Emergency Nurse

Outcomes of administering ondansetron to children with gastroenteritis in emergency departments: an integrative review

Elizabeth Lloyd-Martin

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Correspondence
elizabeth.lloydmartin@wlv.ac.uk

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Abstract

Practice in the UK regarding the use of antiemetics in children with acute gastroenteritis is controversial and there is no standardised management. Ondansetron is an antiemetic that in practice is prescribed for and administered to children for the treatment of gastroenteritis. However, it is not listed in the British National Formulary for Children for administration in the treatment of gastroenteritis and it is not included the National Institute for Health and Care Excellence algorithm for management of gastroenteritis. This article discusses the findings of an integrative review of the outcomes of administering ondansetron to children with gastroenteritis in emergency departments. The article concludes that ondansetron appears to be a beneficial useful adjunct to the treatment of gastroenteritis in children.

Author details

Elizabeth Lloyd-Martin, paediatric advanced nurse practitioner and senior lecturer in Children's Nursing, University of Wolverhampton, Walsall, England, UK

Keywords

antiemetic, children, emergency department, gastroenteritis, Ondansetron

Key points

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Introduction

Gastroenteritis, which is classified as a sudden change in stool consistency and/or a sudden onset of vomiting (National Institute for Health and Care Excellence (NICE) 2009), is extremely common and many children in the UK have more than one episode a year. Diarrhoea results in the secretion of electrolytes and water in the gut (Kelly et al 2018 [Please add to ref list COMPLETED]) which can be potentially life-threatening, particularly in infants as it can cause dehydration leading to hypovolemic shock (Advanced Paediatric Life Support 2016). Other complications include sepsis or malnutrition (Tomasik et al 2016).

Although gastroenteritis can be managed at home many parents and carers seek advice from medical professionals (NICE 2009). Gastroenteritis is responsible for 20% of GP consultations in children under five years of age and results in 24,000 UK hospital admissions annually (Flake et al 2014). It is a major cause of paediatric presentations at emergency departments (EDs) (Romano et al 2019), resulting in significant financial and resource costs for the NHS (The King's Fund 2012).

NICE (2009) guidelines for Diarrhoea and vomiting caused by gastroenteritis in the under 5s provides an algorithm for health professionals to follow to support management. If a child is dehydrated NICE recommends oral rehydration therapy (ORT), which is the administration of oral rehydration solution (ORS). ORS is readily available and can replace electrolyte deficits adequately and

safely, contains an alkalinising agent to counter acidosis and is simple to use in hospital and at home (British National Formulary for Children (BNFC) 2020).

However, [practice observed by the author] suggests that clinicians often depart from the NICE guidelines (2009) and prescribe and administer an antiemetic for the treatment of paediatric gastroenteritis, in particular ondansetron. Hanif et al (2019) highlighted that the treatment of gastroenteritis in young children in the UK is controversial [because] there is no standardised management of antiemetic administration. Other authors (Fedorowicz et al 2011, Thompson et al 2016) agree that there appears to be a lack of consensus among clinicians about indications for administering antiemetics [for the treatment of gastroenteritis in children]. The topic is current and there is a considerable amount of recent research (Danewa et al 2016, Freedman et al 2019a, 2019b, Hanif et al 2019, Romano et al 2019).

Ondansetron is an antiemetic (BNFC 2020), that is a 5HT3 receptor antagonist that blocks the receptors in the gastrointestinal tract. However, the precise mode of action to cause [do you mean to stop/prevent? Amend to "However, the precise mode of action in the control of nausea and"] vomiting is unknown (Electronic Medicines Compendium (EMC) 2020). Peak plasma concentrations depend on whether it is administered orally or intravenously; the oral route takes 1.5 hours to peak (EMC 2020). As with most drugs ondansetron has contraindications, including cardiac arrhythmias (BNFC 2020). Despite being an antiemetic, ondansetron is not listed in the BNFC (2020) for administration in the treatment of gastroenteritis and despite multiple reviews (NICE 2014, 2019 [please add these to ref list COMPLETED]) NICE does not advocate its use [for this specific condition in children or in general? for the treatment of this specific condition in children.].

This article…….. This article intends to positively contribute to the research area by reviewing recent studies and concluding on the outcomes of administering ondansetron for the treatment of gastroenteritis in children in the ED.

Integrative review

Search strategy

This review followed the population (children and ED), intervention (ondansetron), comparison (placebo and/or oral hydration solution) and outcome framework (PICO) (Sackett et al 1996). CINAHL, PUBMED, COCHRANE and Medline were electronically searched using four concepts, ondansetron, gastroenteritis, children and emergency department and the terms Zofran, vomiting, diarrhoea, diarrhea, nausea, child, paediatric, paediatrics, pediatric, pediatrics, infants, ED, casualty, accident and emergency and A&E as databases use different indexing terms and spellings (Coughlan et al 2013). Using a range of search terms ensures all pertinent studies are captured. 'Boolean' operators were also used giving greater control over search results (Coughlan et al 2013).

Using inclusion and exclusion criteria (Table 1) provides clear information about the remit of the review (Aveyard 2014) and ensures that studies are relevant and will help to answer the review question.

Consideration of 'grey literature' such as trust policies and NICE guidelines is also an advocated strategy when compiling an integrative review as there is usually unpublished evidence about the topic (Adams et al 2016). However, although NICE guidelines were considered the lack of grey literature on the topic is a limitation of the review's methodology.

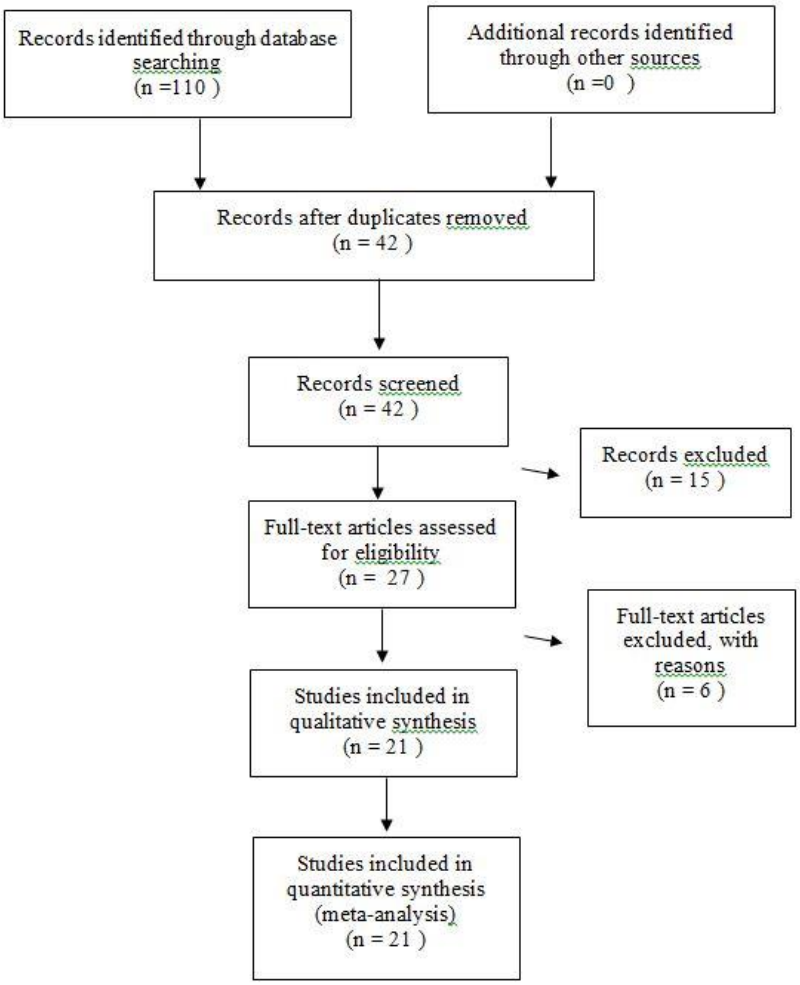
Figure 1 illustrates the search strategy that generated 21 articles suitable for inclusion in the review. The articles are summarised in Table X [note to author and editor – Table X is on a separate file for online version only.]

Table 1. Inclusion and exclusion criteria

Criteria	Rationale
Search terms	To ensure that the papers are relevant to the research question. For example, those based in emergency departments only, those where the use of ondansetron was for the treatment of gastroenteritis only and those in which the outcomes were discussed
Date of publication	Papers dated from 2011 to ensure adequate and up-to-date research is included and to explore research after the latest National Institute for Health and Care Excellence (NICE) (2009) guidelines were published
Worldwide, published studies, written in English	To yield an adequate number of papers for the integrative review. Limited papers were found in a search of UK only studies
Type of literature	NICE (2009) guidelines were considered, but other grey literature was not explored due to the expected volume

[Note to sub-editor. The flow chart needs to be edited but RW can't do that on home PC]

Figure 1. PRISMA flow diagram of search strategy



Findings

A data extraction tool which converts extracted data into systematic categories was devised using a combination of models (Woodward and Webb 2000, Kudchadkar et al 2014). This ensured information was easily extracted in systematically and comprehensively giving clarity to study interventions. A critical appraisal skills programme (CASP) (2013) tool was used to critique the studies followed by thematic data analysis. This was supported by the data extraction table, providing a robust, systematic framework for identifying patterns across the data (Braun and Clarke 2014).

Seven outcomes following the administration of ondansetron emerged from the review of the studies (Table 2). The remainder of the studies either did not discuss the outcome or reported a different outcome to those shown in Table 2. It would be remiss to conclude that the seven outcomes arose solely from the administration of ondansetron without addressing the different indications noted in the studies which may have contributed to the outcomes reported.

Table 2. Outcomes of literature review following administration of ondansetron

Outcome		Number of the 21 studies that reported this outcome
1. Cessation and reduction of vomiting		**11**
2. Reduced hospital admission rates		**11**
3. Positive effect on intravenous therapy		**11**
4. Positive effect on oral rehydration therapy (tolerance of oral rehydration solution)		**10**
5. No effect on emergency department re-attendance rate		**5**

6. Increased the number of participants' stools		**5**
7. Ondansetron is a cost-effective treatment		**3**

Discussion

The definition of 'gastroenteritis' was not consistent throughout the studies reviewed. Gastroenteritis is a clinical diagnosis (Freedman et al 2013) and its severity [can vary greatly?]. None of the studies used NICE guidelines (2009) to aid diagnosis, [which would have given more consistency.] However, these are only applicable in England and Wales and most of the studies were pan-European. Ondansetron was therefore administered to participants who could have been in different clinical states which may have caused or contributed to the outcomes reached, rather than the intervention of the drug alone. The NICE (2009) guidelines include a table that defines hydration, highlighting clinical appearance and 'red flag' features such as tachycardia, tachypnoea and sunken eyes. The table was not referenced by any of the studies, which presents another potential for variation in participants' clinical state at presentation.

Some studies only administered the antiemetic if [participants presented with] mild to moderate dehydration. Four studies (Golshekan et al 2013, Danewa et al 2016, Freedman et al 2019a, 2019b) used the World Health Organization (WHO) (2013) dehydration tool, however several (Cheng 2011, Freedman et al 2011b, Colletti 2012, Levine 2012, Freedman et al 2013, Mullarky et al 2013, Zanon et al 2013, Freedman et al 2014b, Pelc et al 2014, Freedman et al 2015, Schnadower et al 2015, Marzuillo et al 2016, McLaren 2016, Tomasik et al 2016) provided no details on how hydration was classified, which introduces bias and variance [to the results?].

Cessation and reduction of vomiting

Eleven studies concluded that ondansetron assists the cessation and reduction of vomiting (Cheng 2011, Fedorowicz et al 2011, Freedman et al 2011a, Colletti 2012, Levine 2012, Freedman et al 2015, Marzuillo et al 2016, McLaren et al 2016, Tomasik et al 2016, Freedman et al 2019a, 2019b). While this is clearly a positive finding it is perhaps unsurprising given that ondansetron is classified as an antiemetic in the BNFC (2020). The remaining 10 studies did not mention the effect on vomiting.

The 11 studies reached this outcome despite variations in population size, ages and study design. For example, Cheng (2011) had 466 participants while Freedman et al (2015) had 4,444. Bragadottir (2000) highlighted that in paediatric studies achieving a large sample is not always possible due to this population's vulnerability, which could affect participant enrolment. However, studies with a large number of participants, such as Freedman et al (2015), is more powerful (Fletcher 2008) and increases confidence that findings could be extrapolated to a wider population. Smaller sample sizes mean that a single participant has a much larger effect on and ability to skew findings, which could be regarded as a limitation as anomalies would also have a greater effect.

Study designs varied with a mixture of randomised control trials (RCTs), systematic reviews and retrospective studies. RCTs are considered 'gold-standard' evidence and are best used when evaluating the effectiveness of an intervention (Evans 2007), particularly if they are multi-centred (Bowling 2009). Freedman et al (2019a, 2019b) were double-centre RCTs. Evans (2007) argued that a well-conducted RCT, whether single or multicentred, produces results with a low risk of error or bias that can provide valid evidence of the effectiveness of the intervention under investigation.

A number of systematic reviews only considered RCTs (Fedorowicz et al 2011, Freedman et al 2015, Tomasik et al 2016). Cheng (2011) carried out a literature review that examined three RCTs, however unlike the other reviews the researcher does not discuss the RCT selection process, which is a limitation and may introduce an element of bias. Further, Cheng (2011) does not establish whether there was blinding in the RCTs reviewed.

The reduction in vomiting outcome is important as vomiting can be parents' main concern when their child has gastroenteritis due to the associated issues related to hydration, general uncomfortableness and visual distress (Flake et al 2014). Therefore, the positive visual improvement seen by parents when their child stops vomiting following administration of ondansetron should be considered an advantage of its use.

Reduced hospital admission rates

Eleven studies (Cheng 2011, Fedorowicz et al 2011, Colletti 2012, Levine 2012, Freedman et al 2013, Mullarky et al 2013, Schnadower et al 2014, Freedman et al 2015, Marzuillo et al 2016, McLaren et al 2016, Tomasik et al 2016) concluded that the use of ondansetron decreased hospital admission rates. Non-admission to hospital is likely to have psychological benefits for parents and children (Power et al 2020) and alleviate some of the cost/resource burden on the NHS (King's Fund 2012).

Only Freedman et al (2014), who conducted a retrospective observational analysis, concluded there was no change in hospital admission rates, but they did report a reduction in reattendance rates. The reduced hospital admission rates outcome was unaffected by differences in participants' ages, population sizes, study design (three involved RCTs or systematic reviews involving RCTs, Cheng 2011, Fedorowicz et al 2011, Tomasik et al 2016) and inclusion criteria, which supports validity.

Three of the 11 studies that reported reduced admissions were cohort studies (Mullarky et al 2013, Marzuillo et al 2016, McLaren et al 2016). Compared to RCTs, cohort studies have a disadvantage in that data analysis produces the 'cohort effect'. This refers to the problem that each group experiences its society under its unique condition (Bowling 2009), introducing differences between and issues related to control of the consistency of participants' experience. Further, cohort studies cannot exclude etiological factors, causation factors of the condition, that may contribute to or affect the findings. Mullarky et al (2013) acknowledged this as a limitation of their study.

Eight of these 11 studies also stated that ondansetron is effective in the cessation of vomiting, therefore that outcome could have been responsible for reduced admission rates.

Positive effect on IV therapy

Eleven studies found that ondansetron use reduces the need for IV therapy (Cheng 2011, Fedorowicz et al 2011, Colletti 2012, Levine 2012, Freedman et al 2013, Mullarky et al 2013, Freedman et al 2015, Schnadower et al 2015, Tomasik et al 2016, Freedman et al 2019a, 2019b), reducing the associated risks of and patients' concern about this treatment.

The benefits of not requiring IV therapy are extensive. The NICE guideline (2015) for the use of IV therapies in children [includes an? YES] extensive list of considerations, for example assessment aid, monitoring and implications [is this list from the NICE 2015 guidelines? YES]. Reducing or removing the need for this invasive procedure should benefit patients and NHS trusts.

Although the 11studies had different primary outcomes they all reached this conclusion, however definitions of gastroenteritis varied as did the point at which participants were assessed to establish whether the ORT regime was successful. The studies also had different population sizes, ranging from 73 (Schnadower et al 2014) to 4,444 (Freedman et al 2015), and designs such as double-blinded RCTs (Freedman et al 2019a, 2019b) and retrospective studies (Mullarky et al 2013).

Positive effect on ORT (tolerance of ORS)

Administration of ondansetron appeared to have a positive effect on ORT (Fedorowicz et al 2011, Freedman et al 2011a, 2011b, Golshekan et al 2013, Mullarky et al 2013, Zanon et al 2013, Pelc et al 2014, Freedman et al 2014b, Tomasik et al 2016, Freedman et al 2019a). These 10 studies span eight years from 2011 to 2019, participants ages ranged from one to 10 years (Golshekan et al 2013) and 'less than 18 years' (Zanon et al 2013) and designs varied, yet the outcomes were the same which supports validity.

Tomasik et al (2016) reported that blinding in the studies they reviewed was unclear which may be considered a limitation, while Mullarky et al (2013) did not discuss blinding which creates potential bias. Fedorowicz et al (2011) included seven RCTs in their review which were all double-blinded, strengthening the credibility of findings and reducing bias (Miller and Stewart 2011).

Mullarky et al (2013) argued that ORT is detrimentally time-consuming and does not meet the expectations of an ED, but despite this ondansetron was described [by Mullarky et al? (2013)] as a 'useful adjunct' alongside ORT.

Increased tolerance of ORS, when administered with ondansetron, may ease dehydration concerns brought about by the presence of increased stools, cited as an adverse effect when ondansetron is administered on its own [please add the ref for this reworded beforehand in blue, references regarding increased stools are below] (discussed further below). The individual benefits of each treatment may be enhanced, and detriments reduced, when ondansetron and ORT are administered together. Conversely, Freedman et al (2011a) reported that administering ORT in hospital is not a positive intervention. Caregivers can give it at home therefore it is not a 'value-adding' action by EDs. However, this provides no justification for not administering ondansetron, the patient and their condition must be treated not the expectations of the caregiver [is this whole para the Freedman et al reference? YES].

No effect on ED re-attendance rate

Of the eight studies that discussed this topic, five (Fedorowicz et al 2011, Levine 2012, Golshekan et al 2013, Freedman et al 2015, Tomasik et al 2016) concluded that there was no effect on reattendance rates following administration of ondansetron These studies were RCTs and most involved double-blinded scenarios which increase credibility of and confidence in the outcomes. Sample sizes ranged from 176 (Golshekan et al 2013) to 4,444 (Freedman et al 2015). Concerns about reliability and validity are associated with low sample sizes.

Participant age appeared to have effect on this outcome, for example Golshekan et al (2013) included children aged one to 10 years, while Freedman et al (2015) and Fedorowicz et al (2011) included children up to 18 years.

Golshekan et al (2013) conducted a double-blinded RCT, where neither the caregiver nor patient was aware of the treatment assignment. Combining these two factors is considered the pinnacle of research design (Misra 2012).

Two studies (Freedman et al 2011a, McLaren et al 2016) concluded that reattendance rates increased following administration of ondansetron, which may be regarded as a negative outcome as it suggests that treatment was unsuccessful and did not meet parents' expectations. Increased reattendance rates counters the benefits of reduced admission rates. Freedman et al (2011a) had the positive of being multicentred but, like McLaren et al (2016), was a cohort study which has disadvantages as discussed above. Freedman et al (2014) reported a reduction in re-attendance rates.

Increased the number of participants' stools

Six studies discussed the effect of ondansetron on the number of participants' stools, five of which concluded that it increased the number of stools (Fedorowicz et al 2011, Colletti 2012, Levine 2012, Freedman et al 2013, 2015) while one reported no change in the number (Tomasik et al 2016).

Ten studies discussed diarrhoea as an 'adverse effect' [of ondansetron? following the administration of ondansetron] (Cheng 2011, Fedorowicz et al 2011, Colletti 2012, Levine 2012, Freedman et al 2013, Golshekan et al 2013, Pelc et al 2014, Schnadower et al 2014, Freedman et al 2015, McLaren et al 2016), [which supports concerns noted in the NICE (2019) pathway review][please add NICE 2019 to ref list COMPLETED]. However, the definition of 'adverse effect' is not discussed in any of the studies. The BNFC (2020) considers adverse reactions to be those that need to be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA). None of the studies discussed the need for reporting, therefore 'adverse effect' might be referring to less severe, but negative side-effects. Diarrhoea, which would be considered adverse, is not listed as a side-effect of ondansetron in the BNFC but constipation is listed as a side effect (2020). There is clear inconsistency here.

Schnadower et al (2014) gave an overview of four studies but did [not? YES] discuss inclusion criteria which creates a potential for bias.

The 10 studies above had a vast range in population size, from 68 in Pelc et al's (2014) cross-sectional survey to 12,478 in Freedman et al (2013). A single participant in the Pelc et al (2014) study contributed to 1.5% of the findings, which would have a much greater effect on skewing results than one participant in the Freedman et al (2013) study, who each contributed 0.008% to the findings. The response rate in Pelc et al's (2014) survey was 68 and although this is a low number, Rindfuss et al (2015) [please add to ref list COMPLETED] argued that the presence or absence of a low response rate should not alone create a bias. Instead, researchers should test for the presence of bias by considering the specific content under analysis.

Ondansetron is a cost-effective treatment

The cost of drugs is a financial burden to the NHS, for example Moon et al (2010) [please add to ref list COMPLETED] highlighted that drugs approved by NICE between 1999 and 2004 added £800 million a year to the UKs drugs bill. Three studies (Freedman et al 2011a, Mullarky et al 2013, Tomasik et al 2016) addressed the cost implications of ondansetron. Tomasik et al (2016) suggested that its use in treating gastroenteritis is cost-effective, but this was in relation to the reduction in the IV therapy rather than the use of ondansetron.

Mullarky et al (2013) agreed that it is cost-effective despite not undertaking a formal cost/benefit or cost effectiveness analysis, which raises concerns about support for this finding.

Limitations

The limitations of this integrative review were as follows:

» The lack of grey literature, which could provide further insight as to why ondansetron is not advocated [by NICE/BNFC? BOTH] and the rationale [for] and approach [to its use by? YES] NHS trusts.

» The implication of the pharmacokinetics of ondansetron were not addressed. [Timing of administration of ondansetron and time spent in EDs were not measured, which could affect the outcome regarding the tolerance of ORS.]

» Freedman undertook several studies, and his previous findings and personal views could have influenced each subsequent and introduced bias. On the other hand, based on his previous experiences Freedman could enhance the method, design or analysis of further studies thus remedying his own limitations. His findings on the effect on re-attendance rates altered between studies undertaken in 2011 and 2015.

» Most studies were European, with only two studies from other parts of the world [where were these 2 undertaken? Both Pakistan Freedman et al (2019a) and Freedman et al (2019b)]. There may be cultural, national or regional differences that affect administration of ondansetron and different outcomes may arise across continents following its administration.

» Levine (2012) and Colletti (2012) were commentaries on Fedorowicz et al's (2011) systematic review and did not make conclusions about the use of ondansetron themselves.

Conclusion

Although paediatric gastroenteritis can often be managed at home, many parents and carers seek medical advice (NICE 2009), however there is an inconsistency in the approach to management. Ondansetron is not listed in the BNFC for administration for the treatment of gastroenteritis and it is not advocated by NICE (2009). However, the outcomes of this review suggest that ondansetron can have positive effects [on the treatment and management of children with gastroenteritis and associated vomiting.]

Ondansetron appears to help reduce or stop vomiting which in turn can result in reduced hospital admission rates, which is beneficial for patients and for the NHS in terms of costs, resources and capacity which counters concerns about the cost of the drug.

Ondansetron can be a useful adjunct when administered with ORT as it appears to improve tolerance of ORS. Successful oral rehydration in EDs reduces the need for IV therapy and reduces the associated risks of this invasive intervention.

Five studies reported incidences of diarrhoea following administration of ondansetron, but this is contrary to the BNFC (2020) which lists constipation as a side-effect. Further research is required, particularly given the concerns raised by NICE (2019).

The studies reviewed were inconsistent in their definition gastroenteritis and classification of dehydration and there was a wide range of study design, population size and participant age. While these differences may have affected outcomes this could also demonstrate that ondansetron appears to have consistent benefits in terms of reducing or ceasing vomiting, reduction in hospital admission, and improved effects on IV therapy and ORT regardless of the severity of patients' gastroenteritis, state of dehydration or age.

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Table 2. Summary of studies included in integrative review

Author(s), design, sample size [can you add the country to this column] DONE	Study population/inclusion criteria	Data collection	Interventions	Summary of findings
Cheng (2011) Literature review of three random control trials (RCT), one double blinded 466 participants Canada	Children aged six months to 12 years who had vomited at least five times in the previous 24 hours Children aged six months to 10 years who had at least one episode of non-bilious, non-bloody vomiting in the preceding four hours with mild to moderate dehydration Children aged one to 10 years with clinical diagnosis of gastroenteritis with mild to moderate dehydration and failed oral rehydration therapy (ORT)	Review of studies conducted in 2002, 2006 and 2008 that compared oral ondansetron to placebo and ORT	Tablet compared to placebo followed by ORT 15 minutes later Oral solution compared to placebo followed by ORT 30 minutes later Double blind RCT oral ondansetron or placebo followed by ORT 15 minutes later	Children who received a single dose of ondansetron were less likely to vomit, had greater oral intake and were less likely to receive intravenous (IV) fluids compared to those who received placebo Children who received oral Ondansetron were less likely to be admitted to hospital Most common side effect was diarrhoea Number of diarrhoea episodes were similar for both groups
Danewa et al (2016) Single tertiary centre double blind RCT 170 participants India	Children aged three months to five years' Criteria of 'some' dehydration as defined by World Health Organization (WHO) (2005) At least two episodes of non-bilious, non-bloody vomiting within the last six hours Children with diagnosis of acute diarrhoea (duration less than 14 days)	Observation Primary outcome measure was amount of oral rehydration solution (ORS) intake in four hours. Secondary outcomes were duration of dehydration correction, number of vomiting episodes in four hours, adverse effects (rash, headache, diarrhoea) and caregiver satisfaction No follow-up	Syrup ondansetron compared to placebo. A single dose was given and only repeated if patients vomited within 30 minutes of first dose. They were then given ORT at the rate of 75ml/kg in the first four hours	Proportion of children receiving IV fluids was not statistically different between drug and placebo group Amount of ORS consumed in four hours was significantly more in children receiving ondansetron Median duration of dehydration correction was significantly less in children receiving ondansetron Mean number of vomiting episodes during four hours of observed ORT was significantly less in children receiving ondansetron Caregiver satisfaction in all fields was better in drug group than placebo group
Freedman et al (2011a) Cross-sectional internet-based survey 235 participants USA, Canada	Surveys sent to members of Paediatric Emergency Research Canada and the Paediatric Emergency Medicine Collaborative Research Committee who provide care to patients Children under 18 years of age ED settings	41 question survey delivered through SurveyMonkey with reminder email Consent implied by completion of survey Data input into Microsoft excel and comparison conducted using chi-square test	No interventions	Ondansetron was the antiemetic administered most often Reasons for not giving ondansetron were lack of evidence of clinical benefit and concern about side effects Inconsistencies in management between North America and the US
Freedman et al (2011b)	Children aged three to 48 months who presented to 11 EDs with acute gastroenteritis	Surveys, medical record reviews and telephone follow-up evaluations two weeks later	No interventions Review of practice Main discussion about the use of IV therapy and	Ondansetron was administered to 13% of children. Administered more frequently by

Author(s), design, sample size [can you add the country to this column] DONE	Study population/inclusion criteria	Data collection	Interventions	Summary of findings
Prospective multi-centre cohort study 647 participants Canada	(>3 watery stools in 24 hours and within 72 hours before the ED visit)		ORT, but ondansetron is discussed	physicians who had completed a paediatric emergency medicine fellowship 42% of children were discharged with instructions for administrating ondansetron at home Significant variations in the treatment of acute gastroenteritis in Canadian EDs Children who received IV rehydration were more likely to revisit [ED? YES] Use of ondansetron varied significantly
Freedman et al (2013) Overview of systematic reviews 12,478 participants Canada	Four reviews that included 95 RCTs Inclusion of acute gastroenteritis and dehydration [not sure what you mean by underlined bit 2x Inclusion criteria] Children up to 18 years	Literature review Jadad 5 point-scale used to evaluate methodological quality of the RCTs	No interventions Study reviewed probiotics, antiemetics, IV rehydration and ORT	No difference in hospitalisation rate within 72 hours of discharge Some clinicians prescribe multiple [doses of? YES] ondansetron, but this is not supported by evidence Administration of ondansetron increases the likelihood that children will stop vomiting
Freedman et al (2014) Retrospective observational analysis 804,000 participants Canada	Children younger than 18 years treated in 18 participating EDs with a diagnosis of gastroenteritis or dehydration based on discharge diagnosis code	Data collected from the Paediatric Health Information system Children with a diagnosis code of 'gastroenteritis' included	IV rehydration compared to ondansetron	Dramatic increase in the rate of ondansetron [administration? YES] in children with gastroenteritis during a 10-year [review? YES] period During the 'high ondansetron use period' IV rehydration rates were lower Children who presented to EDs in the 'high ondansetron use period' were less likely to return within three days and a revisit was associated with hospitalisation

Author(s), design, sample size [can you add the country to this column] DONE	Study population/inclusion criteria	Data collection	Interventions	Summary of findings
Freedman et al (2015) Systematic review and meta-analysis 4,444 participants Global - developed countries	Children up to 18 years of age with gastroenteritis	Literature review A medical librarian developed the search strategy. MEDLINE, COCHRANE database of systematic reviews and EMBASE were accessed between 2000 and 2015. Grey literature also explored The search was re-run in September 2014 to identify recently published articles	Among the 31 RCTs selected 10 compared ORT to IV therapy, six examined different probiotics, six compared the different rates or compositions of IV fluids, nine studies involving 1691 patients evaluated three antiemetic agents, ondansetron, dimenhydrinate and granisetron	Ondansetron offers short-term benefits, but makes no difference in terms of return ED visits Ondansetron increases the frequency of diarrhoea Despite previous concerns about the arrhythmogenic potential of ondansetron, more recent evidence has reduced concerns relating to single dosing in healthy children
[Please put Freedman et al columns in date order and please check the 2011 a/b studies match the reference list as per notes in the main text DONE] Freedman et al (2019a) Double centre, double blind RCT 626 participants Pakistan	Children aged six months to five years without dehydration who had diarrhoea and greater than or equal to one episode of vomiting within four hours of arrival Illness less than seven days duration	Observation Medical officers documented volumes of oral and IV fluids administered and frequency and volume of vomiting, diarrhoea and urination Dehydration parameters (in accordance with WHO [2005]) and vital signs were documented at four-hour assessment Discharged patients reassessed 24 hours after discharge, followed up at 48 and 72 hours by a telephone call	Disintegrating tablet of ondansetron compared to placebo. Single dose, but repeated if patients vomited within 15 minutes of first dose Volume of ORS measured after four hours	19.6% of children vomited during the four-hour observation period after receiving ondansetron, compared to 24% who received the placebo Receipt of ondansetron or the placebo had no effect on either the proportion of children hospitalised after 24 hours or those becoming dehydrated within 72 hours [not clear what you mean. Can you reword DONE] Number of diarrhoea stools during the 72-hour follow-up period similar between the groups Oral ondansetron did not reduce IV therapy requirements
Freedman et al (2019b) Double centre, double blind RCT 918 participants Pakistan	Dehydrated children aged six months to five years weighing greater than 8Kg with at least one episode of diarrhoea and one episode of vomiting within the preceding four hours Children with 'some' dehydration (quantified by WHO 2005) [add ref DONE] Exclusion criteria included bilious vomiting and illness longer than seven days	Observation Medical officers documented volume of oral and IV fluids administered and frequency and volume of vomiting, diarrhoea and urination Dehydration parameters and vital signs were documented at four hour assessment Discharged patients were reassessed after 24 hours and followed up at 48 and 72 hours by telephone	Disintegrating tablet of ondansetron versus placebo A single dose, but repeated if the patients vomited within 15 minutes of first dose Volume of ORS was measured after four hours	13.2% of children in the ondansetron group vomited during the four-hour observation period compared with 26.1% in the placebo group No difference in volume of oral fluids consumed Number of children hospitalised within 72 hours did not differ Children were less likely to have IV rehydration if they received ondansetron compared to placebo
Golshekan et al (2013)	Children aged one to 10 years with a simple clinical diagnosis of gastroenteritis, dehydration, onset within 24 hours, at least one episode	Blinded investigations through observation Assessed at four hours after administration of	Oral ondansetron compared to oral placebo Drug dosing in accordance with weight	Ondansetron decreased the failure of ORT. There was a reduction of over 50% in the proportion of children

Author(s), design, sample size [can you add the country to this column] DONE	Study population/inclusion criteria	Data collection	Interventions	Summary of findings
Single centre, double blinded RCT 176 participants Iran	of vomiting in the last six hours and no fever	intervention and commencement of ORT After 48 hours, investigator called the child's family for follow up	ORT initiated 30 minutes after medication given	who vomited during ORT and the proportion treated with IV fluids No significant reduction hospital admissions Ondansetron is easy to administer, has few side effects and is safe and effective WHO (2005) [on ?? Also please add year and ref DONE] adhered to for discharge No evidence of complications
Marzuillo et al (2016) Single centre experience 119 participants Italy	Children aged one to 14 years with uncontrolled vomiting	Observation (length of observation and who observed not recorded) No follow up	Single dose of ondansetron IV if patient required IV therapy Single dose of ondansetron IM if ORT only required All patients started ORT according to the local guidelines [what guidelines?] 30 minutes after drug administration	Ondansetron is safe to use despite previous doubts Ondansetron is effective as a first approach to managing gastroenteritis
McLaren et al (2016) Retrospective cohort comparative study 11785 participants USA	Children aged six months to 18 years with a discharge diagnostic code 9 (gastroenteritis) Illness severity determined using the local institutional dehydration score [is this a local score? YES]	Medical records of all children with gastroenteritis reviewed Clinical history, interventions, diagnostic studies and final diagnosis reviewed	No active interventions Review of management	Children were discharged with a prescription for ondansetron Children given a prescription for ondansetron had an increased risk of return ED visits and admission following revisit
Mullarky et al (2013) Retrospective study 234 participants Ireland	Children up to 16 years weighing more than 5Kg who presented to ED with signs and symptoms of acute gastroenteritis (an acute diarrhoeal illness with or without vomiting) and poor oral intake	Data collected over six weeks in 2009. All patients with discharge diagnosis of gastroenteritis on the 'Symphony ED electronic database' included in the study Data collected included age, sex, weight, length of ED stay and documentation of ORT Outcome measures looked at children requiring IV fluids, admission and representation rates	No interventions Retrospective study	Single dose of oral ondansetron reduces the number of children requiring IV fluids Ondansetron in the ED is likely to be cost effective The use of Ondansetron being given by the triage nurse can mask a serious underlying condition Ondansetron is a useful adjunct in managing children with dehydration secondary to acute gastroenteritis
Pelc et al (2014) Cross-sectional survey describing a scenario in which a toddler has moderate dehydration caused by gastroenteritis	Across four countries, primarily teaching hospitals Each centre was asked to include at least three participants	Electronic survey between February and July 2012 Survey was emailed then followed by a telephone call Reminder email sent Data analysed using the Kruskal-Wallis rank test	No active interventions Survey-based study	Antiemetic agents rarely prescribed 90% of respondents reported using ORT as first line rehydration therapy

Author(s), design, sample size [can you add the country to this column] DONE	Study population/inclusion criteria	Data collection	Interventions	Summary of findings
68 completed studies Belgium, France, The Netherlands, Switzerland				
Schnadower et al (2015) 2013 overview of four studies 73 participants USA	Four studies of children with gastroenteritis Not disclosed how studies were selected Gastroenteritis definition not discussed	Review of four studies	No active interventions for review, but looked at ondansetron and probiotics	Administration of a single oral dose of ondansetron aids prevention of nausea and vomiting Use of ondansetron is increasing Ondansetron does not require ECG monitoring of patients with no known risk factors
Tomasik et al (2016) Systematic review with meta-analysis 1215 participants Poland	Review of 10 RCTs comparing ondansetron with placebo or no intervention [in children with? YES] gastroenteritis	Literature review Cochrane Central Register of Controlled Trials, Medline, and Embase databases searched for relevant studies published up to April 2016 Searches undertaken independently by three reviewers	Review of literature, but only of RCTs that compared ondansetron with placebo or no interventions for vomiting in children with acute gastroenteritis	Ondansetron has no effect on ED return [visit YES] rates Evidence of the effect of ondansetron on diarrhoea stools inconclusive Arrhythmias unlikely to occur with a single dose of ondansetron Ondansetron reduces the risk of failure of ORT Does not address cost effectiveness, although ondansetron is likely to be cost effective
Zanon et al (2013) Italy	Children younger than 18 years with vomiting related to acute gastroenteritis	Review of databases across eight EDs in Italy between 2004 and 2007 [of children with? YES] an acute diagnosis of gastroenteritis Included patient data, sex, age and information about drug used (indication, dose, frequency and route of administration)	Different antiemetic drugs used in the management of acute gastroenteritis: Domperidone Metoclopramide Ondansetron Granisetron Thiethyperazine Tropisetron Prochlorperazine	Prescribing of antiemetics off-label is at 30% Domperidone is the only antiemetic used that is labelled for use in gastroenteritis Metoclopramide and ondansetron administered off-label to children with variances in both age and indications [not sure what you mean by both age and indications UPDATED] in all centres reviewed