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

Alhashimi D, Al-Hashimi H, Fedorowicz Z
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**ABSTRACT**

**Background**

Vomiting caused by acute gastroenteritis is very common in children and adolescents. Treatment of vomiting in children can be problematic and the use of antiemetics remains a controversial issue. There have been concerns expressed about apparently unacceptable levels of side effects such as sedation and extrapyramidal reactions, which are associated with some of the earlier generation of antiemetics.

**Objectives**

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

**Search strategy**

We searched the Cochrane Central register of Controlled Trials (CENTRAL), which includes the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group Trials Register (searched 28 July 2005), MEDLINE (1966 to July 2005) and EMBASE (1980 to July 2005). Published abstracts from conference proceedings from the United European Gastroenterology Week and Digestive Disease Week were handsearched. Cochrane UGPD Group members were contacted for details of any ongoing or relevant unpublished clinical trials. The search was re-run on 12th July 2006 and 24th June 2008 and two further trials were found.

**Selection criteria**

Randomised controlled trials comparing antiemetics and/or placebo in children and adolescents, under the age of 18, with vomiting due to gastroenteritis.

**Data collection and analysis**

Two reviewers independently assessed trial quality and extracted data. Study investigators were contacted for additional information.

**Main results**

Four trials involving 501 participants were included. No data was available for the precise time to cessation of vomiting: one trial reported a higher proportion of patients without vomiting over 24 hours in the ondansetron and metoclopramide groups than placebo. Oral ondansetron in one trial ensured cessation of emesis for 8/12 (67%) patients within the first 4 hours and 7/12 (58%) patients in the first 24 hr period. In one trial 14% of patients who received oral ondansetron vomited during oral rehydration compared to 35% to the placebo group. In a further trial intravenous rehydration was required in 21.6% (ondansetron group) versus 54.5% (placebo group) P< 0.001.
Authors’ conclusions

The small number of included trials provided some limited evidence favouring the use of ondansetron and metoclopramide over placebo to reduce the number of episodes of vomiting due to gastroenteritis in children. The increased incidence of diarrhea with both ondansetron and metoclopramide was considered to be as a result of retention of fluids and toxins that would otherwise have been eliminated through the process of vomiting.

PLAIN LANGUAGE SUMMARY

Anti-sickness medications 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 can be problematic and the use of antiemetics remains a controversial issue. There have been concerns expressed about apparently unacceptable levels of side effects. The small number of included trials provided some, albeit weak and unreliable, evidence which appeared to favor the use of ondansetron and metoclopramide over placebo to reduce the number of episodes of vomiting due to gastroenteritis in children. The increased incidence of diarrhea noted with both ondansetron and metoclopramide was considered to be as a result of retention of fluids and toxins that would otherwise have been eliminated through the process of vomiting.

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 over 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 requiring over 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 3 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 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).

Several studies have investigated the effectiveness of prochlorperazine, promethazine hydrochloride, and metoclopramide as antiemetic medications. However, there have been concerns expressed about some of the adverse effects, such as sedation and extrapyramidal reactions, that have been associated with some of these medications. Quite surprisingly, very few of these reports relate directly to children, and the frequencies of such adverse events in pediatric populations are somewhat difficult to determine. The adverse effects of metoclopramide in young children have been well documented and may include fatigue and such extrapyramidal phenomena as dystonia, dyskinesia, akathisia, opisthotonos, and oculogyric crises (Taylor 1999).

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**

Concerns have been expressed about the side effects of antiemetics prescribed to children with vomiting. Several randomised control trials have investigated the effectiveness of different antiemetics but to the present time there has not been a systematic review of the evidence for the effectiveness of these medicines.

**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 and the eventual resumption of oral rehydration therapy.

The following null hypothesis was tested: for gastroenteritis induced vomiting there is no difference in the time taken to achieve cessation of vomiting between patients taking antiemetics as compared to those who have received placebo or nothing.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We only considered randomised 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. Any studies in which patients were vomiting as a result of general anaesthesia or due to chemotherapy were excluded. In addition, 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), were excluded.
infections, pneumonia, meningitis), or metabolic conditions (diabetes mellitus or any other previously diagnosed disorders, including immunodeficiency) were excluded.

Types of interventions

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

Control
Administration of placebo or nothing prescribed to terminate vomiting.

Types of outcome measures

Primary outcomes
The primary outcome for this review was the time taken from the first administration of the treatment measure till 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 subjects who had been admitted due to intractable vomiting.
- Number of subjects who required intravenous fluids.
- Time taken to reduction of episodes of vomiting.
- Number of subjects who revisited.
- Number of subjects resumed oral rehydration.

Search methods for identification of studies

Electronic searches
Searches were conducted on 28th July 2005, and have been updated subsequently, to identify all published and unpublished randomised controlled trials.

There were no language or date restrictions in the electronic searches.

The search strategy for this review was constructed by using a combination of MESH subject headings and text words relating to the use of antiemetics for the treatment of gastroenteritis in children.

Trials were identified 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 2005, Issue 2);
- MEDLINE (1966 to July 2005); and

To identify randomised controlled trials, the search strategy in Appendix 1 was combined with the Cochrane Highly Sensitive Search Strategy phases one, two and three, as contained in the Cochrane Reviewers' Handbook 4.2.5 (Higgins 2005). This search was re-run on 12th July 2006 and one new trial was found. Amendments and additions were made to these earlier search strategies and updated searches were re-run in June 2008 and two new trials were found. For further details see Appendix 2.

Searching other resources
Reference lists from trials selected by electronic searching were handsearched to identify further relevant trials. Published abstracts from conference proceedings from the United European Gastroenterology Week (published in Gut) and Digestive Disease Week (published in Gastroenterology) were handsearched.

In addition members of the Cochrane UGPD Group and experts in the field were contacted and asked to provide details of any ongoing clinical trials and any relevant unpublished materials.

Data collection and analysis

Selection of studies
The abstracts of studies resulting from the searches were independently assessed by two reviewers (DAH/ZF) and all irrelevant studies were excluded. 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, were obtained. Studies not matching our inclusion criteria were excluded and their details and reasons for their exclusion were noted in the ‘Characteristics of excluded studies’.

Data extraction and management
Study details were entered into the ‘Characteristics of included studies’ table in RevMan 5. Outcomes data were collected using a pre-determined form and entered into RevMan 5. The review authors only included data if there was an independently reached
consensus. All disagreements were discussed and resolved by consulting with a third review author Hakima Alhashimi (HAH). The following details were extracted.

1. Study methods: method of allocation, masking of participants and outcomes, exclusion of participants after randomisation 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 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: any adverse effects related to any clinically diagnosed hypersensitivity or other adverse reactions or side effects to the antiemetics were noted. This information was used to help us assess heterogeneity and the external validity of the trials.

Assessment of risk of bias in included studies
Each of the two reviewers then graded the selected studies separately and every study reporting a randomised controlled clinical trial was assessed using a simple contingency form and followed the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.0 (Higgins 2008). The gradings were compared and any inconsistencies in the assessments between the reviewers were discussed and resolved. The following domains were assessed as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (i.e. high risk of bias):

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcomes assessors);
4. incomplete outcome data;
5. selective outcome reporting

These assessments are reported for each individual study in the 'Risk of bias in included studies' table.

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 as specified in the 'Criteria for considering studies for this review'.

Data synthesis
Due to significant clinical heterogeneity and the paucity of data in the few included studies, we were unable to carry out a meta-analysis of the extracted data and therefore only provide a descriptive summary of results of the individual trials. RevMan 2008 will be used to analyse data, should this be possible in updated versions of this review.

Sensitivity analysis
There were insufficient included studies in this systematic review and therefore no attempt was made to conduct a sensitivity analysis.

RESULTS

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

Results of the search
The initial search strategy identified 2443 references (the Cochrane Library = 644, MEDLINE = 628, EMBASE = 1171). After examination of the titles and abstracts of these references, all but six studies were eliminated and excluded from further review. Full text copies of the six remaining studies were obtained and subjected to further evaluation. A search conducted in July 2006 for new trials identified one prospective double blind randomised trial comparing ondansetron and placebo to control vomiting among children 6 months to 10 years (Freedman 2006). In June 2008, updated searches were carried out and a further trial, Roslund 2008, was identified. This study was found to have several errata in the text. ZF wrote to the journal editors who provided clarification.

Included studies
Four trials were included: Cubeddu 1997; Freedman 2006; Ramsook 2002; Roslund 2008. Further details of these are available in the Characteristics of included studies tables. Even though all of the included studies did not fully address the primary outcomes specified in the protocol for this review and therefore did not totally match our inclusion criteria, it was considered that their inclusion and the reporting of their results, some of which matched our secondary outcomes, might help to provide some evidence towards answering this research question. There were some differences between the studies, and we summarise these differences and the main study characteristics below. For further details please see ('Characteristics of included studies').
Methods

All four trials were randomised, double blind, placebo controlled. The total sample size comprised 501 children (272 males and 229 females): Cubeddu 1997 (36); Freedman 2006 (214); Ramsook 2002 (145); Roslund 2008 (106).

Participants and setting

The trials were conducted in the emergency departments of children's hospitals in the USA, Canada and Venezuela and the age of participants ranged from six months to 12 years and the inclusion criteria for enrolment were similar for all four of the studies. The studies were conducted over different time periods. In the Ramsook 2002 study, the patients were discharged to home care after the initial observation period in the emergency department and were followed up for up to 48 hrs, 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 goals and daily follow up continued until symptoms resolved. Patients in Freedman 2006 were only followed up on day 3 and 7 after randomisation.

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 as “the presence of vomiting with or without diarrhoea”. Freedman did not investigate the cause of the gastroenteritis but considered “all children with symptoms consistent with gastroenteritis” eligible for screening Freedman 2006.

Intervention

In three of the trials Freedman 2006; Ramsook 2002; Roslund 2008 participants received orally dissolving tablets of ondansetron or placebo whereas participants in Cubeddu 1997 received either ondansetron hydrochloride dihydrate, metoclopramide hydrochloride, or sterile saline solution (placebo) administered as a single intravenous dose. A single oral dose of ondansetron or placebo was administered in Freedman 2006; Roslund 2008 while in Ramsook 2002 participants received six doses over 48 hours.

In Freedman 2006 intensive oral rehydration therapy 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 thirty minutes after the intervention and, which if they failed, received intravenous rehydration and were considered a treatment failure.

All participants in Cubeddu 1997 were hospitalised for a minimum of 24 hours, orally rehydrated and none received any intravenous fluids but in the remaining three trials if the participants failed oral rehydration or continued to vomit they were admitted, intravenous rehydration was instituted and they were considered treatment failures. Discharge from the emergency department was dependent on oral rehydration status in these three studies.

Only in the Cubeddu 1997 study did the trialists use the WHO standard formulation for oral rehydration fluid. Both Ramsook 2002 and Freedman 2006 used a reduced osmolality formula i.e. Pedialyte and Enfalyte respectively.

Outcomes

The primary outcome for this review (the time taken from the first administration of the treatment measure till cessation of vomiting) was not addressed by any of the included studies, and although none provided explicit data for one of our secondary outcomes (the precise time taken for a reduction in the number of episodes of vomiting) all of them Cubeddu 1997; Freedman 2006; Ramsook 2002; Roslund 2008 did partially address this outcome as the number of vomiting episodes over set periods of time up to and after discharge.

Data for the secondary outcomes of rates of intravenous rehydration and re-hospitalisation were reported in three of the trials Freedman 2006; Ramsook 2002; Roslund 2008. While hospitalisation 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 carer’s in the three 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 to the trialists to confirm the data which had previously been obtained over the telephone but the trialists indicated that losses to telephone follow up and mail-in diary accounted for 10-15% of participants in this study. The carers in the Freedman 2006 study were interviewed on day 3 and 7 by a research assistant and asked whether the child had returned to an emergency department, had been admitted or received intravenous rehydration. In this study follow up on day 3 was 100% for the intervention group and 96% for the placebo group.

Standardised daily symptom diaries were provided for parents or guardians of all participants in Roslund 2008 and were followed-up with daily telephone interviews until symptoms resolved. The symptom diaries and telephone interviews sought information on the number of episodes of vomiting per day. However only 10% of symptom diaries were returned whereas 94% (ondansetron group) and 88% (placebo group) of the carers participated in the telephone interviews.

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

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.

**Excluded studies**

Two studies were excluded, please see Characteristics of excluded studies for details. The Ginsburg study was a non randomised 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**

The Debray trial was translated from the French into the English language and was then assessed 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 over 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, this review will be updated 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 are 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.

Yılmaz 2008, which was identified when we carried out updated searches in June 2008, is a conference proceeding and we have been unable to contact the study investigators to clarify important trial details.

**Risk of bias in included studies**

We assessed each study for risk of bias, please see 'Assessment of risk of bias in included studies'.

**Allocation**

**Randomisation**

In Cubeddu 1997 the investigators stated that the participants were randomly assigned to interventions and control, but the method used to achieve randomisation was not explicit thus this domain was judged unclear. Participants in Freedman 2006 were randomised in blocks of six and an "independent statistician provided the code to the pharmacy", thus randomisation was assessed as adequate. Albeit the investigators in Roslund 2008 only stated that they randomised the participants in blocks of 10, the report also included a Trial flow chart which referred to “Block Randomization.com”, an Internet based randomisation generator, and therefore this domain was judged as clear. In Ramsook 2002 the method used to randomise participants was described as, “using standard random number allocation tables” and thus was judged as clear.

**Allocation concealment**

The allocation sequence was considered to have been adequately concealed by the investigators in Ramsook 2002 who stated that the randomisation 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" and therefore judged adequate. In Freedman 2006 the pharmacy code was provided by an independent statistician and the weight-appropriate intervention was placed in an opaque bag and therefore allocation concealment was considered adequate. It was not possible to ascertain from the trial details reported in Roslund 2008 if adequate measures were taken to ensure that investigators were unaware of the upcoming assignment and thus this domain was judged as unclear.

**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 this domain was graded as ‘unclear’. Blinding of participants, healthcare providers and outcomes assessors was adequately described in Freedman 2006 and was judged as ‘yes’. In Ramsook 2002 knowledge of the allocated interventions by the participants, the emergency department staff, patients, carers and outcomes assessors was adequately prevented during the course of the study and thus this criterion was judged as ‘yes’. 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 ‘yes’.

**Incomplete outcome data**

Losses to follow and ‘treatment failures’ were clearly reported in all four trials Cubeddu 1997; Freedman 2006; Ramsook 2002
and Roslund 2008. Trial Randomisation Flow diagrams which comprehensively charted the path of all the participants through each study were provided in Freedman 2006; Ramsook 2002 and Roslund 2008 and outcomes data were complete for the 24hr study period in Cubeddu 1997. Data were analysed in all of the included studies following the the intention-to-treat principle.

**Selective reporting**

There was no evidence of selective outcome reporting in Cubeddu 1997; Freedman 2006, Ramsook 2002 and Roslund 2008 and the outcomes listed in the methods sections were comparable to the reported results.

**Other potential sources of bias**

Pharmaceutical companies supported the research reported by Cubeddu 1997; Freedman 2006, Ramsook 2002 and although placebo tablets were supplied by GlaxoSmithKline in Roslund 2008 the investigators indicated that they provided no other financial or in-kind support.

**Effects of interventions**

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. None of the included trials provided any data addressing this outcome but some of the secondary outcomes were reported. Because clinical heterogeneity between the studies did not permit pooling of data we did not conduct a meta-analysis and therefore only report outcomes individually for each of the four included studies (Cubeddu 1997; Freedman 2006; Ramsook 2002; Roslund 2008).

**Cubeddu 1997**

**Primary outcome: time to cessation of vomiting**

Although this report did not provide data for this outcome in any of the groups, it did indicate that the proportion of patients experiencing no vomiting in the time period 0-24 hours was higher in the ondansetron group 7/12 (58%) than placebo 2/12 (17%) and 4/12 (33%) in the metoclopramide group P= 0.039 (Table 1).

<table>
<thead>
<tr>
<th>Ondansetron (n=12)</th>
<th>Metoclopramide (n=12)</th>
<th>Placebo (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vomiting</td>
<td>7 (58%)</td>
<td>4 (33%)</td>
</tr>
</tbody>
</table>

Ondansetron ensured complete anti-emesis for 8/12 (67%) patients within the first 4 hours and in 7/12 (58%) patients in the first 24 hr period.

**Secondary outcomes: admission and revisit rate, intravenous rehydration**

Intravenous fluid therapy for diarrhoea induced fluid loss was given to 3 (25%) patients in the ondansetron group and to 1 (8%) in the metoclopramide group during the first 24 hour period after treatment.

No data was available for either admission beyond the study period or the revisit rates. The trialists did not include any data on assessment of parental satisfaction.

**Side effects**

Adverse events were noted in all treatment groups. All patients in the study experienced at least one episode of diarrhoea but compared with placebo there were significantly more episodes of diarrhoea in the ondansetron (P= 0.013) and metoclopramide (P= 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.

**Freedman 2006**

**Primary outcome: time to cessation of vomiting**

This trial did not provide the precise time to cessation of vomiting ceased after administration of ondansetron or placebo. Fifteen patients in the ondansetron and 37 in the placebo group vomited...
while receiving oral rehydration. The authors also included the overall time spent in the emergency department for both groups.

**Secondary outcomes: admission and revisit rate, intravenous rehydration**

Four patients in the treatment group were admitted and five in the placebo group. Fifteen participants (14%) in the ondansetron group compared to 33 (31%) in the placebo group received intravenous therapy (P= 0.003). The revisit rate was 19% in the ondansetron group and 22% in the placebo group.

**Side effects**

A higher frequency of diarrhea was the only adverse effect reported in the ondansetron group. There was one case of urticaria in the placebo group.

**Ramsook 2002**

**Primary outcome: time to cessation of vomiting**

This report did indicate that the number of participants who received ondansetron and had no vomiting was greater than those who received placebo during the emergency department stay and during the first and second 24-hour period (Table 2). However it was not explicit about the precise time to cessation of vomiting in each person in each group during the study period.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Ondansetron group</th>
<th>Placebo Group</th>
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<tbody>
<tr>
<td>ED Stay</td>
<td>64 (87%)</td>
<td>46 (65%)</td>
</tr>
<tr>
<td>First 24 hours</td>
<td>37 (58%)</td>
<td>30 (54%)</td>
</tr>
<tr>
<td>24 -48 hours</td>
<td>43 (70%)</td>
<td>30 (59%)</td>
</tr>
</tbody>
</table>

Table 2. Proportion of patients without vomiting (Ramsook 2002)
Secondary outcomes: Admission and revisit rate, intravenous rehydration

The only secondary outcomes specified for this review and included in this trial were the rates of intravenous fluid administration, and admission for each group. Two participants in the placebo and 11 in the ondansetron group who had persistent vomiting, or refused oral rehydration, or were administered intravenous fluids were subsequently admitted (Table 3). Although no exact data were made available, the trialists confirmed that a smaller proportion of patients in the ondansetron group compared with placebo required intravenous fluid therapy. The revisit rate was higher in the ondansetron group (4/74; 5.41%), two for persistent vomiting and two for persistent diarrhea, compared with the placebo group (0/71) \( P=0.047 \).

Table 3. Admission rate including the number requiring intravenous fluids (Ramsook 2002)

<table>
<thead>
<tr>
<th>Ondansetron Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

This trial did not include any assessment of parental satisfaction.

Side effects:
Apart from diarrhea the only other side effect reported in this trial was the development of a macular rash in one patient who had received ondansetron.

Roslund 2008

Primary outcome: time to cessation of vomiting
Although this report did not provide precise data for this outcome it did indicate that after discharge 93% of patients in the ondansetron group and 88% in the placebo group had less than 3 episodes of vomiting and that the median number of episodes was 0 (range 0-13) in the ondansetron group and 0 (range 0-4) in the placebo group. Table 4

Table 4. Number of vomiting episodes after discharge (Roslund 2008)

<table>
<thead>
<tr>
<th>Ondansetron</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median 0</td>
<td>Median 0</td>
</tr>
<tr>
<td>(range 0-13)</td>
<td>(range 0-4)</td>
</tr>
<tr>
<td>Mean 0.71</td>
<td>Mean 0.5</td>
</tr>
</tbody>
</table>
Secondary outcomes: Admission and revisit rate, intravenous rehydration, parental satisfaction

Three participants (5.9%) 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 seven (12.7%) in the placebo group were unable to tolerate oral fluids, received intravenous hydration and were admitted Table 5. Two participants in the ondansetron group and one in the placebo group were discharged but returned to the emergency department within 72 hours. A further two participants, one in each group, who had previously failed the oral challenge and had received intravenous rehydration, revisited were readmitted and received further intravenous rehydration.

The self assessed symptom diaries and structured telephone interviews conducted after discharge included questions related to satisfaction with the medicine and the care given in the emergency department but no relevant data were made available in this report.

Table 5. Admission rate (Roslund 2008)

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3/51 (5.9%)</td>
<td>7/55 (12.7%)</td>
</tr>
</tbody>
</table>

Side effects

No side effects to the intervention or adverse events were reported by the investigators in this trial.

**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. It was thus somewhat disappointing to find such a small number of clinical trials that would either robustly support or refute this opinion and which might ultimately support the necessity of immediate changes to that guidance. 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 four trials which were at least partially industry funded and whilst we were unable to conduct a meta-analysis they provided some limited evidence regarding the clinical effectiveness and safety of antiemetics prescribed for children vomiting due to gastroenteritis.

**Quality of the evidence**

Whilst recognising the methodological limitations of some of the included studies and the inability of their data to answer our patient preferred primary outcomes, we have chosen to include them but advise caution in the interpretation of their results. We expect that, with a response from trialists in either of the studies awaiting assessment (Reeves 2002; Yilmaz 2008), we will be able to add to the data available and build on the strength of evidence for the planned outcomes specified in the protocol of this review.
Authors’ Conclusions

Implications for practice

It appears that ondansetron may reduce the amount of acute vomiting as well as reducing the number of children who required intravenous rehydration, and admission for acute gastroenteritis. However this conclusion is only based on four studies. In addition, participants in the ondansetron group did have more diarrhoea than in the placebo group, but the amount is likely not clinically significant. The four included trials reported on two possible routes of administration for two antiemetics: either oral or intravenous ondansetron or intravenous metoclopramide. It is conceivable that in the presence of persistent vomiting the intravenous single dose of ondansetron, if available, may offer some advantages over the oral route particularly in that the intravenous route is most likely to obviate any further irritation to the gastric mucosa.

Implications for research

In view of the likelihood of a higher incidence of gastroenteritis in developing countries the importance of further research into the effectiveness and cost effectiveness of antiemetics cannot be underestimated, particularly if this may lead to a reduction in the frequency with which costly intravenous fluids and hospitalisation are required.

Future research should also focus on outcomes that are of relevance to patients and thus the time to cessation of vomiting rather than a reduction in the number of episodes of vomiting as outcomes would appear to be more appropriate.

Acknowledgements

The reviewers would like to thank Janet Lilleyman, the Review Group Coordinator of the Cochrane UGPD Group, for her support throughout this review. We also are very grateful to Iris Gordon for her tireless effort in developing the search terms and strategy and running the searches for this review. Madame Ricks of the British School of Bahrain also very kindly undertook the translation of the French study into English for which we are extremely grateful. Dr Cathy Bennett worked with ZF to update the review.

References

References to studies included in this review

Cubeddu 1997 (published data only)

Freedman 2006 (published data only)

Ramsook 2002 (published data only)

Roslund 2008 (published data only)

References to studies excluded from this review

Ginsburg 1980 (published data only)

Van Eygen 1979 (published data only)

References to studies awaiting assessment

Debray 1990 (published data only)

Reeves 2002 (published data only)

Yilmaz 2008 (published data only)

Additional references

AAP1996
### Characteristics of included studies [ordered by study ID]

**Cubeddu 1997**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised double blind placebo-controlled parallel group trial in a children's hospital in Venezuela. (No date specified) Participants hospitalised for a minimum period of 24 hours during the course of the trial.</th>
</tr>
</thead>
</table>
| 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.  
**RANDOMISED:** N = 36 into three groups.  
**WITHDRAWALS/TREATMENT FAILURES:**  
• Treatment failures at 0-4hrs: four (33%) placebo, two (17%) metoclopramide and one (8%) ondansetron. At 0-24hrs: 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 | • a single vomit or retch or any number of continuous vomits and/or retches |
| Notes | Study supported by Glaxo Wellcome Research and Development, UK. |
### Cubeddu 1997 (Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Quote: “Patients were randomly assigned to receive either...” Comment: Unclear</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>Quote: “The study medication was prepared by a pharmacist not involved in patient care...” Comment: Probably done</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Unclear</td>
<td>Participants: Not applicable. Healthcare providers: Quote: “The study medication was prepared by a pharmacist not involved in patient care...” Although intervention and control were similar 15mL IV infusion not clear if similar 'packaging'. Comment: Unclear Outcomes assessors &amp; Data analysts: no indication from the study details if persons assessing the outcomes of care were blinded to which treatment the participants received (detection bias).</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>The report was fairly explicit about the losses due to 'treatment failures'.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>No evidence of selective choice of data for outcomes. Outcomes listed in the methods section comparable to the reported results.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>It was stated that two of the authors of this trial obtained funding from GlaxoWellcome.</td>
</tr>
</tbody>
</table>

### Freedman 2006

**Methods**

Prospective, double blind randomised clinical trial conducted in a children's hospital in Chicago, USA (Study conducted Jan 2004 - April 2005). Block (6) randomisation 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.

**RANDOMISED:** 215 (107 to ondansetron and 107 to placebo, 1 withdrawal ondansetron group) 214 analysed.

**WITHDRAWALS:**
- 3 (ondansetron group) before the intervention.
- 5 (ondansetron group) vomited within 15mins and received a second dose.
- 3 (placebo group) vomited within 15mins. 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 2mg (8-15kg), 4mg (15-30kg) 8mg (>30kg), placed on the tongue by the bedside nurse only, swallowed five seconds later. Children who vomited within 15 minutes received a second dose of ondansetron.

Oral rehydration:
- (Enfalyte, Mead Johnson Nutritional)15 minutes (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 minutes.

**Outcomes**
- number of episodes of vomiting during oral rehydration.

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 hospitalised. 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**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>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 independent statistician provided the code to the pharmacy”. The report included a randomization flow chart with enrolment details Comment: Probably done.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>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”. Comment: Probably done.</td>
</tr>
</tbody>
</table>
### Freedman 2006 (Continued)

<table>
<thead>
<tr>
<th>Blinding? All outcomes</th>
<th>Yes</th>
<th>Participants/Healthcare providers: Quote: “active drug or placebo of similar taste and appearance”. Comment: Probably done. Outcomes assessors &amp; 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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td>The authors followed the intention to treat principle.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear</td>
<td>No evidence of selective choice of data for outcomes. Outcomes listed in the methods section comparable to the reported results.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>This trial was supported partly by a grant from GlaxoSmithKline.</td>
</tr>
</tbody>
</table>

### Ramsook 2002

#### Methods

Prospective double blind randomised 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 randomised and packaged by a pharmacy. (No date specified)

#### Participants

Children: aged 6 months to 12 years

**INCLUSION CRITERIA:**
- Clinically confirmed diagnosis of gastroenteritis, ≥5 five 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.

**RANDOMISED:** oral ondansetron (74), placebo (71).

**BASELINE DATA:** See (Table 6).
- <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 2mL (1.6mg) for ages 6 months to 1 yr, 4mL (3.2mg) aged 1-3 yrs, and 5mL (4mg) 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 (5mL/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 hour period, participants were progressively weaned onto a diet of bananas, rice, applesauce and toast (BRAT).

| Outcomes | frequency of vomiting during the 48 hour period after enrollment 
| admission rates 
| frequency of diarrhea.

| Adverse events were recorded.

| Notes | Study funding was obtained from Glaxo Wellcome.

| Risk of bias |
|---|---|---|
| Item | Authors' judgement | Description |
| Adequate sequence generation? | Yes | Quote: “random allocation procedure was designed using standard random number allocation tables”. Comment: Probably done. |
| Allocation concealment? | Yes | 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”. Comment: Central allocation. Probably done. |
| Blinding? All outcomes | Yes | Participants/Healthcare providers: Quote “the pharmacy provided the drug or a color-, taste-, and odor-matched placebo in
identical packaging..”
Comment: Probably done.
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”.
Comment: Probably done.

Incomplete outcome data addressed?
All outcomes: Yes

Losses to follow up at two time periods were accounted for and were similar in both groups.

Free of selective reporting?
Yes

No evidence of selective choice of data for outcomes. Outcomes listed in the methods section comparable to the reported results.

Free of other bias?
Unclear

Quote: “Supported in part by a grant from GlaxoWellcome Research and Development”.

### Table 6. Baseline characteristics 24hr preceding the study (Ramsook 2002)

<table>
<thead>
<tr>
<th>Emesis episodes</th>
<th>Ondansetron group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 10</td>
<td>37(50%)</td>
<td>40(56.33%)</td>
</tr>
<tr>
<td>more than 10</td>
<td>37(50%)</td>
<td>31(43.66%)</td>
</tr>
</tbody>
</table>

### Roslund 2008

Methods
Prospective, double-blind, placebo-controlled, randomised study conducted in the emergency department of a medical center in Chicago, USA. Method of randomisation 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 years
INCLUSION CRITERIA:
- Clinical diagnosis of acute gastritis or acute gastroenteritis and mild to moderate dehydration.
- Aged 1-10 years
- Failed controlled oral challenge in ED
EXCLUSION CRITERIA:
- Antiemetics in the previous 6 hours
- Underlying chronic illness
- Shock state requiring immediate IV fluids
- Severe dehydration
Known sensitivity to 5-HT₃ receptor antagonists

RANDOMISED: Ondansetron (51), placebo (55).

BASELINE DATA: See (Table 7; Table 8)

Episodes of vomiting:
- ondansetron group 1-30 (median 10) in preceding 1-4 (median 1) days,
- placebo group 1-30 (median 10) in preceding 1-6 (median 2) days

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: 2mg (<15kg), 4mg (15-30kg), 6mg (>30kg).
Placebo “looked smelled and tasted like ondansetron”.

Oral rehydration:
- 30 mins after medication: Pedialyte popsicle (Abbott Laboratories) or Pedialyte 5mL/3 minutes via oral syringe
Discharge when able to tolerate oral fluids (40mL/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-completed standardised symptom diary/data collection form.

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

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “patients were randomized to receive oral ondansetron or placebo”, “block randomization of 10”. Trial flow chart refers to Block Randomization.com. Comment: Probably done.</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>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”. Comment: Unclear.</td>
<td></td>
</tr>
</tbody>
</table>
Blinding?
All outcomes: Yes
Healthcare providers: Quote. “The packets were prefilled (oral ondansetron or placebo).” “The markings on the blister pack were obscured”. Comment: Probably done.
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 addressed?
All outcomes: Yes
Flow chart tracking participants through the study. Failures and withdrawals accounted for and “data were analyzed using intention to treat”, which included all of the participants randomised.
Comment: Probably done.

Free of selective reporting?
Yes
No evidence of selective choice of data for outcomes. Although the outcomes listed in the methods section were comparable to the reported results, the post discharge symptom diary did include several questions related to patient and carer satisfaction. The investigators indicated a lower return rate on these questionnaires than the responses to follow-up telephone calls but these outcomes data were unavailable in this report.

Free of other bias?
Yes
Quote: “GlaxoSmithKline supplied placebo tablets but no other financial or in-kind support for this study.”

Table 7. Baseline characteristics: median days of vomiting (Roslund 2008)

<table>
<thead>
<tr>
<th>Ondansetron (n=51)</th>
<th>Placebo (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>1-6</td>
</tr>
</tbody>
</table>
Table 8. Baseline characteristics: median episodes of emesis (Roslund 2008)

<table>
<thead>
<tr>
<th></th>
<th>Ondansetron (n=51)</th>
<th>Placebo (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 (range1-30)</td>
<td>10 (range1-30)</td>
</tr>
</tbody>
</table>

Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginsburg 1980</td>
<td>This was a non randomised controlled study.</td>
</tr>
<tr>
<td>Van Eygen 1979</td>
<td>No outcomes matching those specified in the protocol of this review.</td>
</tr>
</tbody>
</table>

Characteristics of studies awaiting assessment [ordered by study ID]

Debray 1990

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

Reeves 2002

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Quote: “A randomized, double blind, placebo-controlled trial, conducted in the emergency department of a tertiary-care children's hospital. (Boston USA). &quot;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&quot;. “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&quot;.</td>
</tr>
<tr>
<td>Participants</td>
<td>107 children enrolled, 2 losses to follow up, age range 3 months to 22 years.</td>
</tr>
<tr>
<td>Interventions</td>
<td>54 to intravenous ondansetron 0.15mg/kg (maximum 8mg), 53 to placebo 0.9% saline solution.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>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</td>
</tr>
</tbody>
</table>
### Reeves 2002 (Continued)

| 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”. |

### Yilmaz 2008

| Methods | Quote: “A randomized double blind, placebo-controlled trial was performed in an university hospital and a government hospital ED” “Children ... were randomized to...” No further details provided in the report regarding sequence generation or concealment of allocation. |
| Participants | 109 children 5 months to 8 years vomiting ≥4 times in preceding 24 hours |
| Interventions | Oral disintegrating ondansetron (54) tablets or placebo(55) |
| Outcomes | Oral fluid tolerance, IV rehydration requirement and hospitalisation at 8 and 36 hours |
| Notes | No details available regarding the blinding of participants, investigators, outcomes assessors & data analysts: |
DATA AND ANALYSES

This review has no analyses.

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.
orf/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$).tw.
dolasetron.tw.
granisetron.tw.
donansetron.tw.
tropisetron.tw.
exp anticholinergic agent/
scopolamine.tw.
exp antihistamines/
buclizine.tw.
cyclizine.tw.
dimenhdydrinate.tw.
diphenhydramine.tw.
trimethobenzamide.tw.
meclizine.tw.
BENZODIAZEPINES/
lorazepam.tw.
exp corticosteroids/
dxamethasone.tw.
methylprednisolone.tw.
exp cannabinoids/
cannabinoid$.tw.
marijuana.tw.
mariol.tw.
orf/42-75
infant$.tw.
child$.tw.
neonat$.tw.
pediatric$.tw.
paediatric$.tw.
juvenile$.tw.
orf/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 ? maximising 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

WHAT'S NEW
Last assessed as up-to-date: 4 February 2009.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 February 2009</td>
<td>New citation required but conclusions have not changed</td>
<td>Updated, new citation.</td>
</tr>
<tr>
<td>29 January 2009</td>
<td>New search has been performed</td>
<td>Text in 'Assessment of risk of bias in included studies' modified.</td>
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</table>

HISTORY
Protocol first published: Issue 4, 2005
Review first published: Issue 3, 2006

<table>
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<tbody>
<tr>
<td>15 October 2008</td>
<td>Amended</td>
<td>Converted to new review format.</td>
</tr>
<tr>
<td>23 June 2008</td>
<td>New search has been performed</td>
<td>Amendments and additions to the search strategy and new searches.</td>
</tr>
<tr>
<td>7 December 2006</td>
<td>New search has been performed</td>
<td>New studies sought but none found.</td>
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<tr>
<td>21 August 2006</td>
<td>New citation required and conclusions have changed</td>
<td>Substantive amendment.</td>
</tr>
<tr>
<td>28 July 2006</td>
<td>New search has been performed</td>
<td>New studies found and included or excluded.</td>
</tr>
<tr>
<td>11 January 2005</td>
<td>New search has been performed</td>
<td>Minor update.</td>
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</table>
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 and Hakima Alhashimi (HAH) 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 DAH were responsible for:

Organising retrieval of papers
Writing to authors of papers for additional information
Providing additional data about papers.

DAH conceived the idea for the review and is the guarantor for the review.
ZF updated 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 the review.
NOTES

In view of the absence of any trials addressing the primary outcome of this review, ‘the time taken from the first administration of treatment measure to cessation of vomiting’, we report only on the outcomes presented in the four included trials, which specifically refer to some of the secondary outcomes specified 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 2008.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Adolescent; Antiemetics [adverse effects; therapeutic use]; Gastroenteritis [*complications]; 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