'. Participants in Freedman 2006 were randomized in blocks of six and an "independent statistician provided the code to the pharmacy", thus sequence generation was assessed as 'low risk of bias'. The investigators in Roslund 2008 stated that they randomized the participants in blocks of 10, and the report also included a Trial flow chart which referred to "Block Randomization.com", an Internet-based randomization generator. We therefore judged this domain as 'low risk of bias'. In Ramsook 2002, the method used to randomize participants was described as "using standard random number allocation tables" and thus we have judged it as 'low risk of bias'.
We judged sequence generation in the remaining three studies as 'low risk of bias'. Central randomization was carried out by the pharmacy using a table of random numbers in Stork 2006. Block randomization in blocks of four and stratified by body weight was used in Uhlig 2009 and randomization was in blocks of six in Yilmaz 2010.

Allocation concealment

The methods used to generate the allocation sequence and how the sequence was concealed, such that participants and investigators enrolling participants could not foresee the upcoming assignment, are the most important and sensitive indicators that bias has been minimized in a clinical trial (Schulz 1995).
The allocation sequence was considered to have been adequately concealed by the investigators in Ramsook 2002, who stated that the randomization code was locked away and was only broken and revealed to the assessors at the conclusion of the trial. It was also clearly described in Cubeddu 1997 as the "study medication was prepared by a pharmacist not involved in patient care". In Freedman 2006, the pharmacy code was provided by an independent statistician and the weight-appropriate intervention was placed in an opaque bag. Central randomization in the pharmacy ensured adequate concealment of the allocation sequence in Stork 2006, and in both Uhlig 2009 and Yilmaz 2010 the randomization lists were prepared independently by statisticians not involved with the study. We made a judgment of 'low risk of bias' for this domain in all six of these studies, but in Roslund 2008 it was unclear if adequate measures were taken to ensure that investigators were unaware of the upcoming assignment. Therefore we judged this domain as 'unclear risk' of bias for this study.

Blinding

Although the investigators in Cubeddu 1997 reported that the study medication was prepared by an independent pharmacist, they were not explicit as to whether persons assessing the outcomes of care were blinded to which treatment the participants received, and thus we graded this domain as 'unclear risk of bias'. Blinding of participants, healthcare providers and outcomes assessors was adequately described in Freedman 2006 and was judged as 'low risk of bias'. In Ramsook 2002 "the pharmacy provided the drug or a color, taste, and odor-matched placebo in identical packaging.." and the " code remained locked within the pharmacy research section and was broken and revealed to the investigators only at the close of the study". We judged this criterion as 'low risk of bias'. The trial details reported in Roslund 2008 confirm the adequate blinding of participants, trialists and outcomes assessors and support the grading of this criterion as 'low risk of bias'.
Although the active intervention and placebo suppositories in the Uhlig 2009 study were manufactured and supplied by Sandoz Pharmaceuticals, it was unclear if they were similar in appearance or packaging and thus we judged this domain as 'unclear risk of bias'. In Stork 2006 all the study drugs were "uniform in design and color", and the placebo liquid in Yilmaz 2010 was identical in appearance to the active intervention, therefore we categorized blinding in both studies as 'low risk of bias'.

Incomplete outcome data

Reporting inconsistencies and missing outcome data were noted in several of the studies (Freedman 2006; Ramsook 2002; Roslund 2008; Stork 2006; Yilmaz 2010), some of which we clarified after contacting the study investigators. Additional data which were not available in Freedman 2006 were provided by the investigators. After correspondence and further discussion with the investigators in Yilmaz 2010, we are still unclear about the outcome of several of the participants. Attempts to contact the investigators in Ramsook 2002 proved unsuccessful. The investigators in Stork 2006 conceded that their study was "hampered by a large amount of missing data from subjects who were lost to follow-up after two to four hours", which was their a priori primary endpoint.

All of the studies with the exception of Cubeddu 1997 provided flow diagrams charting the path of participants through each study, but losses to follow-up, treatment failures and protocol violators were still variably reported. These inconsistencies and losses to follow-up limit the availability of data for some study outcomes and potentially represent a 'high risk of bias' in several of the included studies.

Data analysis in most of the studies was reported to have followed the intention-to-treat principle (ITT), even though in some instances it was fairly clear that a per-protocol analysis had been carried out (see Chapter 16.2 *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2011).

The investigators in Uhlig 2009 randomized a total of 243 participants and reported data at 18 to 24 hours and at seven to 14 days based on telephone interviews (n = 224). Outcomes were reported for the period between these two follow-up visits and were partitioned into primary outcomes reporting data for 208 participants, and secondary outcomes for 199 participants. The report was unclear how each of these populations were defined, or how the primary outcomes were justified and pre-defined, and neither analysis used the full ITT analysis set of participants.

Selective reporting

There was no evidence of selective outcome reporting in the included trials and it appeared that the outcomes reported were comparable to those specified in the methods section of the reports.

Other potential sources of bias

Other potential sources of bias in the studies were those associated with trial conduct: for example subjects being randomized in error or not being accounted for once randomized (Freedman 2006; Roslund 2008; Stork 2006; Uhlig 2009; Yilmaz 2010). These errors were likely to be the result of poor screening methodologies or inadequate follow-up or both, of study participants (Roslund 2008; Stork 2006; Yilmaz 2010).

A "convenience sample" of participants was enrolled in Roslund 2008, but no justification was provided by the investigators to substantiate the generalizability of this sample. Such an ad hoc method of recruitment, when combined with an unclear allocation concealment, further exposes this study to an assertion of selection bias.

The baseline imbalance reported in Cubeddu 1997 indicated that a larger number of older children were randomized to the placebo as opposed to the active intervention group and reflects another potential source of bias in this study.

External funding and commercial interests are well recognized as a potential source of bias in clinical trials (Lexchin 2003), and although pharmaceutical companies supported the research reported in most of the studies (Cubeddu 1997; Freedman 2006, Ramsook 2002; Roslund 2008; Stork 2006; Uhlig 2009), the investigators provided reasonable reassurances that the manufacturers had no, or a very limited, active role in influencing the design and conduct of most of the studies.

Effects of interventions

See: **Summary of findings for the main comparison** Oral ondansetron (weight based) compared to placebo for vomiting related to acute gastroenteritis in children

We categorized all seven of the studies included in this review as either 'unclear' or 'high' risk of bias (see Figure 2 and Figure 3) and therefore caution is advised in interpretation of their findings and in the extrapolation of the effects of the interventions into clinical decision-making.

Four studies compared orally administered ondansetron to placebo (Freedman 2006; Ramsook 2002; Roslund 2008; Yilmaz 2010), and two studies compared intravenous ondansetron versus intravenous metoclopramide (Cubeddu 1997) and intravenous ondansetron versus intravenous dexamethasone in (Stork 2006); both included a placebo arm. Dimenhydrinate administered as a suppository was compared with placebo in Uhlig 2009.

The primary outcome specified in the protocol for this review was the time taken from the administration of the treatment measure until cessation of vomiting but only one of the included studies provided data addressing this outcome (Uhlig 2009).

Pooling of outcomes data across studies to provide a summary estimate of effect was only possible for one comparison which investigated orally administered ondansetron against placebo (See Data and analyses). We have presented outcomes data which could not be pooled separately in the Additional tables.

(1) Comparison of oral ondansetron with placebo

Four studies compared orally administered ondansetron to placebo (Freedman 2006; Ramsook 2002; Roslund 2008; Yilmaz 2010).

Primary outcomes

Time taken from the first administration of the treatment until cessation of vomiting

None of the studies reported the precise time to complete cessation of vomiting.

Secondary outcomes

Parental satisfaction

This outcome was not assessed in any of the four studies examining this comparison.

Hospitalization

a) Hospital admission rate during the ED stay

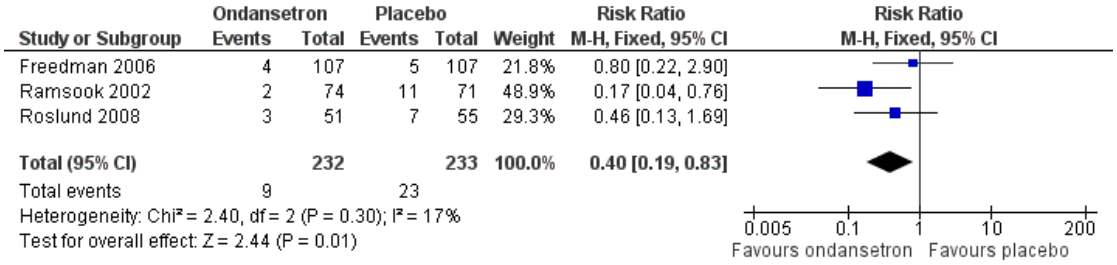
The admission rate in Freedman 2006 was similar for both groups, with 4/107 participants admitted in the ondansetron and 5/107 in the placebo group (see Table 1). In Ramsook 2002 it was reported that 2/74 participants in the ondansetron and 11/71 in the placebo group who had persistent vomiting, or refused oral rehydration, or were administered intravenous fluids were subsequently admitted (see Table 2).

In Roslund 2008, 3/51 participants in the ondansetron group were admitted, of which two were unable to tolerate the oral challenge and one was subsequently diagnosed with a brain tumour. A further 7/55 participants in the placebo group were unable to tolerate oral fluids, received intravenous rehydration and were admitted to hospital (see Table 3).

In Yilmaz 2010 the number of participants admitted during the 24 hours following the eight-hour ED observation period was 2/55 in the ondansetron group and 10/54 in the placebo group (See Table 4).

The pooled data for the admission rate across the studies are presented in Analysis 1.1 and Figure 4. These data illustrate that ondansetron reduced the immediate hospital admission rate during the ED stay when compared to placebo (risk ratio (RR) 0.40, 95% CI 0.19 to 0.83, P value = 0.01). When the meta analysis was repeated using a random-effects model to adjust for heterogeneity between the trials the RR was similar but with a wider confidence interval (RR 0.43, 95% CI 0.18 to 1.00, P value = 0.05, I^2 = 17%, P value = 0.30, see Table 5).

Figure 4. Forest plot of comparison: 1 Oral ondansetron (weight dependent dose) vs placebo, outcome: 1.1 Rate of admission to hospital (during ED stay).



b) Hospital admission rate (up to 72 hours following discharge from the ED stay)

In Roslund 2008, four participants who had not previously been admitted, revisited within 72 hours after discharge from ED stay and were admitted, thus the total numbers of participants hospitalized were 6/51 in the ondansetron and 8/55 in the placebo group (See Table 3).

In Ramsook 2002, four participants who were randomized to ondansetron revisited, but the report was unclear and we were unable to confirm with the investigators if these had previously been hospitalized, or were hospitalized on their re-visit. Therefore, it would appear that between two and six of the 74 participants in the ondansetron group and 11/71 in the placebo group were admitted to hospital (see Table 2).

After correspondence with the principal investigator in Freedman 2006, we were able to confirm that at 72 hours following randomization, there were 10/107 admissions in the ondansetron group and 11/103 in the placebo group (unpublished data, see Table 1).

The pooled data for the admission rate (up to 72 hours following discharge from the ED stay) are presented in a best-worst and a worst-best scenario analysis (Gamble 2005; Higgins 2011). The best-case for the treatment effect is shown (Analysis 1.2) with an RR 0.60, 95% CI 0.34 to 1.04, P value = 0.07 (I^2 statistic = 49%), and a worst-case for the treatment effect is shown in (Analysis 1.3) with an RR 0.73, 95% CI 0.43 to 1.22, P value = 0.23 (I^2 statistic = 0%). From this analysis, it is unclear whether ondansetron compared to placebo is effective at reducing the hospital admission rate for patients up to 72 hours following discharge from the ED stay.

When compared to the random-effects sensitivity analysis, the

results were similar and the conclusions were unchanged (Table 5). There was no statistically significant heterogeneity among the trials (I^2 = 49%, P value = 0.14).

Intravenous rehydration

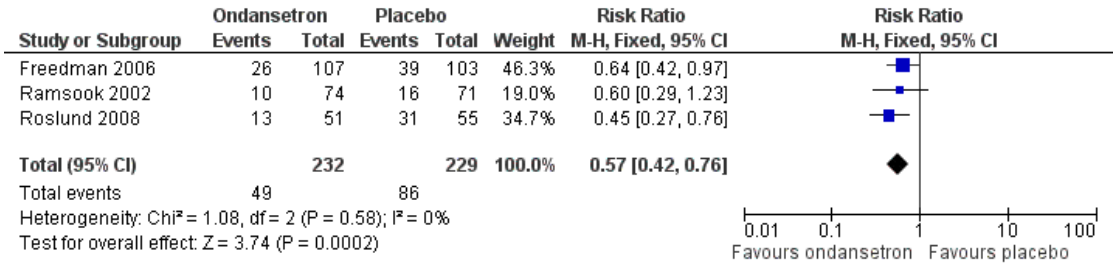
a) Intravenous rehydration rate during the ED stay

In the Freedman 2006 study 15/107 participants in the ondansetron group compared to 33/107 in the placebo group received intravenous therapy; P value = 0.003 (see Table 1).
In Ramsook 2002, 6/74 and 16/71 were administered intravenous fluids in the ondansetron and placebo groups (see Table 2).
In Roslund 2008, 11/51 participants in the ondansetron and 30/55 in the placebo group were unable to tolerate oral fluids and required intravenous fluids (see Table 3). In Yilmaz 2010, none of the participants in the ondansetron group, compared with 2/54 in the placebo group, required intravenous rehydration during the first eight-hour ED stay.
The pooled data for intravenous rehydration across studies are presented in Analysis 1.4, which show that ondansetron reduced the need for intravenous rehydration therapy during the ED stay RR 0.41, 95% CI 0.29 to 0.59, P < 0.0001, with a number needed to treat (NNT) of 5. Thus, to prevent one intravenous rehydration on placebo, five children needed to be treated (NNT) with 95% CI of 4 to 8.

b) Intravenous rehydration rate (up to 72 hours following discharge from the ED stay)

In Roslund 2008, three participants who had not received IV rehydration previously revisited within 72 hours of discharge and received intravenous rehydration, thus a total of 13/51(ondansetron) and 31/55 (placebo) of the participants received intravenous rehydration (Table 3).
In Ramsook 2002, four participants randomized to the ondansetron group revisited, but it was unclear if these received intravenous rehydration at either their initial ED stay, or during their revisit. Therefore, between 6/74 and 10/74 of the participants in the ondansetron group and 11/71 in the placebo group received intravenous rehydration (Table 2).
After discussion with the investigators in Freedman 2006, 26/107 in the ondansetron and 39/107 in the placebo group received intravenous rehydration up to 72 hours following discharge from the ED stay (previously unpublished data) (Table 1).
The pooled data for the intravenous rehydration outcome (up to 72 hours following discharge from the ED stay) are presented in a best-worst case analysis (Gamble 2005; Higgins 2011). The best-worst case for the treatment effect is shown (Analysis 1.5) with a RR 0.52, 95% CI 0.38 to 0.71, P value < 0.0001, and a worst-best case for the treatment effect (Analysis 1.6 and Figure 5) with an RR 0.57, 95% CI 0.42 to 0.76, P value = 0.0002. The NNT is 6, thus one child will benefit for every six, by not receiving IV when treated with ondansetron compared to placebo, with a possible 95% CI of 4 to 13 (after combining the best-worst and worst-best confidence intervals for the most extreme uncertainty).
These analyses indicate that ondansetron appears to be effective at reducing the need for intravenous rehydration therapy up to 72 hours after discharge.

Figure 5. Forest plot of comparison: 1 Oral ondansetron (weight dependent dose) vs placebo, outcome: 1.6 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), worst-best case scenario.



The random-effects sensitivity analyses for the intravenous rehydration outcomes were similar, see Table 5. There was no statistically significant heterogeneity among these trials (I^2 = 0%).

Mean number of episodes of vomiting

In Freedman 2006, the mean frequency of vomiting was 0.18 and 0.65 in the ondansetron group and placebo groups respectively (P

value < 0.001). In Ramsook 2002 the mean frequency of vomiting was 0.18 in the ondansetron group and 0.83 in the placebo group (P value < 0.001).

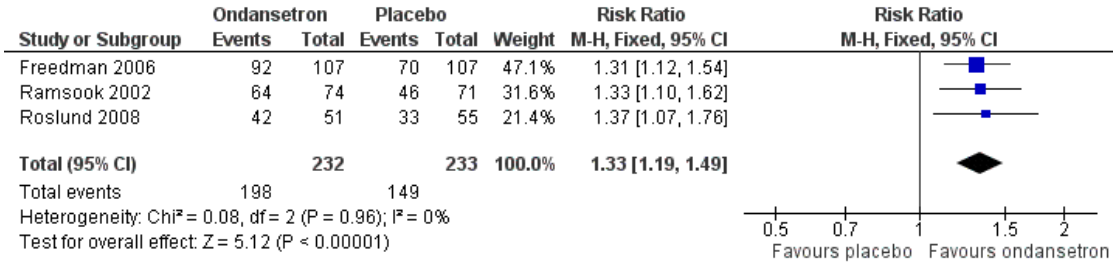
Proportion of participants with cessation of vomiting

In Freedman 2006, 92/107 of the participants in the ondansetron versus 70/107 in the placebo group ceased vomiting while receiving oral rehydration (Table 6). There were 64/71 and 46/71 participants who ceased vomiting during the ED stay in the ondansetron and placebo groups in Ramsook 2002 (Table 7). In Roslund 2008, after discharge from the emergency department, 42/51 and 33/55 of participants in the ondansetron group and placebo group ceased vomiting (Table 8).

In Yilmaz 2010, this outcome was not reported as a specific time-point, but during the first eight-hour period the proportion of participants who were no longer vomiting was 43/55 in the ondansetron group and 18/54 in the placebo group. At 24 hours the proportion of participants no longer vomiting was 49/55 in the ondansetron group compared with 15/54 in the placebo group (See Table 9).

After pooling the data we found a very significant and consistent treatment effect RR of 1.33 (95% CI 1.19 to 1.49), see Analysis 1.7 and Figure 6. The NNT is five (95% CI 3 to 7); therefore for every five children treated with ondansetron one would benefit from the antiemetic effect of ondansetron compared to placebo.

Figure 6. Forest plot of comparison: 1 Oral ondansetron (weight dependent dose) vs placebo, outcome: 1.7 Proportion of participants with cessation of vomiting.



The random-effects sensitivity analyses for the cessation of vomiting outcome were similar; see Table 5. There was no statistically significant heterogeneity among the trials (I^2 = 0%).

Revisit rate

In the ondansetron groups 20/105 (Freedman 2006), 4/74 (Ramsook 2002) and 3/51 (Roslund 2008) of the participants revisited. The revisit rate to the ED in the placebo groups was 22/101 (Freedman 2006), 0/71 (Ramsook 2002) and 2/55 (Roslund 2008) (Table 2, Table 3, and Table 1).

The pooled data from three studies in Analysis 1.8 indicated no difference in the revisit rate when ondansetron was compared to placebo (RR 1.09, 95% CI 0.66 to 1.79, P value = 0.73).

The random-effects sensitivity analyses for the revisit outcome were similar; see Table 5. There was no statistically significant heterogeneity among these trials (I^2 = 28%, P value = 0.25).

Resumption of oral rehydration

Only Yilmaz 2010 provided data for this outcome. At eight hours the proportion of participants in the ondansetron group who were able to tolerate oral hydration was significantly higher at 50/55, compared with 42/54 in the placebo group (RR 1.17, 95% CI 0.99 to 1.38, P value = 0.06). At 24 hours, by comparison, there was no statistically significant difference between the two groups (see Table 10).

Proportion of participants reporting adverse events

Side effects in the ondansetron group, consisting of a higher frequency of diarrhea, were reported in three of the studies which evaluated this comparison (Freedman 2006; Ramsook 2002; Yilmaz 2010). The only adverse events reported were urticaria in one participant in the placebo group (Freedman 2006) and a macular rash in one participant who received ondansetron in Ramsook 2002.

(2) Comparison of intravenous ondansetron with dexamethasone or placebo

Only one study examined these interventions (Stork 2006).

Primary outcomes

Time taken from the first administration of the treatment until cessation of vomiting

This study did not provide data for this outcome.

Secondary outcomes

Parental satisfaction

Parental satisfaction data were not collected by the investigators in this study.

Hospital admission rate during the ED stay

Significantly fewer hospital admissions occurred in the ondansetron group compared with the placebo (normal saline): two participants (4.4%) in the ondansetron group; nine (20.5%) in the normal saline and dexamethasone seven participants (14.9%); however, these data only covered the first four hours of the ED stay (See Table 11). The relative risk for admission when ondansetron was compared to normal saline was RR 0.21, 95% CI 0.05 to 0.81.

Intravenous rehydration rate during the ED stay

All of the participants received intravenous rehydration as part of the study protocol, but this was discontinued for those able to tolerate oral rehydration.

Mean number of episodes of vomiting and proportion of patients with cessation of vomiting

There was no statistically significant difference between the groups in the median (IQR) number of vomiting episodes at 24 hours i.e. normal saline group 0 (0 to 0); dexamethasone group 0 (0 to 1) and ondansetron group 0 (0 to 1) P value = 0.49. At the 72-hour follow-up, the median number of episodes of vomiting was 0, with no statistically significant differences between the groups for any end point (P value = 0.46).

Revisit rate

This outcome was not assessed for this comparison.

Resumption of oral rehydration

At two hours after treatment, 39/45 (86.6%) participants in the ondansetron as opposed to 29/43 (67.4%) in the normal saline group were able to tolerate oral rehydration. At four hours 9/14 (64.3%) in the ondansetron group compared to 12/21 (57.1%) in the normal saline group were able to accept oral rehydration, although the difference was not significant (RR 1.12, 95% CI 0.66 to 1.92). At two hours, the relative risk for tolerance of oral hydration significantly favoured ondansetron when compared with dexamethasone (RR 1.40, 95% CI 1.09 to 1.88). However, this difference disappeared at four hours (RR 0.86, 95% CI 0.54 to 1.38) (See Table 12).

Proportion of participants reporting adverse events

The investigators indicated that they "did not find any significant side effects".

(3) Comparison of intravenous ondansetron with metoclopramide or placebo

Only one study examined these interventions (Cubeddu 1997).

Primary outcomes

Time taken from the first administration of the treatment until cessation of vomiting

This study did not provide data for this outcome.

Secondary outcomes

Parental satisfaction

No data were reported.

Hospital admission rate

All of the participants were admitted for the duration of the study period and no data were available for re-admission beyond this time.

Intravenous rehydration rate

Intravenous rehydration therapy for diarrhea-induced fluid loss was given to 3/12 participants in the ondansetron group and to 1/12 in the metoclopramide group during the first 24-hour period.

Mean number of episodes of vomiting and proportion of patients with no vomiting

The mean number of vomiting episodes during the first 24 hours was two in the ondansetron and five in the placebo group (P value = 0.048). The proportion of patients experiencing no vomiting in the period 0 to 24 hours was higher in the ondansetron group 7/12 (58%) than placebo 2/12 (17%) and was 4/12 (33%) in the metoclopramide group, P value = 0.039 (See Table 13).
Ondansetron ensured complete cessation of vomiting for 8/12 (67%) patients within the first four hours and in 7/12 (58%) patients in the first 24-hour period.

Revisit rate

No data were available for the revisit rate.

Resumption of oral rehydration

No data were available.

Proportion of participants reporting adverse events

These were noted in all treatment groups. All patients in the study experienced at least one episode of diarrhea but compared with placebo there were significantly more episodes of diarrhea in the ondansetron (P value = 0.013) and metoclopramide (P value = 0.004) groups in the first 24 hours, although there was no significant difference between these two groups.
Other side effects included general drowsiness in 90% of the patients, a cough experienced by a few patients in both groups and tremor by one patient in the metoclopramide group.

(4) Comparison of dimenhydrinate with placebo

Only one study examined this intervention (Uhlig 2009).

Primary outcomes

Time taken from the first administration of the treatment until cessation of vomiting

Based on telephone interviews at seven to 14 days, the mean time to cessation of vomiting was 0.60 days in the dimenhydrinate group compared with 0.94 in the placebo group with a mean difference -0.34, 95% CI -0.66 to -0.02, P value = 0.036 (See Table 14).

Secondary outcomes

Parental satisfaction

Parental satisfaction (rated 1 = best, 6 = worst) with treatment, assessed by telephone interview at seven to 14 days, was 2.39 in the dimenhydrinate group versus 2.31 in the placebo group with a mean difference of 0.08, 95% CI -0.28 to 0.45, P value 0.651 (See Table 15).

Hospital admission rate during the ED stay

Four participants in the dimenhydrinate group compared with five in the placebo group were hospitalized within the 18- to 24-hour period. The overall admission rates reported at telephone follow-up were 10/106 participants in the dimenhydrinate compared with 13/103 in the placebo group. Criteria for admission were not reported and only that of these, "9 versus 11 were hospitalized for gastroenteritis" (See Table 16).

Intravenous rehydration rate during the ED stay

Not reported.

Mean number of episodes of vomiting

The mean number of vomiting episodes between randomization and the 18- to 24-hour follow-up was 0.64 in the dimenhydrinate and 1.36 in the placebo group (P value = 0.001).

Proportion of patients with no vomiting

At the 18- to 24-hour follow-up visit 71/106 (69.6%) of the participants in the dimenhydrinate group compared with 46/102 (47.4%) in the placebo group were free of vomiting (P value = 0.001).

Revisit rate

Not reported.

Resumption of oral rehydration

Not reported.

Proportion of participants reporting adverse events

Sedation was the main side effect which occurred in 22 (21.6%) participants in the dimenhydrinate group and 18 (18.6%) in placebo. One participant in each group developed a rash, and there were three severe adverse events which were not medication related.

DISCUSSION

Overall completeness and applicability of evidence

The AAP guidelines (AAP1996), published almost 10 years ago, stated that there was a consensus of opinion that antiemetics were not needed for the management of vomiting due to gastroenteritis in children. The AAP guidelines did also warn that clinicians should be aware of certain potential, but unspecified, adverse effects associated with antiemetics, yet these studies, whilst reporting some side effects, appeared to indicate that other than diarrhoea, all of the drugs were reasonably well tolerated.

This review included seven trials which were at least partially industry funded and provided some evidence regarding the clinical effectiveness and safety of antiemetics prescribed for children vomiting due to gastroenteritis.

Quality of the evidence

Limitations in study design and implementation

Although study design in the included studies appeared to have been adequate overall, our study-level assessments of the risk of bias for a number of the domains in several of these studies revealed some of the limitations in their implementation, which have been reported in the 'Risk of bias in included studies' section of this review.

Even though we were successful in contacting the investigators in a number of the included studies, the disposition of some of the participants remains unclear. Whilst these inconsistencies are more likely to be as a result of systematic error and most probably associated with the rolling recruitment of participants and the challenges faced in the follow-up of pediatric participants, they do not necessarily indicate any intentional subversion of the trials. In two of the studies, false inclusions were excluded from an ITT analysis. It is considered that this may have occurred as a result of poor screening methodology applied in a busy hospital environment, and thus the entry criteria were not applied consistently across study participants.

However, whilst recognizing these limitations, the authors consider that the body of evidence summarized in this review is sufficient to allow certain conclusions to be drawn about the effectiveness of the interventions used in the treatment of vomiting related to acute gastroenteritis in children and adolescents.

Indirectness of the evidence

All of the included studies matched the eligibility criteria for this review, but the majority of participants enrolled in these studies were suffering from mild to moderate acute gastroenteritis, and six of the studies were conducted in the emergency departments of hospitals as opposed to only one in an outpatient pediatric practice setting. The potential impact of these factors on the generalizability and external validity of the evidence provided in this review needs to be considered by clinicians when extrapolating it into clinical decision-making. The use of placebo as the comparator in most of the studies would not readily facilitate future assessments on the advantages or disadvantages of newer to existing interventions. To fill the evidence, gap clinicians need to have access to not only the risk and benefits of individual interventions, but also the relative efficacy of these interventions and thus head-to-head trials are more likely to have provided evidence that is both relevant and direct.

Unexplained heterogeneity or inconsistency of results

Studies identified for inclusion in this systematic review considered a relatively narrow range of interventions, and the results for specific outcomes were fairly consistent across the limited number of studies and interventions where pooling of data was feasible. However, in one of these studies we were unable to clearly determine if four of the participants had either been admitted to hospital or had received IV rehydration therapy. In view of the uncertain status of these participants, we carried out best-worst and worst-best case scenario sensitivity analyses and found that the hospital admission outcome was sensitive to the missing data. More precisely, whilst the best-worst case scenario offered limited data to suggest ondansetron may reduce the rate of admission (up to 72 hours after discharge from ED stay) (I^2 statistic = 49%), the worst-best scenario indicated that it was unlikely that ondansetron reduced the hospital admission rate (I^2 statistic = 0%). After taking into consideration the degree of heterogeneity in the two scenarios, the worst-best case scenario would be more typical and therefore it would appear less likely that ondansetron reduces the hospital admission rate (up to 72 hours after discharge from ED stay).

Imprecision of results

The paucity of studies (although they were of adequate sample size and duration, and examined similar interventions) that were included in this review provided limited amounts of data which could be pooled and therefore any substantive assessment of the degree of precision of effect was not feasible. We have exercised caution when extracting data from the primary research studies and have provided confidence intervals to indicate the strength of the data on which conclusions might be drawn. We have reported uncertainty in conjunction with 95% CIs and have presented the impact of a minimal set of missing observations on the 95% CIs and on the conclusions which we have highlighted within Analysis 1.2 and Analysis 1.3.

Publication bias

In view of the low number of trials included in this review this assessment was not estimable.

Potential biases in the review process

We made every attempt to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. The authors' independent assessments of eligibility of studies for inclusion in this review and the extraction of data minimized the potential for additional bias beyond that detailed in the Risk of bias in included studies tables.

Agreements and disagreements with other studies or reviews

The update of this Cochrane review, together with the additional trials, complements two recent non-Cochrane reviews (Colletti 2009; DeCamp 2008) and contributes further to the body of evidence supporting the effectiveness of antiemetics for vomiting related to acute gastroenteritis in children.

One of these reviews (DeCamp 2008) has been assessed and reported as a reliable and valid source of evidence on the use of antiemetics for vomiting related to acute gastroenteritis in the child and adolescent (Vreeman 2008). The review authors identified 11 eligible studies; used a check list (Downs 1998) to assign a quality score to each study; and indicated that they had carried out sensitivity analyses on the basis of quality; however the details of these analyses were not reported.The authors also carried out meta-analyses on the basis of treatment and utilized a pragmatic approach in pooling data across different modes of administration and ages of participants. We question the validity of the decision by the review authors to pool some of these data in view of the apparent clinical diversity between the selected studies and most specifically in the differences in their routes of administration.

In this updated version we have assessed the risk of bias in each included study and, based on clarification sought and received from trial investigators, have amended some of the judgements in several of the domains accordingly. Additional data received from the investigators in (Freedman 2006; Roslund 2008) has also allowed us to carry out ITT analyses as compared to the complete-case analysis used by the review authors in DeCamp 2008.

The findings in this systematic review are to a large extent in agreement with those reported in DeCamp 2008; however this review does also differ somewhat by considering two clinically important time-points: outcomes occurring during the ED stay and those up to 72 hours following discharge from the ED stay. Whilst these would appear to strengthen the conclusions relevant to the ED stay, questions still remain whether oral ondansetron does in fact reduce the hospital admission rate in the period up to 72 hours following discharge from the ED stay. Furthermore, although the review by DeCamp 2008 discusses the variability between studies in showing the effectiveness of ondansetron in reducing the admission rate, it also suggests a potential cost saving associated with a reduction in hospital admission and use of intravenous rehydration, an assumption unsupported by the somewhat inconclusive evidence reported in our review.

The literature review by Colletti 2009 evaluated studies published from 1966 to 2006, but provided very limited detail about any assessments of the methodological quality of the included studies, and reported the results and conclusions in a descriptive manner which added very little to the body of evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Clinical practice guidelines for the treatment of children with gastroenteritis recommend supportive care using oral rehydration therapy (ORT) for mild to moderate dehydration, but provide no recommendations on the additional use of antiemetic medication for vomiting. However, in practice it would appear that there is now an increased tendency towards the prescribing of antiemetic medication by clinicians (Li 2003; Kwon 2002). Antiemetics such as promethazine, prochlorperazine, and metoclopramide are known to have serious side effects, hence they are less commonly prescribed. This systematic review provides evidence which supports the use of ondansetron as an adjunct to oral rehydration therapy in the treatment of children with acute gastroenteritis exhibiting mild to moderate dehydration.

Ondansetron given as a single dose (0.1 mg/kg) (Freedman 2006; Roslund 2008) orally, or intravenously in the emergency department to children with mild to moderate dehydration, appears to decrease the number of children who have persistent vomiting as a barrier to ORT. In addition, it decreases the number of children requiring intravenous rehydration and hospital admission, although it may not either reduce the chance of a revisit or admission after departure from the emergency department. Oral ondansetron may also prove to be useful as an adjunctive measure to ORT in the outpatient or home-care setting.

Implications for research

A review of antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents provides an example of where there is evidence of a benefit of the intervention. This review shows that the question of the effects of antiemetics on children with vomiting related to acute gastroenteritis should now be considered as broadly answered. Further research may be justified to investigate the relative effects of different dosage regimes, different settings i.e. outpatient and home-based care; hydration status and

severity of disease; and on outcomes that are of relevance to patients such as, for example, the time to cessation of vomiting from administration of antiemetic. This research should also include a formal cost effectiveness analysis across treatments, routes of administration and follow-up regimens, and be evaluated separately for developed and developing countries because clinical decision-making, patients' preferences and carer expectations of outcomes do differ across these variables.

Future randomized controlled trials must be well-designed, well-conducted, and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Rigorous reporting needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org/) which will enable appraisal and interpretation of results, and accurate judgements to be made about the risk of bias, and the overall quality of the evidence. Although it is uncertain whether reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995). Adherence to guidelines, such as the CONSORT statement, would help ensure complete reporting.

For further research recommendations based on the EPICOT format (Brown 2006) see (Table 17).

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REFERENCES

References to studies included in this review

Cubeddu 1997 *{published data only}*
Cubeddu LX, Trujillo LM, Talmaciu I, Gonzalez V, Guariguata J, Seijas J, et al.Antiemetic activity of ondansetron in acute gastroenteritis. *Alimentary Pharmacology and Therapeutics* 1997;**11**(1):185–91.

Freedman 2006 *{published data only}*
Freedman SB, Adler M, Seshadri R, Powell EC. Oral ondansetron for gastroenteritis in a pediatric emergency department. *New England Journal of Medicine* 2006;**354**(16):1698–705.

Ramsook 2002 *{published data only}*
Ramsook C, Sahagun-Carreon I, Kozinetz CA, Moro-Sutherland D. A randomized clinical trial comparing oral ondansetron with placebo in children with vomiting from acute gastroenteritis. *Annals of Emergency Medicine* 2002;**39**(4):397–403.

Roslund 2008 *{published data only}*
Fedorowicz, Z. Letter to editors. Erratum in. *Annals of Emergency Medicine* 2008;**52**(4):406.
* Roslund G, Hepps TS, McQuillen KK. The role of oral Ondansetron in children with vomiting as result of acute gastritis/gastroenteritis who have failed oral rehydration therapy: a randomized controlled trial. *Annals of Emergency Medicine* 2008;**52**(1):22–9.

Stork 2006 *{published data only}*
Stork CM, Brown KM, Reilly TH, Secreti L, Brown LH. Emergency department treatment of viral gastritis using intravenous ondansetron or dexamethasone in children. *Academic Emergency Medicine* 2006;**13**(10):1027–33.

Uhlig 2009 *{published data only}*
Uhlig U, Pfeil N, Gelbrich G, Spranger C, Syrbe S, Huegle B, et al.Dimenhydrinate in children with infectious gastroenteritis: a prospective RCT. *Pediatrics* 2009;**124**(4):e622–32.

Yilmaz 2010 *{published data only}*
Yilmaz HL, Yildizdas RD, Sertdemir Y. A randomized clinical trial: oral ondansetron for reducing vomiting secondary to acute gastroenteritis in children. *Annals of Emergency Medicine* 2008;**51**(4):482–3.
* Yilmaz HL, Yildizdas RD, Sertdemir Y. Clinical trial: oral Ondansetron for reducing vomiting secondary to acute gastroenteritis in children - a double-blind randomized study. *Alimentary Pharmacology and Therapeutics* 2010;**31**(1):82–91.

References to studies excluded from this review

Ginsburg 1980 *{published data only}*
Ginsburg CM, Clahsen J. Evaluation of trimethobenzamide hydrochloride (Tigan) suppositories for treatment of nausea and vomiting in children. *Journal of Pediatrics* 1980;**96**(4):767–9.

Van Eygen 1979 *{published data only}*
Van Eygen M, Dhondt F, Heck E, Ameryckx L, Van Ravensteyn H. A double blind comparison of domperidone and metoclopramide suppositories in the treatment of

nausea and vomiting in children. *Postgraduate Medical Journal* 1979;**55**(Suppl 1):36–9.

References to studies awaiting assessment

Debray 1990 *{published data only}*
Debray H, Guihard J, Peyramond D, Tron P. Treatment of vomiting in infants and children induced by acute infectious pathology. A comparative study of alizapride versus metopimazine. *Annales de Pediatrie* 1990;**37**(10): 683–7.

Reeves 2002 *{published data only}*
Reeves JJ, Shannon MW, Fleisher GR. Ondansetron decreases vomiting associated with acute gastroenteritis: a randomized, controlled trial. *Pediatrics* 2002;**109**(4):e62.

References to ongoing studies

NCT00124787 *{published data only}*
NCT00124787. A trial comparing the effect of oral dimenhydrinate versus placebo in children with gastroenteritis. http://clinicaltrials.gov/ct2/show/NCT00124787 (accessed 14 June 2011).

NCT01165866 *{published data only}*
NCT01165866. Ondansetron versus metoclopramide in treatment of vomiting in gastroenteritis. http://clinicaltrials.gov/ct2/show/NCT01165866 (accessed 14 June 2011).

NCT01257672 *{published data only}*
NCT0125762. Symptomatic treatment of acute gastroenteritis. http://clinicaltrials.gov/ct2/show/NCT0125762 (accessed 14 June 2011).

Additional references

AAP1996
Nazarian LF, Berman JH, Brown G, Margolis PA, Matson DO, McClung J, et al.Practice Parameter: the Management of acute gastroenteritis in young children. *Pediatrics* 1996; **97**:424–35.

Brown 2006
Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al.How to formulate research questions. *BMJ* 2006;**333**(7572):804–6.

Brunton 1996
Brunton LL. Agents affecting gastrointestinal water flux and motility; emesis and antiemetics; bile acids and pancreatic enzymes. In: Goodman, Gilman editor(s). *The Pharmacological Basis of Therapeutics*. 9th Edition. New York: McGraw-Hill, 1996:928–932.

Colletti 2009
Colletti JE, Brown KM, Sharieff GQ, Barata IA, Ishimine P. The management of children with gastroenteritis and dehydration in the emergency department. *Journal of Emergency Medicine* 2010;**38**(5):686–98.

DeCamp 2008
DeCamp LR, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(9):858–65.

Doan 2003
Doan LT, Okitsu S, Nishio O, Pham DT, Nguyen DH, Ushijima H. Epidemiological features of rotavirus infection among hospitalised children with gastroenteritis in Ho Chi Minh City, Vietnam. *Journal of Medical Virology* 2003;**69**: 588–94.

Downs 1998
Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health* 1998;**52**:377–84.

Feldman 1989
Feldman M. Nausea and vomiting. In: Sleisenger MH, Fordtran JS editor(s). *Gastrointestinal Disease: Pathophysiology, Diagnosis, Management*. 4th Edition. Philadelphia, PA: Saunders, 1989:222–6.

Flake 2004
Flake ZA, Scalley RD, Bailey AG. Practical selection of antiemetics. *American Family Physician* 2004;**69**(5):1171.

Friedman 1998
Friedman LS, Isselbacher KJ. Nausea, vomiting, and indigestion. In: Fauci AS, Braunwald E, Isselbacher KJ, et al. editor(s). *Harrison's Principles of Internal Medicine*. 14th Edition. New York: McGraw-Hill, 1998:230–2.

Gamble 2005
Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. *Journal of Clinical Epidemiology* 2005;**58**(6):579–88.

Herikstad 2002
Herikstad H, Yang S, Van Gilder TJ, Vugia D, Hadler J, Blake P, et al.A population - based estimate of the burden of diarrhoeal illness in the United States: FoodNet 1996-7. *Epidemiology and Infection* 2002;**129**(1):9–17.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. The Cochrane Collaboration.

Kwon 2002
Kwon KT, Rudkin SE, Langdorf MI. Antiemetic use in pediatric gastroenteritis: a national survey of emergency physicians, pediatricians, and pediatric emergency physicians. *Clinical Pediatrics* 2002;**41**(9):641–52. [PUBMED: 12462313]

Lexchin 2003
Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;**326**(7400):1167–70.

Li 2003
Li ST, DiGiuseppe DL, Christakis DA. Antiemetic use for acute gastroenteritis in children. *Archives of Pediatrics*

and Adolescent Medicine 2003;**157**(5):475–9. [PUBMED: 12742884]

RevMan 2011

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Schulz 1995

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

Taylor 1999

Taylor AT. Nausea and vomiting. In: DiPiro JT, Talbert RL, Yee Gl, et al. editor(s). *Pharmacotherapy, A Pathophysiologic Approach*. 4th Edition. Stanford CT: Appleton & Lange, 1999:586–96.

Treadwell 2006

Treadwell JR, Tregear SJ, Reston JT, Turkelson CM. A system for rating the stability and strength of medical evidence. *BMC Medical Research Methodology* 2006;**6**:52. [DOI: 10.1186/1471-2288-6-52]

Vreeman 2008

Vreeman RC, Finnell SM, Cernkovich ER, Carroll AE. The effects of antiemetics for children with vomiting due to acute, moderate gastroenteritis. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(9):866–9.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Cubeddu 1997

Methods	Randomized double blind placebo-controlled parallel group trial in a children's hospital in Venezuela (no date specified). Participants hospitalized for a minimum period of 24 hours during the course of the trial
Participants	Children (21 males, 15 females) aged 6 months to 8 years. Not balanced for age, height, weight and degree of hydration INCLUSION CRITERIA: • Acute gastroenteritis, diagnosed and confirmed by a positive stool analysis for adenovirus or rotavirus (all but two had positive stool cultures) • Vomiting episodes (either spontaneous or oral-rehydration induced) > 2 within one hour. Vomiting episode: defined as an "expulsion of stomach contents" and was recorded as a single vomit or retch or any number of continuous vomits and/or retches with a minimum one minute interval separating each episode. Retching: an attempt to vomit that was not productive of any stomach contents. EXCLUSION CRITERIA: • Severe dehydration, seizures, significantly elevated rectal temperatures, had received any parenteral antiemetic medication in the six hours previously or diagnosed with a parasite-induced gastroenteritis. Randomized: N = 12 (ondansetron), 12 (metoclopramide), 12 (placebo) BASELINE DATA: (See Table 18) WITHDRAWALS/TREATMENT FAILURES: • Treatment failures at 0-4 hrs: four (33%) placebo, two (17%) metoclopramide and one (8%) ondansetron. At 0-24 hrs: four (33%) placebo, five (42%) metoclopramide and two (17%) ondansetron. Treatment failures: patients who had experienced two vomiting episodes in any 90 minute period 1-8 hours after the administration of the intervention, or had three episodes during the hour following the end of administration of treatment. Treatment failures accounted for 50% of the participants in this study
Interventions	Three groups of 12: single IV dose of ondansetron (0.3mg/kg) or metoclopramide (0.3mg/kg) or placebo (sterile saline) Oral rehydration: • solution of sodium, potassium, citrate and glucose, started 30 minutes after administration of either antiemetic or control and continued at 30-minute intervals for up to four hours. No food permitted during rehydration period but gradually introduced based on individual status (i.e. level of hydration, the presence or absence of retching and/or diarrhea)
Outcomes	• Number of vomiting episodes over 24-hr period. • Proportion of participants with no vomiting episodes. • Treatment failures (0 to 4 hr; 0 to 24 hr).
Notes	Study supported by, and two of the investigators were affiliated with, Glaxo Wellcome Research and Development, UK

Cubeddu 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to receive either...." Pg 186 Comment: unclear.
Allocation concealment (selection bias)	Low risk	Quote: "The study medication was prepared by a pharmacist not involved in patient care..." Pg 186 Comment: probably done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants: not applicable. Healthcare providers: Comment: unclear how knowledge of the allocated interventions by the personnel was adequately prevented during the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes assessors & data analysts: not reported if persons assessing the outcomes of care were blinded to which treatment the participants received
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data appear to have been reported in the study outcomes.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting. Outcomes listed in the methods section were comparable to those reported
Other bias	High risk	The authors reported a baseline imbalance in age; weight; and height between the ondansetron and placebo treatment arm. Mean age yrs (range); ondansetron 1.0 (0.5 to 2), metoclopramide 1.8 (0.5 to 8) and placebo 2.5 (0.5 to 8). (See Table 18). This imbalance was not adjusted for in the analysis. The trialists reported that the study was supported by Glaxo Wellcome and although the level of support was unclear two of the investigators were in the employment of Glaxo Wellcome

Freedman 2006

Methods	Prospective, double blind randomized clinical trial conducted in a children's hospital in Chicago, USA (study conducted Jan 2004 - April 2005). Block (6) randomization and stratified by dosage of medication
Participants	214 children (122 males, 92 females) aged 6 months to 10 years. Participants in the groups were comparable for gender, age, weight and dehydration score INCLUSION CRITERIA: • Vomiting and dehydration as a result of gastroenteritis, at least one episode of non-bilious vomiting within the four hours preceding triage. A vomiting episode: the forceful expulsion of stomach contents. Episodes separated by no more than two minutes were considered as one episode. EXCLUSION CRITERIA: • Severe dehydration or underlying disease or hypersensitivity to ondansetron. Randomized: 215 (108 to ondansetron and 107 to placebo, 1 early withdrawal due to no parental consent in ondansetron group); 214 analyzed WITHDRAWALS: • 3 (ondansetron group) before the intervention. • 5 (ondansetron group) vomited within 15 mins and received a second dose. • 3 (placebo group) vomited within 15 mins. Parents of two children refused to allow a second dose, other child received the second dose, which was well tolerated.
Interventions	A single dose of orally disintegrating ondansetron tablet or placebo: weight-based dose 2 mg (8-15 kg), 4 mg (15-30 kg) 8 mg (> 30 kg), placed on the tongue by the bedside nurse only, swallowed five seconds later. Children who vomited within 15 mins received a second dose of ondansetron Oral rehydration: • (Enfalyte, Mead Johnson Nutritionals) 15 mins (up to 30ml/ five minutes) after ondansetron administration and continued until disposition. After oral rehydration period If intravenous fluids were required: 20-ml boluses of 0.9 percent normal saline per kilogram of body weight, given over 30 mins
Outcomes	• Number of episodes of vomiting during oral rehydration. • Number of admissions to hospital and IV rates per treatment group. Telephone-call follow-up on days 3 and 7 after randomization. Caregivers were asked whether the child returned to the emergency department, had received intravenous fluids, had additional symptoms or had been hospitalized. Hospital records were reviewed to confirm the caregivers' report. Adverse events were recorded.
Notes	Supported by grants from the National Institutes for Health and GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly assigned in blocks of six to receive Ondansetron or placebo and were stratified according to the dose of medication". "An in-

		dependent statistician provided the code to the pharmacy". The report included a randomization flow chart with enrolment details. Comment: Probably done.
Allocation concealment (selection bias)	Low risk	Quote: "An independent statistician provided the code to the pharmacy, which dispensed in an opaque bag a weight-appropriate dose of active drug or placebo". Pg1700 Comment: Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants/ Healthcare providers: Quote: "active drug or placebo of similar taste and appearance". Pg1700 Comment: Probably done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors & data analysts: Quote: "the bedside nurse administered the medication while the research assistant was outside the room to ensure that the research assistant, physician, child and caregivers remained unaware of the treatment assignment". Comment: Probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors indicated that they followed the intention to treat principle
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section comparable to the reported results. No evidence of selective choice of data for outcomes
Other bias	Unclear risk	Although no potential conflicts of interest were reported, this trial was supported partly by a grant from GlaxoSmithKline but the level of support was not declared. The risk of 'other bias' was therefore judged unclear

Ramsook 2002

Methods	Prospective double blind randomized study in the emergency department of a university-affiliated hospital in Texas, USA. Random allocation tables were used to assign treatment or placebo. Treatment was blinded randomized and packaged by a pharmacy (no date specified)
Participants	Children: aged 6 months to 12 years. INCLUSION CRITERIA: • Clinically confirmed diagnosis of gastroenteritis, > 5 episodes of vomiting in the preceding 24 hrs, with or without diarrhea. EXCLUSION CRITERIA: • No serious underlying chronic systemic conditions, no antiemetics in the preceding 24 hrs or if requiring immediate rehydration. Randomized: oral ondansetron (74), placebo (71). BASELINE DATA: • < 10 episodes of vomiting in the preceding 24 hours: 37 (50%) ondansetron group and 40 (56.33%) placebo group. • ≥ 10 episodes of vomiting 37 (50%) patients in the ondansetron group and 31 (43.66%) in the placebo group. WITHDRAWALS/TREATMENT FAILURES: • Ondansetron group 74 enrolled, 1 developed a rash after the first dose and withdrew. 7 lost to follow-up and 2 were admitted. Only 64 out of the 73 patients completed the 24-hour follow-up. 62 completed the trial at 48 hours • Placebo group 71 enrolled, 4 lost to follow-up, 11 were admitted. Only 56 completed the 24-hour follow-up. Further 5 losses to follow-up at 48 hours. 51 completed the trial at 48 hours Intravenous fluids: 13 (11 placebo, 2 ondansetron) had persistent vomiting, were admitted and classified as treatment failures
Interventions	Oral ondansetron 2 mL (1.6 mg) for ages 6 months to 1 yr, 4 mL (3.2 mg) aged 1-3 yrs, and 5 mL (4 mg) aged 4-12 (all 8 hourly) or placebo. Participants received a total of six doses of the ondansetron or placebo, a single dose in the emergency department followed by an additional five doses taken eight hourly for up to 48 hours when discharged to home Oral rehydration: • unflavored Pedialyte (5 mL/min)15 mins after the initial dose of ondansetron or placebo was administered in the emergency room. Patients were only discharged after they were able to successfully tolerate oral fluids and after successful rehydration. At the end of the 24-hr period, participants were progressively weaned onto a diet of bananas, rice, applesauce and toast (BRAT)
Outcomes	• Frequency of vomiting during the 48-hr period after enrolment. • Rates of intravenous fluid administration. • Admission rates. • Frequency of diarrhea. Adverse events were recorded.
Notes	Study funding was obtained from Glaxo Wellcome.
Risk of bias	

Ramsook 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "random allocation procedure was designed using standard random number allocation tables". Pg 399 Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "The pharmacy research section assigned treatment or placebo according to this individual randomization". "The pharmacy team was not privy to the enrolled patients or the outcome measures. This code remained locked within the pharmacy research section and was broken and revealed to the investigators only at the close of the study". Pg 399 Comment: central allocation. Probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants/Healthcare providers: quote "the pharmacy provided the drug or a color, taste, and odor-matched placebo in identical packaging." Pg 399. Comment: probably done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors & data analysts: quote: "This code remained locked within the pharmacy research section and was broken and revealed to the investigators only at the close of the study". Pg 399 Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up at two time periods were accounted for and were similar in both groups
Selective reporting (reporting bias)	Low risk	No evidence of selective choice of data for outcomes. Outcomes listed in the methods section comparable to the reported results
Other bias	Unclear risk	Quote: although the study was "supported in part by a grant from GlaxoWellcome Research and Development" the level of support was not declared Comment: unclear.

Roslund 2008

Methods	Prospective, double-blind, placebo-controlled, randomized study conducted in the emergency department of a medical center in Chicago, USA. Method of randomization not specified other than blocks of (10) but trial flow chart refers to Block Randomization.com. (Study conducted July 2004-August 2005)
Participants	Children: aged 1 to 10 yrs. INCLUSION CRITERIA: • Clinical diagnosis of acute gastritis or acute gastroenteritis and mild to moderate dehydration. • Aged 1-10 yrs. • Failed controlled oral challenge in ED. EXCLUSION CRITERIA: • Antiemetics in the previous 6 hrs. • Underlying chronic illness. • Shock state requiring immediate IV fluids. • Severe dehydration. • Known sensitivity to 5-HT_3 receptor antagonists. Randomized: ondansetron (51), placebo (55). BASELINE DATA: Episodes of vomiting: • ondansetron group 1-30 (median 10). • placebo group 1-30 (median 10). PROTOCOL VIOLATION: (3) In the ondansetron group, ultimately diagnosed with other than acute gastritis/ acute gastroenteritis: brain tumor (1), pneumonia (1), and pancreatitis (1) and were not included in the analysis WITHDRAWALS/TREATMENT FAILURES: • ondansetron group 51 enrolled : 40 able, 11 unable to tolerate oral hydration. • placebo group 55 enrolled: 25 able, 30 unable to tolerate oral rehydration. Participants continuing to vomit or refusing to drink/tolerate oral hydration, received IV and considered a treatment failure
Interventions	Orally dissolving ondansetron weight-based dose: 2 mg (< 15 kg), 4 mg (15-30 kg), 6 mg (> 30 kg) Placebo “looked smelled and tasted like ondansetron”. Oral rehydration: • 30 minutes after medication: Pedialyte popsicle (Abbott Laboratories) or Pedialyte 5 mL/3 minutes via oral syringe Discharge when able to tolerate oral fluids (40 mL/kg over 2 hours), after successful rehydration. Failure to tolerate oral challenge: revert to ’standard care’ i.e. IV normal saline and admission
Outcomes	• Proportion of participants who received IV rehydration in each group. • Admissions, number of episodes of vomiting during ED stay, and need for return visit. After discharge: self - standardized symptom diary/data collection form

Notes	Quote: "GlaxoSmithKline supplied placebo tablets but no other financial or in-kind support for this study."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to receive oral Ondansetron or placebo", "block randomization of 10" Pg 24. Trial flow chart refers to Block Randomization.com Pg 25. Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Quote: "Each subject was assigned a packet with a corresponding number. Each packet contained a tracking form used for documenting the subject's course in the ED" Pg 24. Comment: unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants: quote. Placebo "looked smelled and tasted like ondansetron". Pg 24 Comment: probably done. Healthcare providers: quote. "The packets were prefilled (oral ondansetron or placebo) ." "The markings on the blister pack were obscured". Pg 24 Comment: probably done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors & data analysts: the healthcare providers were the assessors during the study and the research nurse, who was blinded to the treatment allocation, completed the follow-up for the study. Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	High risk	Trialists use different denominators (n = 48, or 51) in the ondansetron group, when reporting different outcomes Post-discharge symptom diary (questions related to patient and carer satisfaction), outcomes data were unavailable
Selective reporting (reporting bias)	Low risk	The outcomes listed in the methods section were comparable to those reported in the results

		No evidence of selective reporting of outcomes.
Other bias	High risk	Quote: the investigators "enrolled a convenience sample of patients". Pg 23 Comment: this, in isolation, limits the possibility of making robust inferences from the study, but when combined with unclear allocation concealment, facilitates unintentional subversion

Stork 2006

Methods	Double-blind randomized placebo controlled trial. Setting: emergency department, single tertiary care academic hospital, US Date of study November 1999 to February 2005.
Participants	INCLUSION CRITERIA: • Children: aged 6 months to 12 yrs. • Clinical diagnosis of acute gastritis or acute gastroenteritis (more than 3 episodes of vomiting in previous 24 hrs). • Mild to moderate dehydration. • Failed attempts at oral rehydration. EXCLUSION CRITERIA: • Antiemetic use within the previous week. • Underlying chronic illness (excluding asthma). • History of abdominal surgery. • Requiring chronic medications (excluding vitamins). • Use of corticosteroid including inhaled corticosteroid in previous two weeks. • History and physical examination findings inconsistent with the diagnosis of isolated acute viral gastritis. Randomized: N = 166, ondansetron (56), dexamethasone (55), placebo/saline (55) BASELINE DATA: Episodes of vomiting: • Placebo group 6 (median), 4-10 (interquartile range (IQR)). • Dexamethasone group 5.5 (median), 4-10 (IQR). • Ondansetron group 9.0 (median), 4-12 (IQR). WITHDRAWALS/TREATMENT FAILURES: 19 excluded due to missing data or due to violations of the inclusion or exclusion criteria: placebo/saline 11/55; dexamethasone 8/55, ondansetron 10/56 Reasons: (1) not judged to be dehydrated; (10) not vomited > three times in the last 24 hrs; (3) with a blood glucose level >150 mg/dL; (5) with undocumented failed oral hydration
Interventions	INTERVENTION: • Dexamethasone 1 mg/kg IV (maximum dose, 15 mg). • Ondansetron 0.15 mg/kg IV. PLACEBO: • 10-mL bolus of normal saline.

	REHYDRATION THERAPY: All participants received IV rehydration: 0.9% sodium chloride solution 10-20 mL/kg/hr. Nature of ORT not reported Participants judged to be hydrated and able to tolerate oral rehydration were discharged. Those unable to tolerate oral rehydration continued to receive IV therapy, re-evaluated at 4 hrs. Admission at the discretion of the treating pediatric emergency physician. Patients discharged < 72 hours followed up via telephone (24 &72 hrs) regarding further vomiting, the need for further health care
Outcomes	PRIMARY OUTCOME: • Need for admission. SECONDARY OUTCOME: • Tolerance of oral hydration and dehydration status at 2 and 4 hrs
Notes	The investigators declared that the study was "supported by an unrestricted grant from Glaxo-Wellcome", which did not appear to represent a risk of bias

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed in the pharmacy using specific instructions to access a provided table of random numbers to identify the patient's study group". Pg 1029 Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed in the pharmacy...." Pg1029 Comment: a form of central allocation was used and it would appear that participants and investigators enrolling participants could not foresee the upcoming assignment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants/ Healthcare providers: Quote: "all study drug dispensed was uniform in design and color". Pg1028 Comment: probably done.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors & data analysts: The healthcare providers were the assessors but blinding was ensured, and unlikely that the blinding could have been broken

Stork 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "our study was hampered by a large amount of missing data from subjects who were lost to follow-up after two to four hours" Pg 1032 Comment: losses to follow-up resulted in incomplete data for several of the outcomes which were pre-specified for this review
Selective reporting (reporting bias)	Low risk	No evidence of selective choice of data for outcomes, and the outcomes listed in the methods section were comparable to the reported results
Other bias	High risk	The study randomized patients before their full eligibility had been ascertained which resulted in 19 patients dropping out and a further 10 being discharged shortly after randomization

Uhlig 2009

Methods	Randomized, placebo controlled multi-center (5 children's hospitals and 6 pediatric practices) in Germany. Conducted December 2005 - May 2007. Stratified randomization categorized by body weight (< 15kg, ≥ 15kg)
Participants	INCLUSION CRITERIA: • Age 6 months to 6yrs, body weight > 7kg. • "[S]uspected infectious gastroenteritis". • Acute (< 24hrs) onset of vomiting, 2 episodes within prior 12 hrs. • Outpatient attendance. • No or mild dehydration. EXCLUSION CRITERIA: • Moderate to severe gastroenteritis (criteria: acute weight loss, bloody stools, requirement for IV rehydration, metabolic acidosis). • Pre-existing diseases for which dimenhydrinate is contraindicated (epilepsy, glaucoma, acute asthma, porphyria, pheochromocytoma). • Concomitant treatment with other antiemetics. Randomized: 243 dimenhydrinate (124), placebo (119). BASELINE DATA: > 5 vomiting episodes prior 24 hrs; dimenhydrinate (27/122), placebo (29/115) WITHDRAWALS/TREATMENT FAILURES: *Early losses* dimenhydrinate (2), placebo (4). *Lost to follow-up* dimenhydrinate (16), placebo (13). (n) Available for analysis of study "primary end point": • dimenhydrinate 106/124, placebo 102/119. (n) Available for analysis of study "secondary end point": • dimenhydrinate 102/124, placebo 97/119.

Uhlig 2009 (*Continued*)

Interventions	INTERVENTION: Dimenhydrinate (40 mg) suppository (< 15kg = 1, 15-25 kg = 2, > 25kg = 3) CONTROL: placebo suppository. First suppository placed in outpatient department, caregivers instructed to give additional suppositories only if persistent vomiting. ORT: powdered oral rehydration solution 200 ml (100 mmol/L glucose, 60 mmol/L sodium, 20 mmol/L potassium) provided for home care
Outcomes	PRIMARY OUTCOME: • weight gain (for the period, randomization to follow-up at 18-24 hrs). SECONDARY OUTCOMES: *Early phase:* • number of episodes of vomiting and diarrhea; • volume of fluid intake; • hospitalization; • self-assessed well being (6-point 'smiley faces' scale). *Long term* Structured telephone interviews: history of adverse events, hospitalization, carer satisfaction (6-point scale) Adverse events and concomitant medication recorded.
Notes	The primary outcome for this study (but not for this systematic review) was weight gain at 18-24 hrs. No difference reported in this outcome between the two groups Although the active intervention, placebo, an independent biostatistician who generated the randomization list, and an unconditional grant were supplied by Sandoz Pharmaceuticals (Germany), the investigators declared that the funders had "no role in the conception, design, or conduct of the study or in the analysis of interpretation of the data", and that they also had no personal financial relationships of relevance to this study. Pg 627

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "blocked random allocation sequence was generated (block randomization in blocks of 4)". Pg 623. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "an independent biostatistician from Sandoz Pharmaceuticals generated the randomization list". Pg 623. Comment: the investigators provided reasonable assurances that adequate steps had been taken to ensure that participants and investigators enrolling participants could not foresee assignment in advance of, or

Uhlig 2009 (*Continued*)

		during, enrolment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants: not applicable. Healthcare providers: not reported, judged unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes assessors & data analysts:the caregivers were healthcare providers as well as outcomes assessors after discharge. Several of the trialists/healthcare providers carried out the data analysis Comment: overall judgement unclear for this domain.
Incomplete outcome data (attrition bias) All outcomes	High risk	Flow chart indicating losses of participants to follow-up. Pg 625. Authors report, "Main and Secondary Outcomes according to Intention-to-treat analysis" but only provide data for 114/122 (dimenhydrinate) and 109/115 (placebo). Pg 632 Inconsistent reporting of numbers of participants "available for primary.. and secondary end points" (Fig 1 Pg 625 and Appendix 4 Pg 632). Comment: losses to follow-up, incomplete data for outcomes, several of which were pre-specified for this review, and per-protocol analysis represent a high risk of bias
Selective reporting (reporting bias)	Low risk	No evidence of selective choice of data for outcomes, and outcomes listed in the methods section were comparable to the reported results
Other bias	High risk	6/243 randomized participants were excluded after randomization as they did not match eligibility criteria

Yilmaz 2010

Methods	Randomized, double blind placebo controlled trial conducted in the emergency departments (one university hospital, one government hospital) in Turkey. Study conducted August 2003 - September 2004. Block (6) randomization by an independent statistician
Participants	Children aged 5 months to 8 yrs. INCLUSION CRITERIA: • Clinical diagnosis of acute gastroenteritis by paediatrician; but of unconfirmed aetiology.

	• Nonbilious, nonbloody vomit > 4 times/6 hr period. • 4 episodes diarrhoea in previous 24 hrs. • Mild to moderate dehydration. • Unable to tolerate oral feeding. • Timing of arrival at emergency department (potentially excluded many cases of acute gastroenteritis). EXCLUSION CRITERIA: • Use of anti-emetics in prior 72 hrs. • History of liver disease. • Congenital heart disease, immune deficiency, malignancy, malnutrition, sickle cell anemia. • Clinical findings/physical exam suggesting non gastroenteritis origin. • Severe dehydration. • Oral or inhaled corticosteroids in the previous week. Randomized: 109: ondansetron (55), placebo (54). WITHDRAWALS/TREATMENT FAILURES: IV fluid administration with hospitalization at 24 hrs; ondansetron group (3), placebo (10) Inconsistencies were found between tables 1 & 2 and Figure 1 in the report, for the number of randomized subjects who were administered IV and hospitalized. Lead investigator informed, errata under review by journal
Interventions	INTERVENTION: Orally disintegrating ondansetron tabs in 4 mL 0.9% saline. CONTROL: identical-looking placebo. Administered orally with "injectors". ORT: 75 mL/kg ORT solution (Ge-oral, Kansuk Turkey) containing 3.5 g sodium chloride. 2.9 g trisodium citrate, 1.5 g potassium chloride, 20 g glucose anhydride, following WHO recommendations (0.5 mL/kg every 2 min)
Outcomes	PRIMARY OUTCOMES: • Frequency of emesis over 8-hr period post enrolment. SECONDARY OUTCOMES: • Rate of intravenous fluid administration or admission to hospital. • Ability to tolerate ORT. • Weight gain and frequency of diarrhoea. Side effects were noted.
Notes	Number of participants enrolled and early withdrawals were inconsistently reported, clarification sought and obtained from investigators

Risk of bias

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

Random sequence generation (selection bias)	Low risk	Quote: "computerized randomization codes .. in blocks of six". Pg 83 Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "by a statistician who was not one of the investigators of this study". "Code numbers were written on the injectors and...drawn up.. by a pharmacist who was not one of the investigators in this study". Pg 83 Comment: adequate steps appear to have been taken to ensure that participants and investigators enrolling participants could not foresee assignment in advance of, or during enrolment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants/healthcare providers: Quote: "orally disintegrating Ondansetron tablets dissolved.. and identical looking placebo liquid". "The subjects, parents, study personnel and other medical staff were blinded to which study drug was given". Pg 83 Comment: the investigators appear to have used adequate measures to blind study participants and personnel from knowledge of which intervention a participant received
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes assessors & data analysts: Quote: " identical looking"...."study personnel and other medical staff were blinded to which study drug was given". Pg 83 Comment: adequate measures were taken to blind study personnel who were outcomes assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	A flow chart tracked participants but some were not accounted for at several stages in the study. 109 subjects were randomized to ondansetron (55) and placebo (54) arms. Two participants in the placebo group were removed from the study after receiving IV rehydration and were admitted to hospital but were not included in the analysis
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting of data and outcomes listed in the methods section were comparable to the reported results

Yilmaz 2010 (*Continued*)

Other bias	Low risk	The report appeared to be free of other sources of bias.

IQR:
ORT: oral rehydration therapy

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

Study	Reason for exclusion
Ginsburg 1980	Non RCT.
Van Eygen 1979	No outcomes matching those specified in the protocol of this review

RCT

Characteristics of studies awaiting assessment *[ordered by study ID]*

Debray 1990

Methods	From translation: multi centre (5 hospitals), double blind, randomized study. Blinded data entry
Participants	47 infants, no drop-outs. Only 49% with vomiting related to gastroenteritis
Interventions	23 to alizapride, 24 to metopimazine (oral drops).
Outcomes	Time to cessation of vomiting sorted by 1-2 days, 2-3 days, 3-4 days
Notes	No separate data for participants with gastroenteritis-related vomiting

Reeves 2002

Methods	Quote: "A randomized, double blind, placebo-controlled trial, conducted in the emergency department of a tertiary-care children's hospital" (Boston USA). "A computer randomization code was produced by a member of the medical school's center for clinical investigation. Blocking was used in groups of 4, 6 or 10 as generated randomly by computer". "All providers except the pharmacist were blinded to group assignment until after data analysis. The study investigators remained blinded until after complete statistical analysis was performed"
Participants	107 children enrolled, 2 losses to follow-up, age range 3 months to 22 yrs

Reeves 2002 (*Continued*)

Interventions	54 to intravenous ondansetron 0.15 mg/kg (maximum 8 mg), 53 to placebo 0.9% saline solution
Outcomes	Frequency of vomiting episodes after drug administration; need for hospitalization; duration of vomiting after drug administration; number and duration of diarrhea episodes; frequency of return to ED; need for readministration of IV fluids; need for later hospital admission
Notes	Quote: "Grant support by Glaxo Wellcome Inc, which played no role in the conception, design, conduct, interpretation, or analysis of this study but reviewed the final manuscript before submission". Several unsuccessful attempts were made to contact the investigators to clarify number of participants outside the age range pre-specified for this review

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

NCT00124787

Trial name or title	A trial comparing the effect of oral dimenhydrinate versus placebo in children with gastroenteritis
Methods	RCT ED of an urban pediatric university-affiliated center Canada
Participants	Children 1-12 yrs presenting to ED with > 5 episodes of vomiting in previous 12 hrs and diagnosed with acute gastroenteritis by attending physicians
Interventions	Oral dimenhydrinate 8 doses (1 mg/kg/dose, max 50 mg/dose) or placebo
Outcomes	Primary outcome measure: number of good outcome, defined as 1 episode or less of vomiting 24 hrs after the first dose of drug administration Secondary outcome measures: need for intravenous fluid administration, number and duration of vomiting and diarrhea, side effects, revisit rates and parental absenteeism from work will be compared between the two groups
Starting date	April 2005.
Contact information	Serge Gouin: E mail: sergegouin@aol.com Ste-Justine Hospital, Department of Pediatrics, Montreal University, Canada Tel: 514 345 4031 ext 3498
Notes	Accessed 14 June 2011. Recruiting. Last Updated on 15 February 2011

NCT01165866

Trial name or title	Ondansetron versus metoclopramide in treatment of vomiting in gastroenteritis
Methods	RCT, Qatar.

NCT01165866 (*Continued*)

Participants	Children 1 to 14 yrs, with diarrhea, persistent vomiting , failed oral rehydration and admitted to the observation unit for intravenous hydration
Interventions	Ondansetron 0.15 mg/kg max 4 mg in burette and mixed with normal saline to make up 50 cc of medication and normal saline to be given over 10 minutes Metoclopramide 0.3 mg/kg maximum dose 10 mg will be added in the burette and mixed with normal saline to make up 50 cc of medication for intravenous administration
Outcomes	Primary outcome measures: the proportion of patients with cessation of vomiting after study medication administration in each group. Secondary outcome measures: time to complete cessation of vomiting, time to successful oral therapy, length of hospital stay, parents' perception of the child, nausea symptoms, and oral tolerance on discharge and daily follow-up for 3 days
Starting date	June 2008
Contact information	Khalid M Al-Ansari, Hamad Medical Corporation, Weill Cornell Medical College, Qatar. Email: dkmaa@hotmail.com
Notes	First received on July 18, 2010. Last Updated on October 25, 2010. Accessed 14 June 2011. Study completed not yet published

NCT01257672

Trial name or title	Symptomatic treatment of acute gastroenteritis
Methods	RCT multi-centred Italy.
Participants	Children (age 1-6 yrs) with AG who have failed oral rehydration therapy
Interventions	• Ondansetron syrup (0.15 mg/kg of body weight). • Domperidone syrup (0.5 mg/kg of body weight). • Placebo.
Outcomes	Primary outcome measures: percentage of patients needing nasogastric or intravenous rehydration after symptomatic oral treatment failure, defined as vomiting or fluid refusal after the second attempt of ORT. Secondary outcome measures: percentage of subjects needing hospital admission for the same illness. Percentage of subjects needing observation stay for more than 6 hrs for the same illness. Total emesis duration in the 3 allocation groups. Number of episodes of vomiting in the 3 treatment groups during the follow-up period. Percentage of subjects presenting adverse events.
Starting date	March 2011. Accessed 14 June 2011, not yet recruiting.
Contact information	IRCCS Burlo Garofolo (Dr. Federico Marchetti). Mario Negri Institute for Pharmacological Research.

NCT01257672 (*Continued*)

	Agenzia Italiana del Farmaco, Italy. Contact: Luca Ronfani. E mail: ronfani@burlo.trieste.it Contact: Lorenzo Monasta. Email: monasta@burlo.trieste.it
Notes	This study is not yet open for participant recruitment.

DATA AND ANALYSES

Comparison 1. Oral ondansetron (weight dependent dose) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Rate of admission to hospital (during ED stay)	3	465	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.83]
2 Rate of admission to hospital (up to 72 hrs following discharge from ED stay) best-worst case scenario	3	461	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.34, 1.04]
3 Rate of admission to hospital (up to 72 hrs following discharge from ED stay) worst-best case scenario	3	461	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.43, 1.22]
4 Rate of intravenous rehydration (during ED stay)	3	465	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.29, 0.59]
5 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), best-worst case scenario	3	461	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.38, 0.71]
6 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), worst-best case scenario	3	461	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.42, 0.76]
7 Proportion of participants with cessation of vomiting	3	465	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.19, 1.49]
8 Revisit rate	3	457	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.66, 1.79]

Analysis 1.1. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 1 Rate of admission to hospital (during ED stay).

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 1 Rate of admission to hospital (during ED stay)

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	4/107	5/107		21.8 %	0.80 [0.22, 2.90]
Ramsook 2002	2/74	11/71		48.9 %	0.17 [0.04, 0.76]
Roslund 2008	3/51	7/55		29.3 %	0.46 [0.13, 1.69]
Total (95% CI)	**232**	**233**		**100.0 %**	**0.40 [0.19, 0.83]**

Total events: 9 (Ondansetron), 23 (Placebo)

Heterogeneity: $Chi^2 = 2.40$, df = 2 (P = 0.30); $I^2 = 17\%$

Test for overall effect: Z = 2.44 (P = 0.015)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 2 Rate of admission to hospital (up to 72 hrs following discharge from ED stay) best-worst case scenario.

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 2 Rate of admission to hospital (up to 72 hrs following discharge from ED stay) best-worst case scenario

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	10/107	11/103		37.2 %	0.88 [0.39, 1.97]
Ramsook 2002	2/74	11/71		37.3 %	0.17 [0.04, 0.76]
Roslund 2008	6/51	8/55		25.5 %	0.81 [0.30, 2.17]
Total (95% CI)	**232**	**229**		**100.0 %**	**0.60 [0.34, 1.04]**

Total events: 18 (Ondansetron), 30 (Placebo)

Heterogeneity: $Chi^2 = 3.90$, df = 2 (P = 0.14); $I^2 = 49\%$

Test for overall effect: Z = 1.82 (P = 0.069)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 3 Rate of admission to hospital (up to 72 hrs following discharge from ED stay) worst-best case scenario.

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 3 Rate of admission to hospital (up to 72 hrs following discharge from ED stay) worst-best case scenario

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	10/107	11/103		37.2 %	0.88 [0.39, 1.97]
Ramsook 2002	6/74	11/71		37.3 %	0.52 [0.20, 1.34]
Roslund 2008	6/51	8/55		25.5 %	0.81 [0.30, 2.17]
Total (95% CI)	**232**	**229**		**100.0 %**	**0.73 [0.43, 1.22]**

Total events: 22 (Ondansetron), 30 (Placebo)

Heterogeneity: $Chi^2 = 0.71$, df = 2 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 4 Rate of intravenous rehydration (during ED stay).

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 4 Rate of intravenous rehydration (during ED stay)

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	15/107	33/107		42.2 %	0.45 [0.26, 0.79]
Ramsook 2002	6/74	16/71		20.9 %	0.36 [0.15, 0.87]
Roslund 2008	11/51	30/55		36.9 %	0.40 [0.22, 0.70]
Total (95% CI)	**232**	**233**		**100.0 %**	**0.41 [0.29, 0.59]**

Total events: 32 (Ondansetron), 79 (Placebo)

Heterogeneity: $Chi^2 = 0.23$, df = 2 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 4.78 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 5 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), best-worst case scenario.

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 5 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), best-worst case scenario

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	26/107	39/103		46.3 %	0.64 [0.42, 0.97]
Ramsook 2002	6/74	16/71		19.0 %	0.36 [0.15, 0.87]
Roslund 2008	13/51	31/55		34.7 %	0.45 [0.27, 0.76]
Total (95% CI)	**232**	**229**		**100.0 %**	**0.52 [0.38, 0.71]**

Total events: 45 (Ondansetron), 86 (Placebo)

Heterogeneity: $Chi^2 = 1.92$, df = 2 (P = 0.38); $I^2 = 0.0\%$

Test for overall effect: Z = 4.16 (P = 0.000031)

Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 6 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), worst-best case scenario.

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 6 Rate of intravenous rehydration (up to 72 hrs following discharge from the ED stay), worst-best case scenario

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	26/107	39/103		46.3 %	0.64 [0.42, 0.97]
Ramsook 2002	10/74	16/71		19.0 %	0.60 [0.29, 1.23]
Roslund 2008	13/51	31/55		34.7 %	0.45 [0.27, 0.76]
Total (95% CI)	**232**	**229**		**100.0 %**	**0.57 [0.42, 0.76]**

Total events: 49 (Ondansetron), 86 (Placebo)

Heterogeneity: Chi^2 = 1.08, df = 2 (P = 0.58); I^2 =0.0%

Test for overall effect: Z = 3.74 (P = 0.00018)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 7 Proportion of participants with cessation of vomiting.

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 7 Proportion of participants with cessation of vomiting

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	92/107	70/107		47.1 %	1.31 [1.12, 1.54]
Ramsook 2002	64/74	46/71		31.6 %	1.33 [1.10, 1.62]
Roslund 2008	42/51	33/55		21.4 %	1.37 [1.07, 1.76]
Total (95% CI)	**232**	**233**		**100.0 %**	**1.33 [1.19, 1.49]**

Total events: 198 (Ondansetron), 149 (Placebo)

Heterogeneity: $Chi^2 = 0.08$, df = 2 (P = 0.96); $I^2 = 0.0\%$

Test for overall effect: Z = 5.12 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Oral ondansetron (weight dependent dose) vs placebo, Outcome 8 Revisit rate.

Review: Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

Comparison: 1 Oral ondansetron (weight dependent dose) vs placebo

Outcome: 8 Revisit rate

Study or subgroup	Ondansetron n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Freedman 2006	20/105	22/101		90.2 %	0.87 [0.51, 1.50]
Ramsook 2002	4/74	0/71		2.1 %	8.64 [0.47, 157.62]
Roslund 2008	3/51	2/55		7.7 %	1.62 [0.28, 9.29]
Total (95% CI)	**230**	**227**		**100.0 %**	**1.09 [0.66, 1.79]**

Total events: 27 (Ondansetron), 24 (Placebo)

Heterogeneity: $Chi^2 = 2.79$, df = 2 (P = 0.25); $I^2 = 28\%$

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Admission, IV rehydration, and revisit rates (Freedman 2006)

	Ondansetron	Placebo
Admission rate (during ED stay)	4/107	5/107
Admission rate (Day 3)	10/107	11/103
IV rehydration rate (during ED stay)	15/107	33/107
IV rehydration (Day 3)	26/107	39/103
Revisit rate	20/105	22/101

Table 2. Admission, IV rehydration, and revisit rates (Ramsook 2002)

	Ondansetron	Placebo
Admission rate (during ED stay)	2/74	11/71
Admission rate (up to 48 hrs following discharge from ED stay)	2/74 to 6/74*	11/71
IV rehydration rate (during ED stay)	6/74	16/71
IV rehydration rate (up to 48 hrs following discharge from ED stay)	6/74 to 10/74*	16/71
Revisit rate	4/74	0/71

*Four participants from the ondansetron revisited the ED department and their original and revisit outcomes were unclear.

Table 3. Admission, IV rehydration, and revisit rates (Roslund 2008)

	Ondansetron	Placebo
Admission rate (during ED stay)	3/51	7/55
Admission rate (up to 72 hrs following discharge from ED stay)	6/51	8/55
IV rehydration rate (during ED stay)	11/51	30/55
IV rehydration rate (up to 72 hrs following discharge from ED stay)	13/51	31/55

Table 3. Admission, IV rehydration, and revisit rates (Roslund 2008) (*Continued*)

Revisit rate	3/51	2/55

Table 4. Admission rates (Yilmaz 2010)

Time period	**Ondansetron group**	**Placebo group**
8 hrs Admission rate	0/55	0/54
8 hrs IV rehydration	0/55	2/54
24 hrs Admission rate	2/55	10/54
24 hrs IV rehydration	1/55	1/54

Table 5. Random-effects sensitivity analysis

		95% Confidence Interval			
Analysis	Relative Risk	Lower	Upper	P-Value	I^2
1.1	0.43	0.18	1.00	0.05	17%
1.2	0.59	0.25	1.38	0.23	49%
1.3	0.73	0.43	1.23	0.24	0%
1.4	0.41	0.29	0.59	0.0001	0%
1.5	0.53	0.39	0.72	0.0001	0%
1.6	0.57	0.42	0.76	0.0002	0%
1.7	1.33	1.19	1.49	0.0001	0%
1.8	1.24	0.49	3.15	0.73	28%

Table 6. Participants with cessation of vomiting (Freedman 2006)

Ondansetron group	**Placebo group**
92/107	70/107

Table 7. Participants with cessation of vomiting (Ramsook 2002)

Time period	Ondansetron group	Placebo Group
ED Stay	64/71	46/71
0 to 24 hours	37/64	30/56
24 to 48 hours	43/62	30/51

Table 8. Participants with cessation of vomiting (Roslund 2008)

Ondansetron group	Placebo group
42/51	33/55

Table 9. Participants with cessation of vomiting 8hrs and 24 hrs (Yilmaz 2010)

Time period	Ondansetron group	Placebo group
8 hrs	43/55	18/54
24 hrs	49/55	15/54

Table 10. Tolerance of oral rehydration (Yilmaz 2010)

Time period	Ondansetron group	Placebo group	
8hrs	50/55	42/54	[RR=1.17; 95%CI=0.99 to 1.38].
24 hrs	no statistically significant difference between the two groups		

Table 11. Admission rate (Stork 2006)

Placebo/saline	Dexamethasone	Ondansetron
9/44	7/47	2/46

Table 12. Tolerance of oral rehydration (Stork 2006)

	Placebo/saline	Dexamethasone	Ondansetron
At 2 hours	29/43	26/42	39/45
At 4 hours	12/21	17/23	9/14

Table 13. Participants with no vomiting episodes (0-24hrs) (Cubeddu 1997)

Ondansetron	Metoclopramide	Placebo
7/12	4/12	2/12

Table 14. Time to cessation of vomiting (Uhlig 2009)

	Dimenhydrinate Group	Placebo Group	
Mean number of days	0.60	0.94	95% CI: -0.66 to -0.02

Table 15. Parental satisfaction/improvement in well being (Uhlig 2009)

	Dimenhydrinate Group (1=best, 6=worst)	Placebo Group (1=best, 6=worst)	
7-14 day follow up/telephone interview Mean score	2.39	2.31	Mean difference 0.08 95% CI: -0.28 to 0.45

Table 16. Admission rate (Uhlig 2009)

Time period	Dimenhydrinate Group	Placebo Group
18 to 24 hrs	4	5
Total over study period	10	13

Table 17. Research recommendations based on a gap in the evidence of antiemetic use for acute gastroenteritis in children and adolescents

Core elements	Issues to consider	Status of research for this review
Evidence (**E**)	What is the current state of evidence?	This systematic review identified seven RCTs which, although they failed to address the main primary outcome time to cessation of vomiting, provided some ev-

Table 17. Research recommendations based on a gap in the evidence of antiemetic use for acute gastroenteritis in children and adolescents (*Continued*)

		idence of the effectiveness and safety of the anti-emetic ondansetron in; increasing the number of participants with cessation of vomiting; and decreasing the number of children requiring intravenous rehydration and hospital admission for acute gastroenteritis
Population (**P**)	Diagnosis, disease stage, comorbidity, risk factor, sex, age, ethnic group, specific inclusion or exclusion criteria, clinical setting	Children and adolescents, under the age of 18yrs, who presented with vomiting and a confirmed clinical diagnosis of gastroenteritis with mild to moderate symptoms and in a range of settings i.e. general pediatric practice as well as hospital emergency department
Intervention (**I**)	Type, frequency, dose, duration, prognostic factor	Ondansetron • IV: 0.3 mg/kg; 0.15mg/kg • Oral: *Weight dependent*. 2mg (8 to 15 kgs), 4mg (15 to 30 kgs), 8mg (>30 kgs); 0.2mg/kg; 2 mg (<15 kgs), 4mg (15 to 30 kgs), 6mg(>30 kg). *Age dependent*. 6 mths to 1yr (1.6 mg),1 to 3 yrs(3.2 mg), 4 to 12 yrs (4 mg). Metoclopramide • IV: 0.3mg/kg Dexamethasone • IV: 1mg/kg (max 15mg) Dimenhydrinate • suppository:<15 kgs (40 mg), 15 to 25 kgs (80 mg), >25 kg (120 mg). Multiple dose and repeated dosing.
Comparison (**C**)	Type, frequency, dose, duration, prognostic factor	Other anti-emetics or placebo. Routes of administration i.e. intravenous versus oral. Multiple dose and repeated dosing
Outcome (**O**)	Which clinical or patient related outcomes will the researcher need to measure, improve, influence or accomplish? Which methods of measurement should be used?	Clinical outcomes: • different dosage regimes, • different settings (outpatient and home-based care); • hydration status and severity of disease • cost effectiveness of antiemetics by reducing requirement for IVF and hospitalization. Patient or carer preferred outcomes: • the time from administration of intervention to cessation of vomiting • parental satisfaction Time-points: • during the ED stay • up to 72 hrs following discharge from the ED stay RR for dichotomous outcomes and MD or WMD for continuous outcomes

Table 17. Research recommendations based on a gap in the evidence of antiemetic use for acute gastroenteritis in children and adolescents (*Continued*)

Time Stamp (**T**)	Date of literature search or recommendation	20 July 2010
Study Type	What is the most appropriate study design to address the proposed question?	Randomized controlled trial (adequately powered/multi centred) Methods: concealment of allocation sequence Blinding: patients, therapist, trialists, outcomes assessors, data analysts Setting: inpatient or outpatient care with adequate follow-up

Table 18. Baseline characteristics (Cubeddu 1997)

	Ondansetron Group	Metoclopramide Group	Placebo Group
Age in years, mean (range)	1.0, (0.5 to 2)	1.8 (0.5 to 8)	2.5 (0.5 to 8)
Height in cm, mean (range)	77.3, (64 to 97)	84.2, (67 to 118)	90.6 (72 to 121)
Body weight in kg, mean (range)	9.7 (6.2 to 16.0)	11.4, (6.8 to 23)	14.0, (8.7,32.3)

APPENDICES

Appendix 1. Search strategy for trials

gastroenteritis.tw.
exp rotavirus infections/
exp norwalk virus/
exp vomiting/
vomit$.tw.
exp diarrhea, infantile/
diarrhea.tw.
diarrhoea.tw.
exp dehydration/
dehydrat$.tw.
or/30-40
exp antiemetics/
exp dopamine antagonists/
(dopamin$ adj2 antagonists).tw.
chlorpromazine.tw.
droperidol.tw.
domperidone.tw .

metoclopramide.tw.
haloperidol.tw.
prochlorperazine.tw.
promethazine.tw.
exp serotonin antagonists/
serotonin adj2 antagonist$).tw.
dolasetron.tw .
granisetron.tw.
Ondansetron.tw.
tropisetron.tw.
exp anticholinergic agent/
scopolamine.tw.
exp antihistamines/
buclizine.tw.
cyclizine.tw.
dimenhydrinate.tw.
diphenhydramine.tw.
trimethobenzamide.tw.
meclizine.tw.
BENZODIAZEPINES/
lorazepam.tw .
exp corticosteroids/
dexamethasone.tw.
methylprednisolone.tw.
exp cannabinoids/
cannabinoid$.tw.
marijuana.tw.
marinol.tw.
or/42-75
infan$.tw.
child$.tw.
neonat$.tw.
pediatric$.tw.
paediatric$.tw.
juvenile$.tw.
or/77-82
41 and 76 and 83
84 and 29

Appendix 2. Amendments to search strategies May/June 2008

MEDLINE Update 29.5.08

Filter changed to new version of Cochrane RCT filter for Medline, sensitivity ? maximizing strategy (as per Cochrane Handbook v5)
Subject headings updated as follows:
exp anticholinergic agent changed to exp cholinergic antagonists
exp antihistamines changed to exp histamine H1 antagonists
exp corticosteroids changed to exp adrenal cortex hormones
The previously used subject headings listed above, were retained as .tw. searches.
Subject heading cannabis added for marijuana.tw. and the alternative spelling marihuana added as text word.
Subject heading benzodiazepines was exploded (after PS consulted Iris Gordon)

Subject headings added to the section relating to children, exp infant, exp child, exp child, preschool, exp adolescent. (after PS consulted Iris Gordon)

Embase Update 30.5.08

Filter subject headings updated as follows:
exp single blind method changed to exp single blind procedure
exp double blind method changed to exp double blind procedure
exp evaluation studies changed to exp evaluation
exp prospective studies changed to exp prospective study
Subject headings updated as follows:
exp rotavirus infections changed to exp virus infection
exp Norwalk virus changed to exp Norwalk gastroenteritis virus
exp diarrhea, infantile changed to exp infantile diarrhea
exp antiemetics changed to exp antiemetic agent
exp dopamine antagonists changed to dopamine receptor blocking agent
exp serotonin antagonists changed to exp serotonin antagonist
exp anticholinergic agent changed to cholinergic receptor blocking agent
exp cannabinoids changed to exp cannabinoid
benzodiazepines changed to exp benzodiazepine derivative
The previously used subject headings listed above, were retained as .tw. searches
Subject headings added to the section relating to children, exp infant, exp child, exp pediatrics, exp juvenile, exp adolescent.

EBMR Update 24.6.08

Additional subject headings were added into the children section of the search
Exp child
Exp child, preschool
Exp infant
Exp adolescent
RCT filter was updated

Appendix 3. CENTRAL search strategy

Updated strategy, run July 2010
1. exp gastroenteritis/
2. gastroenteritis.tw.
3. exp Rotavirus Infections/
4. exp Norwalk virus/ or norwalk virus.tw.
5. exp vomiting/
6. vomit$.tw.
7. exp Diarrhea, Infantile/
8. diarrhea.tw.
9. diarrhoea.tw.
10. exp dehydration/
11. dehydrat$.tw.
12. or/1-11
13. exp Antiemetics/ or antiemetic$.tw.
14. exp Dopamine Antagonists/
15. (dopamin$ adj2 antagonist$).tw.
16. (Chlorpromazine or aminazine or chloractil or chlordelazine or contomin or dozine or fenactil or largactil or ormazine or propaphenin or thorazine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

17. (droperidol or dehidrobenzperidol or droleptan or inapsine or Dridol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
18. (domperidon$ or domidon or evoxin or gastrocure or motilium or motillium or motinorm or costi or nauzelin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
19. (metoclopramide or cerucal or clopra or degan or gastrese or gastrobid continus or gastroflux or gastromax or maxolon or maxeran or metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid or primperan or pylomid or reglan or reliveran or rimetin).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
20. (haloperidol or dozic or Aloperidin or Bioperidolo or Brotopon Duraperidol or fortunan or haldol or kentace or Einalon or Eukystol, or Halosten or Keselan or Linton or Peluces or Serenase or Sigaperidol or serenace).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
21. (prochlorperazine or buccastem or compazine or compro or emezine or procot or proziere or Phenotil or stemetil or Stemzine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
22. (promethazine or Avomine or adgan or aler-dryl or aler-tab or aller-dryl topical or allergia or allermax or altaryl or anergan or antihist or antinaus or antituss or atosil or banaril or banophen or beldin or belix or ben tann or benadryl or benahist or bendylate or benekraft or benzhydramine or bromanate or calm-aid or derma-pax or dimedrol or dimine or diphen or diphenadryl or diphenhist or diphenhydramine or diphenmax or diphenyl or diphergan or diprazin or dormarex or dytan or dytuss or eldadryl or Fargan or Farganesse or genahist or hydramine or hyrexin or isopromethazine or Lergigan or medinex or nervine or nightcalm or nu-med or nytol or pardryl or paxidorm or pediacare or pentazine or phenadoz or phenazine or phendry or phenergan or phenerzine or phenoject or phensedyl or phenylbenzene or pipolphen or pro-med or proazamine or progan or promacot or promet or prometazin or promethegan or prorex or prothazin or Prothiazine or provigan or pyrethia or quenalin or remsed or Romergan or Receptozine or rumergan or siladryl or siladyl or silphen or sleep tab* or sleep-ettes or sleep-eze or sleepia or sleepinal or sominex or somnicaps or trux-adryl or tusstat or twilite or uni-hist or uni-tann or unisom sleepgels or unisom sleepmelts or valu-dryl or wehdryl or zipan).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
23. exp Serotonin Antagonists/
24. (serotonin adj2 antagonist$).tw.
25. (dolasetron or anzemet).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26. (granisetron or granisol or kytril or sancuso).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27. (Ondansetron or zensana or zofran).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
28. (tropisetron or Navoban or Setrovel).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
29. exp Cholinergic Antagonists/ or anticholinergic agent$.tw.
30. (scopolamine or atrochin or boroscopol or buscapine or buscolysin or buscopan or butylscopolamine or butylscopolammonium bromide or epoxytropine tropate or hyocine hydrobromide or hyoscinbutylbromide or hyoscine or kwell or levo-duboisine or maldemar or scoburen or scopace or scopoderm or scopolaminebutylbromide or scopolaminum hydrobromicum or scopolan or transderm or transderm-scop or travacalm or vorigeno).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
31. exp Histamine Antagonists/
32. buclizine.tw.
33. cyclizine.tw.
34. (dimenhydrinate or antimo or aviomarin or biodramina or cinfamar or contramareo or dimen heumann or dimen lichtenstein or dimetabs or dinate or diphenhydramine theoclate or dramamine or dramin or Driminate or dramanate or dramoject or dymenate or gravol or Gravamin or marmine or nausicalm or reisegold or reisetabletten ratiopharm or reisetabletten stada or rodovan or rubiemen or superpep or travel-eze or travel-wise or triptone or uni-calm or Vertirosan or Viabom or vomex or vomacur or vomisin or wehamine).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
35. (Trimethobenzamide or barogan or benzacot or tebamide or ticon or tigan).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
36. (meclizine or agyrax or antivert or bonamine or bonikraft or bonine or chiclida or histametizyn or meclicot or meclozine or medivert or parachloramine or ruvertm or univert).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
37. exp Benzodiazepines/
38. (lorazepam or almazine or apolorazepam or ativan or donix or durazolam or idalprem or laubeel or lorazep or novolorazem or nuloraz or orfidal wyeth or sedicepan or sinestron or somagerol or tolid or temesta).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
39. exp Adrenal Cortex Hormones/ or corticosteroids.tw.
40. (dexamethasone or aacidexam or adexone or adrenocot or aeroseb or aknichthol dexa or alba-dex or alin or ambene or amplidermis or anemul mono or antimicotico or aquapred or auricularum or auxiloson or azona or baycadron or baycuten or cebedex or corson

or cortastat or cortidex or cortidexason or cortisumman or corto-tavegil or dalalone or deca or decacort or decaderm or decadron or decalix or decasone or decaspray or dectancyl or deenar or dekasol or deronil or desamethasone or desameton or dexa-mamallet or dexa-rhinosan or dexa-scheroson or dexa-sine or dexacen or dexacort phosphate or dexacort* or dexafarma or dexafluorene or dexair or dexaject or dexalocal or dexamecortin or dexameth or dexamethasonedisodium phosphate or dexamethasonum or dexamonozon or dexapos or dexasol or dexasone or dexinoral or dexium or dexpak or dinormon or doxiproct or fluorodelta or fortecortin or gammacorten or hexadecadrol or hexadrol or lokalison or loverine or maxidex or medidex or metazone or methylfluorprednisolone or millicorten or mymethasone or ocasa or ocu-dex or oradexon or orgadrone or otomize or ozurdex or predni or primethasone or robadex or soludecadron or solurex or spersadex or trabit or visumetazone or voren).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

41. (methylprednisolone or a-methapred or adlone or ak-pred or ak-tate or aprednislon or articulose or asmacortone or balpred or blephamide liquifilm or bubbli-pred or caberdelta or capsoid or codelson or cortalone or corti-clyss or cortimed or cortisolone or cotolone or cryosolona or decaprednil or decortin or delta-cortef or delta-diona or delta-phoricol or deltacortilen or deltacortril or deltahydrocortisone or deltasolone or deltastab or deltidrosol or depmedalone or depo moderin or depo-medrol or depo-nisolone or depoject or depopred or dhasolone or di-adreson-f or diopred or dontisolon or duralone or duro cort or econopred or emmetipi or esametone or estilsona or firmacort or fisopred or flo-pred or frisolona or gupisone or hexacortone or hostacortin or hydeltra or hydeltrasol or hydrocortancyl or inf-oph or inflamase or inflanefran or isolone or key-pred or klismacort or kuhlprednon or lenisolone or lepicortinolo or locaseptil or longiprednil or med-jec or medicort or medlone or medrate or medrol or medrone or mega-star or meprdl or meprolone or metacortandralone or methacort or methylcotol or methylcotolone or methylone or methylpred or methylprednisolonum or meti derm or meticortelone or metilbetasone solubile or metipred or metrocort or metypresol or metysolon or millipred or ocu-pred or omnipred or ophtho-tate or opredsone or orapred or panafcortelone or pediapred or poly-pred liquifilm or polypred or precortalon aquosum or precortisyl or pred-clysma or pred-ject or pred-phosphate or predacorten or predair or predaject or predalone or predate or predcor or predeltilone or predenema or predfoam or predicort or predmix or prednabene or prednefrin or predni-coelin or predni or predni-helvacort or predni-m-tablinen or predni-pos or prednicortelone or prednihexal or prednilen or predniocil or prednisol or prednisolone or prednoral or predonine or predsol or prelone or pri-cortin or pri-methylate or pricortin or radilem or sano-drol or scherisolone-kristall or sieropresol or solpredone or solu moderin or solu-medrol or sterane or stintisone or summicort or urbason or urbasonsoluble or veripred or wyacort).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

42. exp cannabinoids/

43. cannabinoid$.tw.

44. (cannador or charas or ganja* or hashish or hemp or cannabis or marihuana or marijuana).tw.

45. (marinol or dronabinol or tetrahydrocannabinol).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

46. or/13-45

47. exp infant/ or infan$.tw.

48. exp child/ or child$.tw.

49. exp Child, Preschool/

50. neonat$.tw.

51. pediatric$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

52. paediatric$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]

53. juvenile$.tw.

54. exp adolescent/ or adolescen$.tw.

55. or/47-54

56. 12 and 46 and 55

57. limit 56 to yr="2008 -Current"

Appendix 4. MEDLINE search strategy

Updated strategy, run July 2010
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp gastroenteritis/
13. gastroenteritis.tw.
14. exp Rotavirus Infections/
15. exp Norwalk virus/ or norwalk virus.tw.
16. exp vomiting/
17. vomit$.tw.
18. exp Diarrhea, Infantile/
19. diarrhea.tw.
20. diarrhoea.tw.
21. exp dehydration/
22. dehydrat$.tw.
23. or/12-22
24. exp Antiemetics/ or antiemetic$.tw.
25. exp Dopamine Antagonists/
26. (dopamin$ adj2 antagonist$).tw.
27. (Chlorpromazine or aminazine or chloractil or chlordelazine or contomin or dozine or fenactil or largactil or ormazine or propaphenin or thorazine).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
28. (droperidol or dehidrobenzperidol or droleptan or inapsine or Dridol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
29. (domperidon$ or domidon or evoxin or gastrocure or motilium or motillium or motinorm or costi or nauzelin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
30. (metoclopramide or cerucal or clopra or degan or gastrese or gastrobid continus or gastroflux or gastromax or maxolon or maxeran or metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid or primperan or pylomid or reglan or reliveran or rimetin).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
31. (haloperidol or dozic or Aloperidin or Bioperidolo or Brotopon Duraperidol or fortunan or haldol or kentace or Einalon or Eukystol, or Halosten or Keselan or Linton or Peluces or Serenase or Sigaperidol or serenace).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
32. (prochlorperazine or buccastem or compazine or compro or emezine or procot or proziere or Phenotil or stemetil or Stemzine).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
33. (promethazine or Avomine or adgan or aler-dryl or aler-tab or aller-dryl topical or allergia or allermax or altaryl or anergan or antihist or antinaus or antituss or atosil or banaril or banophen or beldin or belix or ben tann or benadryl or benahist or bendylate or benekraft or benzhydramine or bromanate or calm-aid or derma-pax or dimedrol or dimine or diphen or diphenadryl or diphenhist or diphenhydramine or diphenmax or diphenyl or diphergan or diprazin or dormarex or dytan or dytuss or eldadryl or Fargan or Farganesse or genahist or hydramine or hyrexin or isopromethazine or Lergigan or medinex or nervine or nightcalm or nu-med or nytol or pardryl or paxidorm or pediacare or pentazine or phenadoz or phenazine or phendry or phenergan or phenerzine or phenoject or phensedyl or phenylbenzene or pipolphen or pro-med or proazamine or progan or promacot or promet or prometazin or promethegan or prorex or prothazin or Prothiazine or provigan or pyrethia or quenalin or remsed or Romergan or Receptozine or rumergan or siladryl or siladyl or silphen or sleep tab* or sleep-ettes or sleep-eze or sleepia or sleepinal or sominex or somnicaps or trux-adryl or tusstat or

twilite or uni-hist or uni-tann or unisom sleepgels or unisom sleepmelts or valu-dryl or wehdryl or zipan).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
34. exp Serotonin Antagonists/
35. (serotonin adj2 antagonist$).tw.
36. (dolasetron or anzemet).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
37. (granisetron or granisol or kytril or sancuso).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
38. (Ondansetron or zensana or zofran).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
39. (tropisetron or Navoban or Setrovel).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
40. exp Cholinergic Antagonists/ or anticholinergic agent$.tw.
41. (scopolamine or atrochin or boroscopol or buscapine or buscolysin or buscopan or butylscopolamine or butylscopolammonium bromide or epoxytropine tropate or hyocine hydrobromide or hyoscinbutylbromide or hyoscine or kwell or levo-duboisine or maldemar or scoburen or scopace or scopoderm or scopolaminebutylbromide or scopolaminum hydrobromicum or scopolan or transderm or transderm-scop or travacalm or vorigeno).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
42. exp Histamine Antagonists/
43. buclizine.tw.
44. cyclizine.tw.
45. (dimenhydrinate or antimo or aviomarin or biodramina or cinfamar or contramareo or dimen heumann or dimen lichtenstein or dimetabs or dinate or diphenhydramine theoclate or dramamine or dramin or Driminate or dramanate or dramoject or dymenate or gravol or Gravamin or marmine or nausicalm or reisegold or reisetabletten ratiopharm or reisetabletten stada or rodovan or rubiemen or superpep or travel-eze or travel-wise or triptone or uni-calm or Vertirosan or Viabom or vomex or vomacur or vomisin or wehamine).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
46. (Trimethobenzamide or barogan or benzacot or tebamide or ticon or tigan).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
47. (meclizine or agyrax or antivert or bonamine or bonikraft or bonine or chiclida or histametizyn or meclicot or meclozine or medivert or parachloramine or ruvertm or univert).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
48. exp Benzodiazepines/
49. (lorazepam or almazine or apolorazepam or ativan or donix or durazolam or idalprem or laubeel or lorazep or novolorazem or nuloraz or orfidal wyeth or sedicepan or sinestron or somagerol or tolid or temesta).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
50. exp Adrenal Cortex Hormones/ or corticosteroids.tw.
51. (dexamethasone or aacidexam or adexone or adrenocot or aeroseb or aknichthol dexa or alba-dex or alin or ambene or amplidermis or anemul mono or antimicotico or aquapred or auricularum or auxiloson or azona or baycadron or baycuten or cebedex or corson or cortastat or cortidex or cortidexason or cortisumman or corto-tavegil or dalalone or deca or decacort or decaderm or decadron or decalix or decasone or decaspray or dectancyl or deenar or dekasol or deronil or desamethasone or desameton or dexa-mamallet or dexa-rhinosan or dexa-scheroson or dexa-sine or dexacen or dexacort phosphate or dexacort* or dexafarma or dexafluorene or dexair or dexaject or dexalocal or dexamecortin or dexameth or dexamethasonedisodium phosphate or dexamethasonum or dexamonozon or dexapos or dexasol or dexasone or dexinoral or dexium or dexpak or dinormon or doxiproct or fluorodelta or fortecortin or gammacorten or hexadecadrol or hexadrol or lokalison or loverine or maxidex or medidex or metazone or methylfluorprednisolone or millicorten or mymethasone or ocasa or ocu-dex or oradexon or orgadrone or otomize or ozurdex or predni or primethasone or robadex or soludecadron or solurex or spersadex or trabit or visumetazone or voren).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
52. (methylprednisolone or a-methapred or adlone or ak-pred or ak-tate or aprednislon or articulose or asmacortone or balpred or blephamide liquifilm or bubbli-pred or caberdelta or capsoid or codelson or cortalone or corti-clyss or cortimed or cortisolone or cotolone or cryosolona or decaprednil or decortin or delta-cortef or delta-diona or delta-phoricol or deltacortilen or deltacortril or deltahydrocortisone or deltasolone or deltastab or deltidrosol or depmedalone or depo moderin or depo-medrol or depo-nisolone or depoject or depopred or dhasolone or di-adreson-f or diopred or dontisolon or duralone or duro cort or econopred or emmetipi or esametone or estilsona or firmacort or fisopred or flo-pred or frisolona or gupisone or hexacortone or hostacortin or hydeltra or hydeltrasol or hydrocortancyl or inf-oph or inflamase or inflanefran or isolone or key-pred or klismacort or kuhlprednon or lenisolone or lepi-

cortinolo or locaseptil or longiprednil or med-jec or medicort or medlone or medrate or medrol or medrone or mega-star or meprdl or meprolone or metacortandralone or methacort or methylcotol or methylcotolone or methylone or methylpred or methylprednisolonum or meti derm or meticortelone or metilbetasone solubile or metipred or metrocort or metypresol or metysolon or millipred or ocu-pred or omnipred or ophtho-tate or opredsone or orapred or panafcortelone or pediapred or poly-pred liquifilm or polypred or precortalon aquosum or precortisyl or pred-clysma or pred-ject or pred-phosphate or predacorten or predair or predaject or predalone or predate or predcor or predeltilone or predenema or predfoam or predicort or predmix or prednabene or prednefrin or predni-coelin or predni or predni-helvacort or predni-m-tablinen or predni-pos or prednicortelone or prednihexal or prednilen or predniocil or prednisol or prednisolone or prednoral or predonine or predsol or prelone or pri-cortin or pri-methylate or pricortin or radilem or sano-drol or scherisolone-kristall or sieropresol or solpredone or solu moderin or solu-medrol or sterane or stintisone or summicort or urbason or urbasonsoluble or veripred or wyacort).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
53. exp cannabinoids/
54. cannabinoid$.tw.
55. (cannador or charas or ganja* or hashish or hemp or cannabis or marihuana or marijuana).tw.
56. (marinol or dronabinol or tetrahydrocannabinol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
57. or/24-56
58. exp infant/ or infan$.tw.
59. exp child/ or child$.tw.
60. exp Child, Preschool/
61. neonat$.tw.
62. pediatric$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
63. paediatric$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
64. juvenile$.tw.
65. exp adolescent/ or adolescen$.tw.
66. or/58-65
67. 23 and 57 and 66
68. 11 and 67
69. limit 68 to ed=20080515-20100704

Appendix 5. EMBASE search strategy

Updated strategy, run July 2010
1. exp randomized controlled trial/
2. randomized controlled trial$.tw.
3. exp randomization/
4. exp single blind procedure/
5. exp double blind procedure/
6. or/1-5
7. animal.hw.
8. human.hw.
9. 7 not (7 and 8)
10. 6 not 9
11. exp clinical trial/
12. (clin$ adj3 (stud$ or trial$)).ti,ab,tw.
13. (clin$ adj3 trial$).ti,ab,tw.
14. ((singl$ or doubl$ or treb$ or tripl$) adj3 (blind$ or mask$)).ti,ab,tw.
15. exp placebo/
16. placebo$.ti,ab,tw.
17. random.ti,ab,tw.
18. (crossover$ or cross-over$).ti,ab,tw.
19. or/11-18

20. 19 not 9
21. 20 not 10
22. exp comparative study/
23. exp evaluation/
24. exp prospective study/
25. exp controlled study/
26. (control$ or prospective$ or volunteer$).ti,ab,tw.
27. or/22-26
28. 27 not 9
29. 10 or 21 or 28
30. exp gastroenteritis/
31. gastroenteritis.tw.
32. exp virus infection/ or rotavirus infection$.tw.
33. exp norwalk gastroenteritis virus/ or norwalk virus.tw.
34. exp vomiting/
35. vomit$.tw.
36. exp infantile diarrhea/
37. diarrhea.tw.
38. diarrhoea.tw.
39. exp dehydration/
40. dehydrat$.tw.
41. or/30-40
42. exp antiemetic agent/ or antiemetic$.tw.
43. exp dopamine receptor blocking agent/
44. (dopamin$ adj2 antagonists).tw.
45. (Chlorpromazine or aminazine or chloractil or chlordelazine or contomin or dozine or fenactil or largactil or ormazine or propaphenin or thorazine).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
46. (droperidol or dehidrobenzperidol or droleptan or inapsine or Dridol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
47. (domperidon$ or domidon or evoxin or gastrocure or motilium or motillium or motinorm or costi or nauzelin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
48. (metoclopramide or cerucal or clopra or degan or gastrese or gastrobid continus or gastroflux or gastromax or maxolon or maxeran or metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid or primperan or pylomid or reglan or reliveran or rimetin).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
49. (haloperidol or dozic or Aloperidin or Bioperidolo or Brotopon Duraperidol or fortunan or haldol or kentace or Einalon or Eukystol, or Halosten or Keselan or Linton or Peluces or Serenase or Sigaperidol or serenace).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
50. (prochlorperazine or buccastem or compazine or compro or emezine or procot or proziere or Phenotil or stemetil or Stemzine).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
51. (promethazine or Avomine or adgan or aler-dryl or aler-tab or aller-dryl topical or allergia or allermax or altaryl or anergan or antihist or antinaus or antituss or atosil or banaril or banophen or beldin or belix or ben tann or benadryl or benahist or bendylate or benekraft or benzhydramine or bromanate or calm-aid or derma-pax or dimedrol or dimine or diphen or diphenadryl or diphenhist or diphenhydramine or diphenmax or diphenyl or diphergan or diprazin or dormarex or dytan or dytuss or eldadryl or Fargan or Farganesse or genahist or hydramine or hyrexin or isopromethazine or Lergigan or medinex or nervine or nightcalm or nu-med or nytol or pardryl or paxidorm or pediacare or pentazine or phenadoz or phenazine or phendry or phenergan or phenerzine or phenoject or phensedyl or phenylbenzene or pipolphen or pro-med or proazamine or progan or promacot or promet or prometazin or promethegan or prorex or prothazin or Prothiazine or provigan or pyrethia or quenalin or remsed or Romergan or Receptozine or rumergan or siladryl or siladyl or silphen or sleep tab* or sleep-ettes or sleep-eze or sleepia or sleepinal or sominex or somnicaps or trux-adryl or tusstat or twilite or uni-hist or uni-tann or unisom sleepgels or unisom sleepmelts or valu-dryl or wehdryl or zipan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
52. exp serotonin antagonist/

53. (serotonin adj2 antagonist$).tw.
54. (dolasetron or anzemet).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
55. (granisetron or granisol or kytril or sancuso).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
56. (Ondansetron or zensana or zofran).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
57. (tropisetron or Navoban or Setrovel).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
58. exp cholinergic receptor blocking agent/ or anticholinergic agent$.tw.
59. (scopolamine or atrochin or boroscopol or buscapine or buscolysin or buscopan or butylscopolamine or butylscopolammonium bromide or epoxytropine tropate or hyocine hydrobromide or hyoscinbutylbromide or hyoscine or kwell or levo-duboisine or maldemar or scoburen or scopace or scopoderm or scopolaminebutylbromide or scopolaminum hydrobromicum or scopolan or transderm or transderm-scop or travacalm or vorigeno).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
60. exp antihistaminic agent/
61. buclizine.tw.
62. cyclizine.tw.
63. (dimenhydrinate or antimo or aviomarin or biodramina or cinfamar or contramareo or dimen heumann or dimen lichtenstein or dimetabs or dinate or diphenhydramine theoclate or dramamine or dramin or Driminate or dramanate or dramoject or dymenate or gravol or Gravamin or marmine or nausicalm or reisegold or reisetabletten ratiopharm or reisetabletten stada or rodovan or rubiemen or superpep or travel-eze or travel-wise or triptone or uni-calm or Vertirosan or Viabom or vomex or vomacur or vomisin or wehamine).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
64. (Trimethobenzamide or barogan or benzacot or tebamide or ticon or tigan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
65. (meclizine or agyrax or antivert or bonamine or bonikraft or bonine or chiclida or histametizyn or meclicot or meclozine or medivert or parachloramine or ruvertm or univert).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
66. exp benzodiazepine derivative/
67. (lorazepam or almazine or apolorazepam or ativan or donix or durazolam or idalprem or laubeel or lorazep or novolorazem or nuloraz or orfidal wyeth or sedicepan or sinestron or somagerol or tolid or temesta).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
68. exp corticosteroid/
69. (dexamethasone or aacidexam or adexone or adrenocot or aeroseb or aknichthol dexa or alba-dex or alin or ambene or amplidermis or anemul mono or antimicotico or aquapred or auricularum or auxiloson or azona or baycadron or baycuten or cebedex or corson or cortastat or cortidex or cortidexason or cortisumman or corto-tavegil or dalalone or deca or decacort or decaderm or decadron or decalix or decasone or decaspray or dectancyl or deenar or dekasol or deronil or desamethasone or desameton or dexa-mamallet or dexa-rhinosan or dexa-scheroson or dexa-sine or dexacen or dexacort phosphate or dexacort* or dexafarma or dexafluorene or dexair or dexaject or dexalocal or dexamecortin or dexameth or dexamethasonedisodium phosphate or dexamethasonum or dexamonozon or dexapos or dexasol or dexasone or dexinoral or dexium or dexpak or dinormon or doxiproct or fluorodelta or fortecortin or gammacorten or hexadecadrol or hexadrol or lokalison or loverine or maxidex or medidex or metazone or methylfluorprednisolone or millicorten or mymethasone or ocasa or ocu-dex or oradexon or orgadrone or otomize or ozurdex or predni or primethasone or robadex or soludecadron or solurex or spersadex or trabit or visumetazone or voren).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
70. (methylprednisolone or a-methapred or adlone or ak-pred or ak-tate or aprednislon or articulose or asmacortone or balpred or blephamide liquifilm or bubbli-pred or caberdelta or capsoid or codelson or cortalone or corti-clyss or cortimed or cortisolone or cotolone or cryosolona or decaprednil or decortin or delta-cortef or delta-diona or delta-phoricol or deltacortilen or deltacortril or deltahydrocortisone or deltasolone or deltastab or deltidrosol or depmedalone or depo moderin or depo-medrol or depo-nisolone or depoject or depopred or dhasolone or di-adreson-f or diopred or dontisolon or duralone or duro cort or econopred or emmetipi or esametone or estilsona or firmacort or fisopred or flo-pred or frisolona or gupisone or hexacortone or hostacortin or hydeltra or hydeltrasol or hydrocortancyl or inf-oph or inflamase or inflanefran or isolone or key-pred or klismacort or kuhlprednon or lenisolone or lepicortinolo or locaseptil or longiprednil or med-jec or medicort or medlone or medrate or medrol or medrone or mega-star or meprdl or meprolone or metacortandralone or methacort or methylcotol or methylcotolone or methylone or methylpred or methylprednisolonum

or meti derm or meticortelone or metilbetasone solubile or metipred or metrocort or metypresol or metysolon or millipred or ocu-pred or omnipred or ophtho-tate or opredsone or orapred or panafcortelone or pediapred or poly-pred liquifilm or polypred or precortalon aquosum or precortisyl or pred-clysma or pred-ject or pred-phosphate or predacorten or predair or predaject or predalone or predate or predcor or predeltilone or predenema or predfoam or predicort or predmix or prednabene or prednefrin or predni-coelin or predni or predni-helvacort or predni-m-tablinen or predni-pos or prednicortelone or prednihexal or prednilen or predniocil or prednisol or prednisolone or prednoral or predonine or predsol or prelone or pri-cortin or pri-methylate or pricortin or radilem or sano-drol or scherisolone-kristall or sieropresol or solpredone or solu moderin or solu-medrol or sterane or stintisone or summicort or urbason or urbasonsoluble or veripred or wyacort).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
71. exp cannabinoid/
72. cannabinoid$.tw.
73. (cannador or charas or ganja* or hashish or hemp or cannabis or marihuana or marijuana).tw.
74. (marinol or dronabinol or tetrahydrocannabinol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
75. or/42-74
76. exp infant/ or infan$.tw.
77. exp child/ or child$.tw.
78. neonat$.tw.
79. exp pediatrics/ or pediatric$.tw.
80. paediatric$.tw.
81. exp juvenile/ or juvenile$.tw. or exp adolescent/
82. or/76-81
83. 41 and 75 and 82
84. 29 and 83
85. chemotherapy.ti.
86. operat$.ti.
87. surg$.ti.
88. strab$.ti.
89. tonsil$.ti.
90. anesth$.ti.
91. migraine.ti.
92. colitis.ti.
93. crohn$.ti.
94. or/85-93
95. 84 not 94
96. limit 95 to (editorial or letter or note or "review" or short survey)
97. 95 not 96
98. limit 97 to em=200824-201028

WHAT'S NEW

Last assessed as up-to-date: 30 November 2010.

Date	Event	Description
1 July 2011	New search has been performed	We re-ran the literature searches and updated the review to include three new studies

(*Continued*)

1 July 2010	New citation required and conclusions have changed	Post hoc changes include: amendments to outcomes, and sensitivity analyses to explore the effects of missing data on several outcomes

HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 3, 2006

Date	Event	Description
5 February 2009	New citation required but conclusions have not changed	Updated, new citation.
29 January 2009	New search has been performed	Text in 'Assessment of risk of bias in included studies' modified
15 October 2008	Amended	Converted to new review format.
23 June 2008	New search has been performed	Amendments and additions to the search strategy and new searches
7 December 2006	New search has been performed	New studies sought but none found.
21 August 2006	New citation required and conclusions have changed	Substantive amendment.
28 July 2006	New search has been performed	New studies found and included or excluded.
11 January 2005	New search has been performed	Minor update.

CONTRIBUTIONS OF AUTHORS

Dunia Alhashimi (DAH) and Zbys Fedorowicz (ZF) were responsible for:

Designing the review

Co-ordinating the review

Performing previous work that was the foundation of current study

DAH, ZF, Hakima Alhashimi (HAH) and Ben Carter (BC) were responsible for:

Data collection for the review

Screening the search results

Screening retrieved papers against inclusion criteria

Appraising quality of papers

Abstracting data from papers

Obtaining and screening data on unpublished studies

Entering data into RevMan

Analysis of data

Interpretation of data

Writing the review

ZF and BC DAH were responsible for:

Organising retrieval of papers

Writing to authors of papers for additional information

Providing additional data about papers

BC was responsible for the data analysis

DAH conceived the idea for the review

BC and ZF were responsible for:

Contacting authors for clarification

Updating the current version of this review

ZF is the guarantor for the review

DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the reviewers declare that they do not have any associations with any parties who may have vested interests in the results of this review. Dr Cathy Bennett is the proprietor of Systematic Research Ltd. and received payment for her contribution to the process of updating an earlier version of the review.

SOURCES OF SUPPORT

Internal sources

- Ministry of Health, Bahrain.
- Department of Public Health and Primary Care, School of Medicine, Cardiff University, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Several post hoc changes were made to the review. A further secondary outcome was added: mean number of episodes of vomiting and proportion of patients with reduction in vomiting. The expected positive effect of the intervention is to reduce emesis and this can be more directly addressed by this new outcome.

Changes were also made to the secondary outcomes to include hospitalization rates and intravenous rehydration rates at specific and clinically important time-points i.e. at discharge and up to 72 hours following discharge. Assessments of these outcomes at these time-points could help provide additional valuable decision-making information to clinicians on the effectiveness or otherwise of these interventions.

The methodology section of the review has been updated to incorporate the analyses that we have conducted in addition to a sensitivity analysis examining the effect of missing data on the robustness of our review results, such that these can then be compared with other published reviews.

NOTES

Only one of the trials included in this systematic review addressed our primary outcome "the time taken from the first administration of treatment measure to cessation of vomiting", and therefore we report principally the outcomes presented in the seven included trials, which specifically relate to several of the secondary outcomes in the protocol of this review. Two trials are awaiting assessment and, if data relevant to the outcomes of this review become available, we will update the review accordingly.

The review was updated in 2009. At this update, the section 'Assessment of risk of bias in included studies' was modified to comply with changes in RevMan 5.0 software and the publication of Higgins 2011.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adolescent; Antiemetics [adverse effects; *therapeutic use]; Fluid Therapy [statistics & numerical data]; Gastroenteritis [*complications]; Hospitalization [statistics & numerical data]; Metoclopramide [adverse effects; therapeutic use]; Ondansetron [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Vomiting [*drug therapy; etiology]

MeSH check words

Child; Child, Preschool; Humans