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Improving outcome measures for antiemetic efficacy trials in adult emergency department patients with nausea.

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Abstract

Background

Nausea and vomiting are common problems for emergency department (ED) patients. Effective treatment is desirable for reasons of easing patient distress and prevention of the medical complications of vomiting. ED-based research, however, has failed to demonstrate clear benefits for ED patients from antiemetic drug administration, but interpretation of the study results is not straightforward. When comparing potential antiemetic treatments in RCTs, the primary outcome measure should provide the best evidence with regard to the primary objective. For ED patients with nausea, the primary treatment objective is clinically significant symptom improvement. The traditional primary outcome measure, a between-group comparison of mean VAS rating change, provides only indirect and imprecise information with regard to symptom improvement. As a consequence, this measure does not appear to provide the best evidence with regard to the primary treatment objective. Improved outcome measures are required in order to clarify the clinical value of antiemetic drug treatment for ED patients.

Aims

The primary objective of this series of related research projects was to identify and develop improved outcome measures for ED-based antiemetic trials. The purpose was to ensure that ED-based antiemetic study results related directly to the primary treatment objective, and were presented in an easily understandable and clinically meaningful way.

Methods

A sequential series of related research projects was performed. A staff survey was conducted to identify antiemetic drugs for inclusion in local therapeutic RCTs. An initial RCT was conducted to confirm findings of previous research and to enable collection of nausea severity measures on multiple rating scales. A measurement study further analysed the scales to explore potential alternate outcome measures. A narrative review was published to highlight the limitations of the traditional outcome measure and to propose solutions. A patient survey was conducted to determine the desired effect of antiemetic drug treatment. A pooled analysis of all available data linking VAS change and described symptom change was conducted to test the reliability of identified potential outcome measures. A follow-up therapeutic RCT was conducted to prospectively assess the ability of identified alternate outcome measures to meet the research aims.

Results

The staff survey found that metoclopramide and ondansetron were the two most commonly used antiemetic drugs in Australian EDs. The first RCT compared these two drugs with placebo. Consistent with previous literature, difference in mean VAS change was not statistically significant. The measurement component of the study demonstrated that the amount of VAS rating change could reliably predict symptom improvement. The patient survey found that most people expect antiemetic drugs to make symptoms at least 'a lot less'. The pooled analysis confirmed the ability of VAS change to discriminate between improved and non-improved patients. A best VAS change cut-off level of -8 mm was identified for detection of symptom improvement (symptoms 'a little less' or 'a lot less'). VAS change was less accurate for prediction of symptoms becoming 'a lot less'.

From these studies, two new outcome measures were identified for inclusion in the follow-up RCT. These were comparison of symptom improvement rates (defined as VAS change ≥ -8 mm) and numbers experiencing the desired treatment effect (direct questioning). Group mean VAS change and between-group differences were also reported as secondary outcomes.

The final RCT, comparing droperidol and ondansetron with placebo, found that difference in symptom improvement rates between groups was neither statistically significant nor clinically worthwhile. The mean VAS change between groups was also not statistically significant. More experienced the desired treatment effect in the active drug groups, but the clinical value of the differences was debatable.

Conclusions: The aims of this series of research projects were met. A novel outcome measure was identified and its utility demonstrated. A VAS change cut-off of -8 mm reliably identifies patients with symptom improvement. By allowing the number of improved patients to be compared between treatment groups in ED-based antiemetic trials, direct evidence with regard to the primary treatment objective is provided. The additional secondary outcome of experiencing the desired treatment effect appears to add clinical meaning to the between-group differences in mean VAS change. The latter still provides useful, although less specific information on relative treatment effectiveness.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Print Name: Robert Meek

Date: 24th May, 2018

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes seven papers which are either published, or have been submitted for publication in peer reviewed journals. The core theme of the thesis is improving outcome measures for antiemetic trials in adult ED patients with nausea. The ideas, development and writing up of all the major studies in the thesis were the principal responsibility of myself, the student, working within the School of Clinical Sciences, Department of Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, under the primary supervision of Professor Andis Graudins.

Working with multiple co-authors reflects the fact that the work required active collaboration between researchers. This acknowledges that teamwork is needed to conduct and complete this type of research. In particular, a strong collaborative group is essential for the successful conduct of randomized controlled therapeutic trials.

The approximate contributions to the published works which make up the body of the thesis are detailed in the following table. The published studies comprise Chapters 9 to 15 of the thesis. Two additional studies to which I contributed during the course of this thesis are briefly described in Chapter 7. These add to general knowledge on the topic, but do not directly pertain to the primary objective of the series of research outputs which comprise this thesis. Full copies of each are attached as an Appendix.

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
Thesis research output					
9	Treatment and assessment of emergency department nausea and vomiting in Australasia: a survey of anti-emetic management.	Published	Equal first author: 60% contribution to paper as a whole, approx. comprising: 33% concept and collection of data; 80% data analysis; 40% manuscript preparation.	1) Michaela Mee, 33% concept and collection of data; 10% analysis; 50% manuscript preparation 2) Diana Egerton-Warburton, 33% concept and collection of data; 10% analysis; 10% manuscript preparation	No
10	A randomised placebo controlled trial of antiemetic agents in adult emergency department patients with nausea or vomiting.	Published	Equal first author: 60% contribution to paper as a whole, approx. comprising: 30% concept and collecting data; 60% analysis and manuscript preparation.	1) Diana Egerton-Warburton, 30% concept and collecting data; 20% analysis and input into manuscript. 2) Michaela Mee, 30% concept and collecting data; 10% analysis and input into manuscript. 3) George Braitberg, 10% concept and collecting data; 10% input into manuscript.	No
11	Measurement and monitoring of nausea severity in emergency department patients: A comparison of scales and exploration of treatment efficacy outcome measures.	Published	First author: 75% contribution to paper as a whole, approx. comprising: 40% concept and collecting data; 85% analysis and writing first draft.	1) Diana Egerton-Warburton, 40% concept and collecting data; 5% analysis and input into manuscript. 2) Michaela Mee, 10% concept and collecting data; 5% analysis and input into manuscript. 3) George Braitberg, 10% concept and collecting data; 5% input into manuscript.	No
12	Do antiemetic drugs benefit adult emergency department patients with nausea? The literature says no, but is it right?	Published	First author: 90% contribution to paper as a whole.	1) Andis Graudins, 10% concept collection of data, manuscript preparation	No
13	Antiemetic treatment in the emergency department: Patient opinions and expectations.	Published	First author: 80% contribution to paper as a whole.	1) Andis Graudins, 10% concept, collection of data, analysis and manuscript preparation. 2) Shane Anthony, 10% concept, collection of data, analysis and manuscript preparation.	No
14	Visual Analog Scale rating change cut-offs for detection of improvement in nausea severity.	Submitted	First author: 90% contribution to paper as whole.	1) Andis Graudins, 10% concept collection of data, manuscript preparation	No

15	Randomized placebo-controlled trial of droperidol and ondansetron for treatment of adult emergency department patients with nausea: demonstration of a new outcome measure.	Submitted	First author: 70% contribution to paper as a whole, approx. comprising: 32% concept 20% collection of data; 79% analysis and manuscript preparation	1) Diana Egerton-Warburton, 32% concept, 10% collection of data; 3% analysis and manuscript preparation. 2) Michaela Mee, 32% concept, 10% collection of data; 3% analysis and manuscript preparation. 3) Andis Graudins, 4% concept, 10% collection of data; 3% analysis and manuscript preparation 4) Other co-authors: Alastair Meyer, Pourya Pouryaha, James Fahey, Gabriel Blecher and Sallyanne Crow were not involved in the study conception, but played minor roles in data collectin, analysis and manuscript preparation.	No
Related papers published during course of thesis					
7 + App-endix	Drug treatment of adults with nausea and vomiting in primary care.	Published	30% contribution to paper as a whole. (Second author)	1) Jeremy Furyk, 40% concept collection of data, manuscript preparation 2) Suzanne McKenzie, 30% concept collection of data, manuscript preparation	No
7 + App-endix	Drugs for the treatment of nausea and vomiting in adults in the emergency department setting.	Published	35% contribution to paper as a whole. (Second author)	1) Jeremy Furyk, 50% concept collection of data, manuscript preparation 2) Diana Egerton-Warburton, 15% concept collection of data, manuscript preparation	No

I have not renumbered sections of submitted or published papers, in order to generate a consistent presentation within the thesis.

Student: [redacted] **Date: 24th May, 2018.**

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: [redacted]

Date: 25/5/18

Acknowledgements

I gratefully acknowledge the initial encouragement of Professor George Braitberg, in getting me started on this course, along with the additional early support of Professor Don Campbell. Throughout the latter part of the process, the expert support and assistance of my supervisor, Professor Andis Graudins, was invaluable. This series of research projects could not have been completed without him.

I particularly acknowledge the contributions of Associate Professor Diana Egerton-Warburton and Dr Michaela Mee. Professor Egerton-Warburton and I had initial discussions about conducting both an ED-based antiemetic RCT, and an Australasian ED survey of antiemetic management practices prior to 2009. We were joined in the planning of these by Dr Mee in 2009. Funding for these studies was received from the Morson Taylor Award ($10,000), administered by the Australasian College for Emergency Medicine (ACEM), and the Monash Health Emerging Researcher Fellowship ($20,000). The latter Fellowship enabled Dr Mee to work full-time on the research for six months, during which time the national survey was largely completed and the RCT planned. Collaboration on all aspects of the survey and the RCT was equal. The identification, development and testing of alternate binary study outcome measures, however, was not a prominent part of the general collaborative discussions at this stage. The interest in the measurement tools being included in the RCT, and their analysis, was primarily mine. Given the large amount of teamwork involved, it was agreed that Dr Mee, Associate Professor Egerton-Warburton and I would be listed as first authors for the survey, RCT and measurement study respectively. It is not possible to conduct and complete such research, and especially a therapeutic RCT, without a strong team. The core team of Dr Mee, Associate Professor Egerton-Warburton and I again collaborated on the detailed planning and conduct of the second RCT. Funding was obtained for this from the Morson Taylor Award ($10,000), and the Monash Emergency Research Fund ($25,000). The assistance of the other listed co-authors in all of the research papers is also gratefully acknowledged.

Conduct and completion of the studies which took place within Monash Health, could not have occurred without the support of the Monash Health Emergency Programme, in particular the Programme and Departmental Heads during these past eight years: George Braitberg, Neil Goldie, Rachel Rosler, Tony Kambourakis, Garry Wilkes and Alastair Meyer. I also thank all the Monash Health emergency physicians, other ED doctors and medical students whose assistance over this time was vital for the successful completion of these research projects.

Finally, I most gratefully acknowledge the unwavering support of my wife, Vanessa, who generously tolerated my absences during times of study conduct, manuscript and thesis preparation. Her ongoing encouragement and stated belief in the importance and worth of the research were invaluable in bringing the thesis to a successful conclusion.

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List of PhD research-related publications.

Mee MJ, Egerton-Warburton D, Meek R. Treatment and assessment of emergency department nausea and vomiting in Australasia: a survey of anti-emetic management. Emerg Med Australas. 2011; 23(2): 162-8.

Egerton-Warburton D, Meek R, Mee MJ, Braitberg G. A Randomised Placebo Controlled Trial of Antiemetic Agents in Adult Emergency Department Patients with Nausea or Vomiting. Annals of Emergency Medicine. 2014; 64(5):526-532.e1.

Meek R, Egerton-Warburton D, Mee MJ, Braitberg G. Measurement and monitoring of nausea severity in Emergency Department patients: A comparison of scales and exploration of treatment efficacy outcome measures. Acad Emerg Med. 2015; 22(6): 685-93.

Meek R, Graudins A. Do antiemetic drugs benefit adult emergency department patients with nausea? The literature says no, but is it right? Emerg Med Australas. 2017; 29(6): 736-9.

Meek R, Graudins A, Anthony S. Antiemetic treatment in the emergency department: Patient opinions and expectations. Emerg Med Australas. 2018; 30(1): 36-41.

Meek R, Graudins A. Visual Analog Scale rating change cut-offs for detection of improvement in nausea severity. Submitted to Biostatistics & Epidemiology, Mar 2018.

Meek R, Egerton-Warburton D, Mee MJ, Graudins A, Meyer A, Pouryahya P, Blecher G, Fahey J, Crow S. Randomized placebo-controlled trial of droperidol and ondansetron for treatment of adult emergency department patients with nausea: demonstration of a new outcome measure. Submitted to Acad Emerg Med, May 2018.

Related studies published during the course of the thesis:
Furyk JS, Meek R, McKenzie S. Drug treatment of adults with nausea and vomiting in primary care. BMJ. 2014; 349:g4714.

Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD010106. DOI: 10.1002/14651858.CD010106.pub

List of abbreviations or technical terms.

Abbreviation	Definition
5-HT3	5-hydroxytryptamine 3 (receptor)
ACEM	Australasian College for Emergency Medicine
CI	Confidence Interval
CINV	Chemotherapy-induced nausea and vomting
CRTZ	Chemoreceptor trigger zone
D2	Dopamine 2 (receptor)
ED	Emergency Department
Emetogenic	Having the capacity to induce emesis (vomiting)
FDA	Food and Drug Administration (USA)
H1	Histamine 1 (receptor)
IQR	Inter-quartile Range
IV	Intravenous
M	Muscarinic (receptor)
MCSD	Minimum Clinically Significant Difference
NK1	Neurokinin 1 (receptor)
NRS	Numerical Rating Scale
PONV	Post-operative nausea and vomiting
PPV	Positive Predictive Value
RCT	Randomized controlled trial
ROC	Receiver operated characteristic (curve or analysis)
ROC AUC	ROC Area Under the Curve
SD or sd	Standard Deviation
US or USA	United States of America
VAS	Visual Analog Scale
VRS	Verbal Rating Scale (often used interchangeably with NRS)

Improving outcome measures for antiemetic efficacy trials in adult emergency department patients with nausea.

Chapter 1. Nausea and vomiting: neurophysiology and the theoretical basis for pharmacological treatment.

1.1. Introduction

The series of related research projects which make up the body of this thesis by publication, concern outcome measures for use in antiemetic drug trials for adult emergency department (ED) patients with nausea.

To put this research in context, background information relevant to the topic is presented in the following chapters. This is included in order to demonstrate the importance of research in this area, highlight the knowledge gaps, and illustrate how and why this series of related research projects came about.

This first chapter explains, as far as it is known, the physiology of nausea and vomiting. The theoretical basis and mechanism of action for antiemetic drugs is included, along with information on the history of their development.

1.2 The physiology of nausea and vomiting.

As with much neurophysiology, that related to nausea and vomiting remains incompletely understood. With regard to the generation of symptoms in the brain, writers on the topic refer to a 'vomiting center'. [1,2] Sanger (2006) and Horn (2014) point out that while this is a useful concept, the vomiting center is not one discrete structure.[1,2] Becker (2010), Gan (2007) and Horn (2014) describe the vomiting center as being in the hindbrain, within the medulla oblongata.[2–4] The review articles of Gan (2007) and Becker (2010) list afferent inputs to the vomiting center as not only being from the gastrointestinal tract, but from other abdominal viscera, the heart, the vestibular system, the 'chemoreceptor trigger zone' (CRTZ) and higher centers in the forebrain.[3,4] The CRTZ is another useful concept, which is also almost certainly not a single structure. Becker (2010) and Horn (2014) give the location as being near the vomiting center, in the area postrema, between the medulla and the floor of the fourth ventricle.[2,3] An important feature of this area, which has input to the vomiting center, is that it is outside the blood-brain barrier. This means that circulating substances can directly activate the CRTZ and generate nausea and vomiting, without the involvement of any particular body organ. Becker (2010) describes how activation of the vomiting center generates

motor messages to the upper gastrointestinal tract via multiple cranial nerves, to the lower gastrointestinal tract via vagal and sympathetic nerves, and to the diaphragm and abdominal muscles via spinal nerves.[3] This brings about the muscular actions which result in the expulsion of gastric contents, known as vomiting. Gan (2007) also adds that simultaneous motor messages to the pharynx act to close the glottis, thereby preventing pulmonary aspiration of vomitus.[4]

Beyond trying to define and describe the anatomy, research has also focused on neurotransmitters. These either deliver input to the CRTZ and vomiting center, or transmit outbound messages which generate nausea and vomiting. This research is equally imprecise, but a review article by Sanger (2006) provides an excellent summary.[1] Dopaminergic, and to a lesser extent, histaminic and muscarinic receptors, seem to play a key role in activating the vomiting center. The group of serotonin receptors and one sub-type in particular, the 5-hydroxytryptamine 3 (5-HT3) receptor, are also important. They are involved in transmission of input from the gastrointestinal tract, and some other organs, to the CRTZ and vomiting center. The CRTZ also has a number of different opioid receptors. More recent research suggests neurokinin receptors play a role on both the afferent (input) and efferent (output) side. The transmission routes from the forebrain to the vomiting center in the hindbrain are even less well understood. These relate to the triggering of vomiting by strong emotions, for which the transmitters seem to not be the same. Sanger (2006) also speaks of a forebrain 'antiemetic center', where for example, cannabinoids and naloxone appear to act.[1] Cannabinoid receptors in the forebrain and elsewhere appear to have some role in nausea and vomiting. Ultimately, the reasons why some people experience nausea and/or vomiting after a particular stimulus, and others do not, remains unknown. Figures 1-1 and 1-2 illustrate the involved receptors and some of the neural pathways, as far as they are known.

1.3 Antiemetic drugs: rationale and mechanism of action.

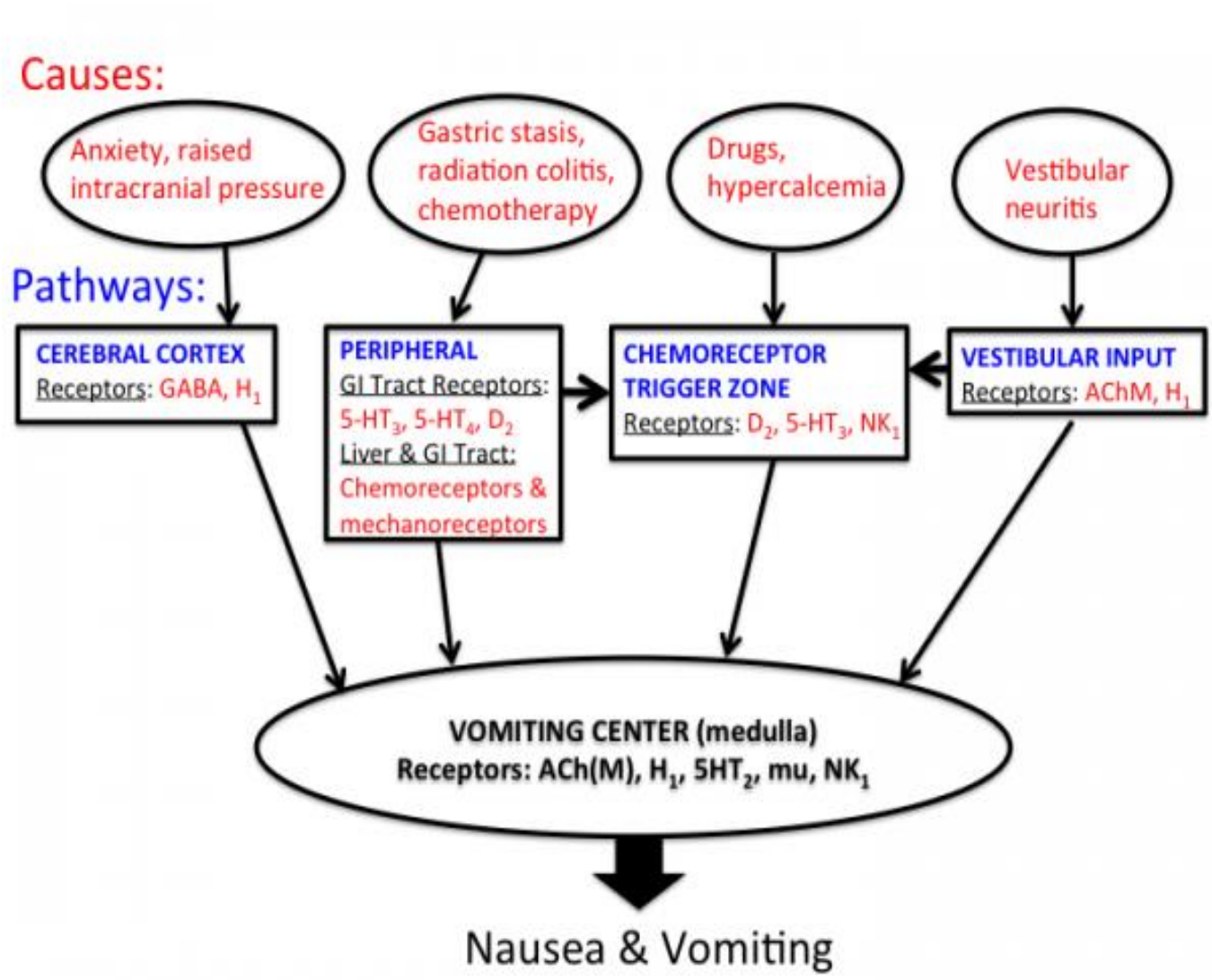
The main receptor types for the generation of nausea and vomiting, and their more specific subsets, are histaminic (H1), muscarinic (M), dopaminergic (D2), serotonergic (5-HT3), neurokinin (NK1) and less clearly identified corticosteroid receptors. [2,4]

Gan (2007) and Horn (2014) give summaries of the sequential development of a number of drugs which act as antagonists at these receptors, and outline their use in different settings. The following brief description, which is sufficient background information for the purposes of this overview, is largely drawn from these two papers.[2,4]

Anticholinergics and antihistamines were the first modern antiemetic drugs, becoming available in the 1950s and 1960s. Early studies on the treatment of patients with post-operative nausea and

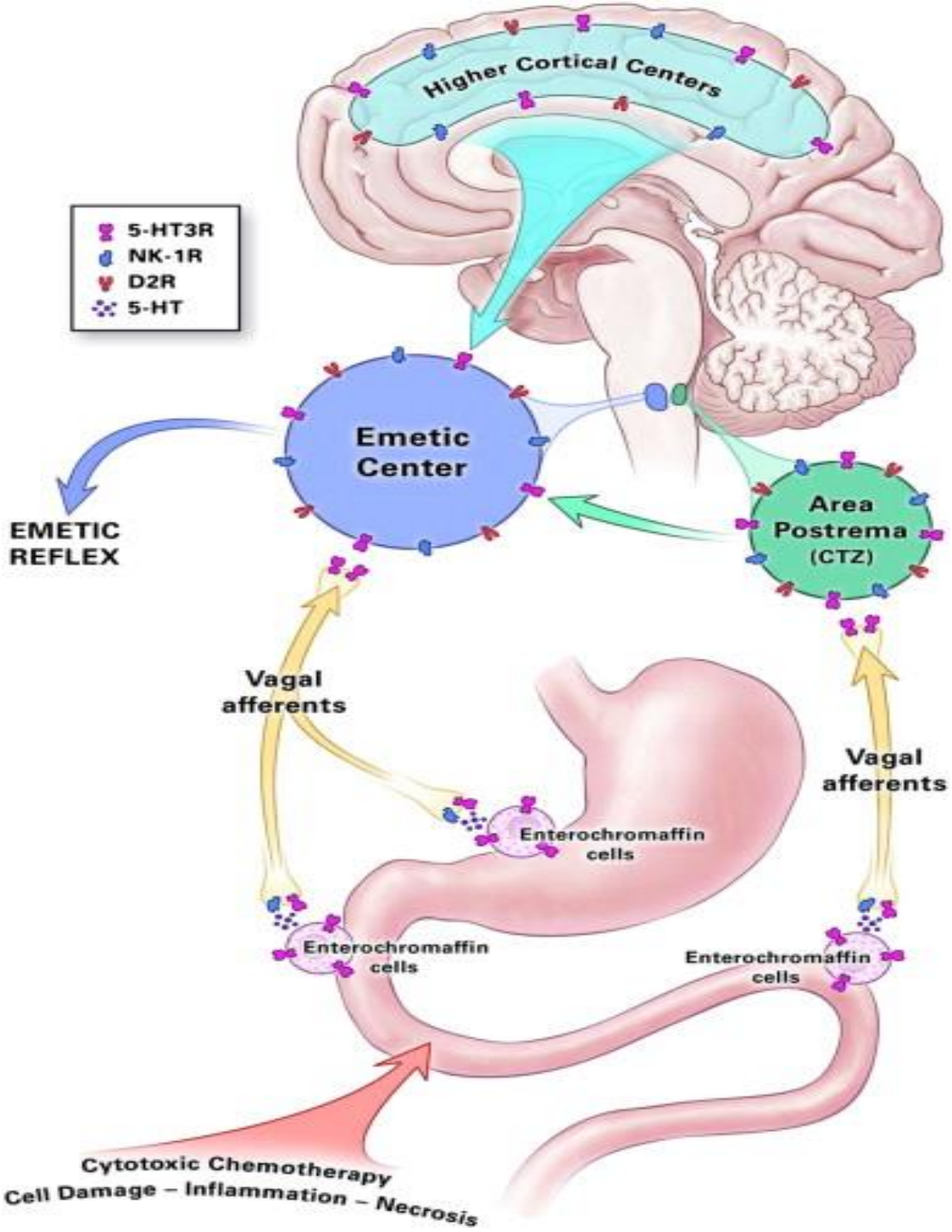
Figure 1-1: Main receptors involved in the emetogenic pathway.

The major receptor subtypes indicated are: muscarinic (AChM); dopamine type 2 (D_2); histamine type 1 (H_1); neurokinin type 1 (NK_1); serotonin type 2 or 3 ($5\text{-}HT_2$ & $5\text{-}HT_3$); opioid mu (mu).



Sourced from URL: http://tmedweb.tulane.edu/pharmwiki/doku.php/nausea_and_vomiting [Accessed 22 March 2017] (Free access on Tulane University Medical School website, Medical Pharmacology section. This figure was an adaptation from that in: Harris DG. Nausea and vomiting in advanced cancer. 2010. Br Med Bull 96:175-185).

Figure 1-2. An illustration of some of the neural pathways involved in the generation of nausea and vomiting.



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vomiting (PONV) suggested that while both were effective, the antihistamines were preferred due to their more favorable side-effect profile.[2,4] One antihistamine in particular, promethazine, is still used as a second-line antiemetic agent today.[5] In the 1960s, drugs from three different groups, the phenothiazines, butyrophenones and benzamides, were found to have antiemetic properties through blockade of dopamine receptors. [2,4]

Most phenothiazines, which have been used as sedatives since the 1940s and 1950s, are too sedating for routine antiemetic use. Only one, prochlorperazine, remains in use as a second-line antiemetic agent today. [2,4,5]

The most well-known butyrophenones, haloperidol and droperidol, were primarily developed as sedative and anti-agitation agents. Droperidol, at the doses used for nausea and vomiting, has fewer extrapyramidal side-effects than haloperidol. Its effectiveness has been demonstrated for the treatment of PONV. In 2001, a 'black box' warning from the US Food and Drug Administration (FDA) resulted in a decline in its use. The warning pertained to a concern about QT prolongation and potential cardiac arrhythmias.[2,4] This risk has since been shown to be negligible at the doses used for treatment of nausea and vomiting.[6] Due to this, there has been a recent resurgence of interest in the use of droperidol as an antiemetic.[6]

Use of the best known benzamide with antiemetic properties, metoclopramide, increased in the US in the late 1970s. It was promoted as being the best treatment for the side-effects of cisplatin. Cisplatin, first used during the 1970s, was the most effective chemotherapeutic agent developed to that time. Unfortunately, however, it is highly emetogenic. Research on treatment for chemotherapy-induced nausea and vomiting (CINV) rapidly increased from this time. While early studies of metoclopramide, for both CINV and PONV, showed positive findings, ongoing research has yielded more equivocal results.[2,4]

In the last twenty years, the role of neurokinin (NK1) receptors in the generation of nausea and vomiting, particularly from the brainstem, has been elucidated. The first NK1 receptor blocker, aprepitant, was approved for use in the US in 2003 and in Australia in 2012. Fosaprepitant was approved for use in the US in 2008. Trials in CINV suggest that aprepitant is particularly useful for suppression of later onset, ongoing vomiting. Surprisingly, for both CINV and PONV, aprepitant seems to significantly reduce the physical occurrence of vomiting, while impacting little on the severity of concurrent nausea.[2,4] As yet, there is not a sufficient body of work in either field to allow for systematic reviews on the effectiveness of NK1 blockers.

A summary of the agents most commonly used as antiemetic drugs, their receptor of action, and the specific conditions for which they are recommended is given in Table 1-1. This is part of a larger table from Horn (2014).[2]

1.4 Implications for ED-based research.

In summary, nausea and vomiting are part of the symptomatology in a wide variety of clinical settings. These include the presence of circulating substances which act directly on the CRTZ, and toxins within the gastro-intestinal tract (GIT) which bring about the release of local mediators. Abnormalities of the vestibular system, various other organ dysfunctions and non-specific higher center stimulation, may also induce these symptoms. All or any of these situations can be present in ED patients. It is possible that a range of antiemetic regimens may be required to treat ED patients with nausea and vomiting from different conditions. If this were so, it may not be reasonable to compare an anti-dopaminergic drug such as metoclopramide, with a 5-HT3 blocker such as ondansetron, in patients with nausea and vomiting from any cause. Condition-specific research, however, is extremely limited.

Sanger (2006) hypothesized that central "disruption of transmission within the integrative mechanism", should mean that the development of a truly universal antiemetic drug is possible.[1] Obviously, this would be ideal in the ED setting, and the concern regarding condition-specific treatments would cease to exist. Interestingly, Sanger (2006) expressed the hope that the universal antiemetic drug might be a neurokinin receptor blocker. Thus far, this is looking unlikely.

Sanger (2006) also made the point, however, that there is extensive overlapping of the involved receptors in different conditions. This would explain why particular receptor antagonists still appear to be effective for conditions thought to predominantly involve a different receptor.[1] (Table 1-1) On balance, the evidence supports that it is reasonable to conduct research which compares the effectiveness of different receptor blockers in ED patients whose nausea is associated with a variety of underlying conditions.

Table 1-1. Common drugs for each receptor site, and conditions for targeted treatment.*

*Adapted from Horn (2014).[2]

Receptor of action	Condition	Representative agent
H1 antagonist	Migraine, motion sickness, vestibular disease, post-operative	Diphenhydramine Cyclizine Promethazine
M antagonist	Motion sickness, vestibular disease	Scopolamine
D2 antagonist	Migraine, gastroenteritis, post-operative	Prochlorperazine Droperidol Metoclopramide
5-HT3 antagonist	Hyperemesis gravidarum, chemotherapy, gastroenteritis, post-operative	Ondansetron Granisetron Tropisetron Ramosetron
NK1 antagonist	Chemotherapy, post-operative	Aprepitant Fosaprepitant
"Corticosteroid"	Hyperemesis gravidarum, post-operative, chemotherapy	Dexamethasone

H = Histaminic, M = Muscarinic, D = Dopaminergic, HT = Hydroxytryptamine, NK = Neurokinin

CHAPTER 2. Reasons for the treatment of nausea and vomiting.

2.1 Introduction

The previous chapter explains the theoretical basis for the pharmacological treatment of nausea and vomiting. Having the potential to modify symptoms, however, does not necessarily mean that this is either desirable or worthwhile. In the case of nausea and vomiting, there are a number of compelling reasons to support the development and use of effective treatments. An overview of these is given in the following sections. This is for purposes of further placing the later research studies in context, and is not intended to be an exhaustive review of the literature on these individual background topics.

2.2 Patient distress and preference.

Patient fear of nausea and vomiting, and desire for its treatment has been investigated in different settings. In a survey of pre-operative patients, Macario (1999) reported that vomiting was the most feared post-operative complication.[7] It ranked ahead of such events as waking with an endotracheal tube in situ and pain. Post-surgery surveys by Parra-Sanchez (2012) and Gan (2007), respectively reported that PONV significantly impacts on quality of life, and that patients would be willing to pay extra for surgery if PONV could be avoided.[4,8] Beusterian (2014) reported that in patients having chemotherapy for breast cancer, choosing a cytotoxic regimen which minimized nausea and vomiting, was as important as minimizing the chance of neuropathy and myalgia.[9] Bridges (2012), in a survey of patients with lung cancer, reported that nausea was viewed as the second least desirable complication of treatment behind fatigue.[10] Kuchuk (2013) and Havrilesky (2014), for patients with breast and ovarian cancer respectively, reported that patients preferred shorter cytotoxic regimens in order to reduce CINV, despite the impact of this on potential recurrence and long-term survival rates.[11,12] Gregorian (2010) conducted a community based survey of patients given opioid prescriptions, and found that nausea and vomiting were the most important side-effects for which trade-offs in pain relief would be taken. [13] No other primary care, and no ED-based research on this topic, could be located.

2.3 Medical complications.

The three most important medical complications reported to arise from vomiting are gastrointestinal bleeding, usually from oesophageal mucosal tears, dehydration with or without electrolyte disturbances, and pulmonary aspiration of vomitus. Despite vomiting being a common problem, there is little information on the true incidence of these complications. A brief description of each is offered.

2.3.1 Acute upper gastrointestinal bleeding.

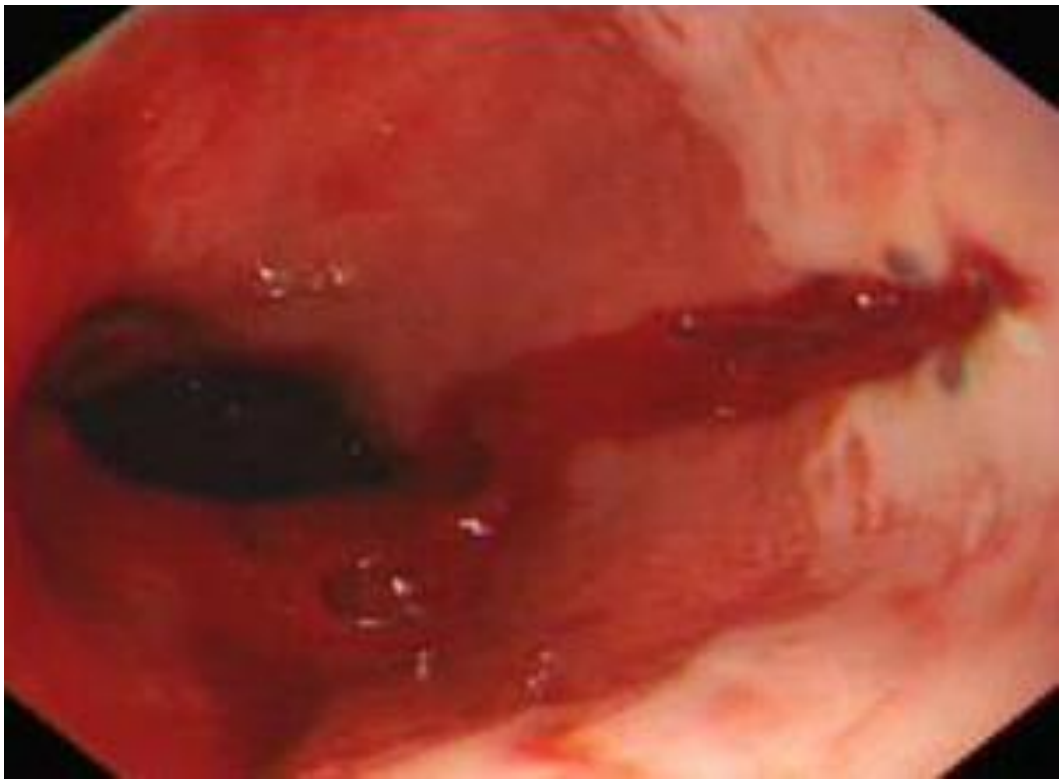
This usually arises from an oesophageal mucosal tear, most often near the gastro-oesophageal junction. This was first described by Mallory and Weiss in 1929, and is generally referred to as Mallory-Weiss Syndrome.[14] An illustration is shown in Figure 2-1. While probably uncommon, the true incidence is not known, since diagnosis requires hospital admission for endoscopy. Ljubicic (2014) reported a large retrospective study, which estimated the one-year cumulative incidence of Mallory-Weiss Syndrome at 7 per 100,000 ED attendances.[15] Reports by Ljubicic (2014), Yin (2012), Marmo (2012), Halland (2010) and Akhtar (2011) all broadly agree that Mallory-Weiss Syndrome accounts for between 3 and 12% of all hospital admissions for acute upper gastrointestinal bleeding. Middle-aged men are most frequently affected. [14–18] The course is usually benign, with management being conservative, although the mortality rate is generally reported at between 5 and 10%. Ljubicic (2014) and Yin (2012) reported that the mortality rate increases with age, presence of comorbidities and presentation in shock.[14,15] Death is usually due to later multi-organ failure, rather than acute blood loss. Oesophageal rupture following forceful vomiting can also occur, but is rare. It was first described by Boerhaave in 1724, and remains known as Boerhaave's Syndrome.[19] The population incidence and proportion of those with acute upper gastrointestinal bleeding who have Boerhaave's Syndrome, have not been well described. A review article and case report by Atallah (2004), suggests that the mortality rate is high, with the majority of cases being middle-aged men with a number of comorbidities.[19]

2.3.2 Dehydration and electrolyte disturbance.

Dehydration is generally accepted as a common complication of ongoing vomiting, but there is little information on true incidence, either from all causes of vomiting, or for specific conditions. Most available information relates to gastroenteritis, particularly in children. For example, one large

Figure 2-1. Gastroscopic view showing a partial thickness lower oesophageal mucosal tear (Mallory Weiss Syndrome).

The tear is on the right of the image (3 o'clock) with the gastro-oesaphageal opening to the left (9 o'clock).



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review by Kaiser (2012) reported that of children admitted to hospital with gastroenteritis, about 1% have evidence of acute kidney injury on blood testing, with a similar proportion having hypernatraemia.[20] Incidence of milder dehydration in those not being admitted to hospital is unknown. A US Center for Disease Control and Prevention report (2009) on a gastroenteritis outbreak in three US colleges in 2008, found that of about 1000 students affected, 10 (1%) were admitted to hospital with dehydration.[21] Again, this will represent the more severe end of the spectrum, and the true incidence of dehydration in gastroenteritis is likely to be higher. Notably, in gastroenteritis, both diarrhea and vomiting usually contribute to body fluid loss.

2.3.3 Aspiration pneumonia.

While pulmonary aspiration is an accepted and potentially serious complication of vomiting, there are little data on its incidence, either overall, or in specific conditions. As highlighted in a review article on protective airway mechanisms by Pitts (2014), aspiration is rare in people with a normal level of consciousness and normal neuromusculature of the pharynx.[22] Hu (2014), reported that in a series of in-hospital deaths from aspiration pneumonia, almost all patients had either a depressed level of consciousness, or some abnormality of swallowing.[23] Similarly, Taylor (2013) reported that the majority of hospital patients with aspiration pneumonia were elderly, with significant comorbidities such as chronic liver disease, cardiac failure and stroke.[24]

2.4 Economic burden.

Costs to the healthcare system from patients suffering with nausea and vomiting are not insubstantial. The literature, although mainly from the US, can probably be extrapolated to other western countries. In the US, Kane-Gill (2014), Parra-Sanchez (2012), and Kranke (2007) report that the additional healthcare costs from PONV, are between $300 and $900 per patient.[8,25,26] Drug costs, staff time, increased lengths of stay and hospital readmission contribute to this total. Costs also vary depending on the type of hospital. While there has been no research on indirect costs to the patient from PONV, such as from delayed return to work, papers by Dzwonczyk (2012), Parra-Sanchez (2012), Kranke (2007) and Kane-Gill (2014) all support the prophylactic provision of antiemetic drugs as being cost-effective for both the hospital and the patient.[8,25–27] This is based on drug use reducing the incidence of PONV from about 60% to 40% in higher risk subgroups and the drug costs being relatively low.

Studies in the US, by Carlotto (2013) and Craver (2011), report that the additional per patient cost of an episode of CINV is between $1400 and $1900, although this varies depending on the cytotoxic regimen. [28,29] Craver (2011) also noted that provision of prophylactic antiemetic drugs is estimated to reduce healthcare costs by an average of $270 per patient. [29] Haiderali (2011) estimated the additional cost of uncontrolled CINV from additional medication purchases, unplanned medical visits, lost work and opportunity, at almost $800 per patient, although the sample size was relatively small.[30]

The costs related to nausea and vomiting in the community are more difficult to study, and research is scarce. Piwko (2013) reported that for pregnant women in the US, the occurrence of ongoing nausea and vomiting generates a total additional cost per patient of $1,800.[31] About 60% of this is incurred by the healthcare system, and 40% by the patient in lost wages, opportunity and additional childcare costs.[31] Kwong (2010) studied the cost to the community of opioid induced nausea and vomiting. It was found that of all patients given a prescription for opioid analgesics, seven percent needed to fill an antiemetic drug prescription in the following days. The cost to the patient and healthcare system then varies widely, from a few hundred to over $1000 per patient. This depends on whether general practice, ED care or hospital admission is required as a consequence.[32] Kane-Gill (2014) also noted that given the growing frequency of opioid use in the community, the total costs to the healthcare system from side-effects such as nausea and vomiting is likely to remain substantial.[25]

The economic burden from ED patients with nausea and vomiting has been less studied. One large US database review by Myer (2013) reported that from 1997 to 2007, total ED visits increased by 23%, but that the proportional increase in attendances for gastrointestinal conditions was relatively greater. Record coding showed that 10% of the gastrointestinal attendances had nausea and vomiting listed as the sole diagnosis. Many other conditions, such as non-specific abdominal pain, gastroenteritis and a variety of surgical conditions, are also likely to have nausea and vomiting as associated symptoms. The average healthcare cost per patient with a gastrointestinal condition, was estimated at $1,500. This varied depending on whether or not hospital admission (22% admission rate) was required. [33] No similar Australian economic data is available, nor has the gastrointestinal caseload in Australian EDs been described. It should be remembered that in the ED, nausea and vomiting are not restricted to gastrointestinal conditions. In ED-based antiemetic trials in Australia and the US, between 40% and 70% of study patients had gastrointestinal conditions. [34–40] The remainder had a range of other conditions, such as non-gastrointestinal infections and

headache. This supports the assertion that basing the economic burden to the healthcare system of ED nausea and vomiting on gastrointestinal conditions alone, is likely to underestimate the true cost.

2.5 Implications for ED-based research.

There is little literature concerning the beliefs or expectations of ED patients with regard to antiemetic drug treatment.[41] Addressing this knowledge gap appears warranted. It seems unlikely, however, that ED patients would view nausea and vomiting with any less fear and distress than do patients with CINV or PONV.

For ED patients, all of the potentially serious medical consequences of ongoing vomiting are relevant. Anecdotally, minor upper gastrointestinal bleeding is not uncommon, but no reliable data is available. Limited evidence suggests that many patients who are admitted to hospital with vomiting conditions have some level of dehydration. Patients with altered levels of consciousness from a variety of causes, along with the elderly and infirm, seem to be at most risk for the medical complications of vomiting. Severe upper gastrointestinal bleeding and significant morbidity from aspiration pneumonia might be relatively uncommon, but if antiemetic treatments were proven to be effective for ED patients, then prevention is clearly better than cure. While the currently planned studies in this series of research projects focus on outcome measures for therapeutic trials, studies of harm arising from nausea and vomiting are still required.

A study on the economic burden from nausea and vomiting in ED patients in the Australian setting would also be of great interest. Methods for calculating costs to both the healthcare system and the patient would need to be determined. If these costs were proven to be significant, there would be an increased incentive for continued ED-based antiemetic research. This would be a worthwhile, but major undertaking.

CHAPTER 3. Research in non-ED clinical settings.

3.1 Introduction.

The majority of research on antiemetic drugs has involved the treatment of patients with PONV and CINV. ED-based antiemetic research is relatively new, and small in quantity. An overview of the PONV and CINV literature is presented to illustrate how antiemetic drug efficacy has been demonstrated in those fields.

3.2 Post-operative nausea and vomiting (PONV).

The most comprehensive assessment of the PONV literature is the Cochrane Systematic Review by Carlisle (2006).[42] This includes 737 RCTs, dating from 1967 to 2006. The two earliest studies, by Snow (1967) and Handley (1967) both compared an antiemetic drug with placebo.[43,44] The drugs studied were trimethobenzamide by Snow, and metoclopramide and perphanazine by Handley. Study drugs were given either immediately post-operatively or intra-operatively. The primary outcome measure for Snow (1967) was presence of 'retching' at an undefined time-point post-operatively, and for Handley (1967) was presence of either nausea or vomiting at any time up to four hours post-operatively.[43,44] A variety of outcomes are considered in the review of Carlisle (2006), but the most frequently used in over forty years of research, is whether or not post-operative nausea and vomiting occurred. The meta-analysis led to the general conclusion that drugs were of benefit over placebo for the prevention of PONV, with a Risk Ratio of 0.33 (95% CI: 0.22 – 0.49). On average, the incidence of PONV was about 30% in placebo groups, compared with 20% in drug groups. The absolute risk reduction of 10% gives a Number Needed to Treat of 10.[42]

Drugs proven to be effective using this outcome measure include:

- antihistamines: cyclizine, diphenhydramine and promethazine
- anti-dopaminergic drugs: droperidol, metoclopramide and prochlorperazine
- 5-HT3 blockers, including ondansetron
- Corticosteroids, including dexamethasone.

Carlisle concludes that there is no convincing evidence for the superiority of any one drug over another, or for drug combinations being superior to single drugs. [42]

In most studies, presence of PONV was determined at one post-operative time-point. A smaller number of studies record presence of symptoms at two or more different times, for up to 72 hours. Some include comparisons of 'early' (up to six hours post-operation) versus 'late' (4 to 24 or 72 hours) onset of PONV. [42]

When present, the severity of the nausea at any time-point is not usually measured or compared between groups. Carlisle (2006) noted that since nausea was an "internal symptom", its severity was difficult to measure. Interestingly, and presumably due to the weight of evidence to that point, Carlisle (2006) concluded that any further comparative drug studies for PONV did not seem a research priority.[42]

Although nausea severity ratings have not been a frequent feature in the PONV research, Boogaerts (2000) described the reliability and high correlation between the VAS and an adjectival scale ('none', 'mild', 'moderate', 'severe') for the rating of post-operative nausea severity. He reported that VAS scores of 0 – 10 mm correlated with no nausea, 11 – 40 mm with 'mild', 41 – 70 mm with 'moderate' and 71 – 100 mm with 'severe' symptoms. He recommended the use of the VAS over the ordinal adjectival scale, due to its generally higher sensitivity and ease of use. He also noted that drugs tended to be given once VAS scores exceeded 40 mm, and recommended this as a threshold for treatment. [45]

Since the review of Carlisle (2006), the outcomes used in PONV trials have remained essentially the same. This is illustrated by the findings from three recently published PONV antiemetic trials. Ham (2016) compared post-operative administration of aprepitant with placebo. Although nausea severity was rated on the NRS at 6, 24 and 48 hours, the primary outcome was prevention of PONV.[46] Joe (2016) compared pre-operative ramosetron with placebo. Nausea severity was rated on the NRS at 0, 6 and 24 hours, but again, the primary outcome was symptom presence (any severity). Occurrence of 'severe' PONV (severity 7 – 10) in each group, and use of rescue medication were other secondary outcomes.[47] While both papers described the severity rating data for patients who developed symptoms, no comparative analyses were performed. A third recent RCT, by Song (2016), was somewhat different, in that it involved patients receiving a post-operative opioid infusion. One group had dexmedetomidine, a sedative and analgesic agent with antiemetic properties, added to the infusion, the other did not. Nausea severity ratings were taken using the VAS on multiple occasions from 1 to 48 hours post-operatively. For the binary primary outcome of presence of PONV (any severity), the between-group difference was statistically significant. The conclusion was that addition of an antiemetic drug to the infusion was effective in preventing PONV.

When nausea was present, the difference in mean VAS ratings was also compared between groups, but was not statistically significant.[48]

3.3 Chemotherapy-induced nausea and vomiting (CINV).

While antiemetic drug trials for PONV and CINV both began in the 1960s, research in CINV increased more rapidly from the 1970s. As an illustration of the volume of research, on 1 March 2017, an Ovid Medline search using the terms chemotherapy and antiemetic, limited to RCTs, yielded 1,885 results.

Gralla (1981), on reviewing the early CINV studies of the 1960s, pointed out that results were equivocal for the anticholinergics and antihistamines available at the time.[49] In the 1970s, there was a burst of interest in cannabinoids as antiemetics for CINV, with a number of RCTs being published between 1975 and 1985. As an example, Herman (1979) administered either nabilone (a new synthetic cannabinoid) or prochlorperazine, prior to chemotherapy, using multiple different regimens. Patients rated their average daily nausea severity on an adjectival scale for some days. The conclusion was that prevention of CINV was rare in both groups, but that nabilone was superior to prochlorperazine for "partial resolution" of symptoms (80% versus 32%).[50] This seemed promising at the time, but after the introduction of cisplatin in 1978, it was clear that more effective antiemetic drugs were needed. Cisplatin was the most effective chemotherapeutic agent yet developed, but induced severe nausea and vomiting in at least 80% of recipients. [49]

To address this need, CINV research output increased rapidly from this time, with RCTs such as those of Williams (1980), Gralla (1981) and Cox (1982) being published in the early 1980s.[49,51,52] These relatively early studies often featured metoclopramide, which was seen as the most promising new antiemetic drug following its introduction to the US in 1979. Williams (1980) compared metoclopramide, cyclizine and nabilone with placebo. An average NRS rating for the preceding day was taken 24 hours post-chemotherapy, and compared between groups. Differences were not statistically significant, which was thought due to the fact that the drugs were given orally.[51] Gralla (1981) compared IV metoclopramide and prochlorperazine with placebo. The number and volume of vomits (measured in mL), and duration of nausea were the primary outcome measures. Metoclopramide was found to be superior to prochlorperazine and placebo based on these outcomes.[49] Cox (1983) compared IV metoclopramide with placebo. It was found that metoclopramide was superior to placebo for the primary outcome of prevention of vomiting (47% versus 17%). [52]

As newer drugs became available in the 1980s, CINV research also increased, but as with the studies of the early 1980s, outcome measures varied. Del Favero (1990) pointed out that the use of different outcome measures made comparison of trials difficult. He compared the VAS and adjectival scale for nausea severity ratings in CINV. There was good correlation between the two, but he pointed out that with the VAS, the distribution of the "maximum intensity" was skewed. He believed this invalidated the use of parametric tests for the analysis, and advised that the VAS had no advantage over the adjectival scale. His final conclusion, however, was that "complete protection from nausea (and vomiting) must remain the prime efficacy parameter with which to assess the validity of any new antiemetic treatment." [53] As with PONV research, the binary outcome of presence, or not, of nausea and vomiting, was becoming more clearly accepted as the universal primary outcome measure. Difference in severity of symptoms, when present, remained of secondary interest only.

Ten years on from the Del Favero (1990) paper, the study of Bosnjak (2000) is a typical example of the outcome measures being used. In this RCT, all patients received a steroid and a benzodiazepine, with one group also receiving metoclopramide, and the other ondansetron. The primary outcome was a comparison of the occurrence of nausea and/or vomiting. Some recent papers include severity ratings, but these remain secondary.[54] For example, Lindley (2005) compared two different antiemetic regimens for CINV. Outcome measures were presence of vomiting, use of 'rescue' antiemetic medication and daily average VAS ratings for up to 5 days post-chemotherapy. The primary outcome was control of vomiting, which was defined as: no vomiting episodes, no use of rescue medication and a nausea severity rating of less than 10 mm on the VAS. Numbers per group in a few VAS ranges (10 – 20 mm, 21 – 50 mm, and > 50 mm) were described, but not analyzed for difference.[55] In a more recent study by Albany (2012), all patients received dexamethasone, with one group receiving aprepitant and the other placebo.[56] As with the study by Lindley (2005), the primary outcome was 'complete response', meaning no vomiting and no rescue medication. Patients similarly nominated an average daily nausea severity rating on the VAS for several days. However, in the Albany (2012) study, these were compared as a secondary outcome. For the binary primary outcome, the aprepitant group was superior to placebo (42% versus 13%). When nausea did occur, the between-group differences in the daily mean VAS ratings were not statistically significant.[56]

Interestingly, there is no current Cochrane systematic review on the general effectiveness of drugs versus placebo, or a comparison between drugs, for adults with CINV. Presumably this is due to a combination of the volume of the literature, and the general acceptance that treatment is effective.

The most recent effort, by Billio (2013),[57] was restricted to a review of the 5-HT3 antagonists in CINV. Although said to be accurate at the time of publication, it was considered to be obsolete by 2015, and has been withdrawn. For example, in the twelve months from 1 April 2016 to 31 March 2017, 20 new CINV-related RCTs were listed on Ovid Medline. The most recent of those, by Takemoto (2017), also uses the binary primary and secondary outcomes of 'complete response' and 'complete protection'. These are defined respectively as: no vomiting and no use of rescue antiemetic medication; no vomiting, no rescue medication and a severity rating of 'none' or 'mild'. The latter severity ratings were taken daily on an adjectival scale ('none', 'mild', 'moderate', 'serious') and were only used to determine the 'complete protection' outcome.[58] They were not separately reported or compared between groups.

3.4 Discussion and implications for ED-based research.

The standard primary outcome used for both PONV and CINV research is prevention of nausea and vomiting. The binary outcome measure, of no nausea versus any amount of nausea, is easy to understand and the clinical interpretation is straightforward. Based on findings using this outcome measure, the PONV and CINV research has consistently reported that antiemetic drugs are effective in comparison with placebo. Although there is variability between drug regimens following different types of surgery, the review of Carlisle (2006) suggests that, in general, drugs reduce the risk of PONV from about 30% to 20%.[42] It is more difficult to give a global figure for CINV, because different chemotherapy regimens vary widely in their emetogenic potential. Consequently, effect sizes also vary widely, but findings in favour of antiemetic drug effectiveness have been consistently reported.

In the ED, where the patient already has nausea, the primary objective of antiemetic therapy is the fairly rapid reduction of symptom severity. Ideally, the symptoms might be reduced to zero, but unless the underlying condition is rapidly curable, this is unlikely to occur during the ED episode of care. Symptom presence and severity could be followed to resolution after ED discharge, but again, the duration of the symptoms will be influenced by the type and severity of the underlying condition. This is quite different to the situation in PONV and CINV research, where the emetogenic stimulus is given only once, and the drugs which precipitate the symptoms have a known and finite duration of action.

For those who develop nausea post-operatively or following the administration of chemotherapy, between-group comparisons of symptom severity at different time-points are sometimes performed. For this outcome, the VAS, validated in these settings by Boogaerts (2000) and Del

Favero (1990),[45,53] has been used to measure severity and monitor change. The degree of difference which might be clinically significant, however, has never been investigated or discussed in the PONV and CINV literature.

In conclusion, the primary outcome for PONV and CINV studies is nausea prevention. For this, a binary outcome measure of no nausea versus presence of nausea can be used. This allows treatment success rates to be directly compared between groups. Findings are easy to interpret and clinically meaningful. In the ED, patients already have nausea and the aim of treatment is a relatively rapid reduction in symptom severity. This means that the outcome measures used in ED-based studies must necessarily be different. The issues associated with this are discussed in the following chapters.

CHAPTER 4. Measurement and monitoring of subjective symptoms.

4.1 Introduction.

Demonstration of change in nausea severity requires a comparison of severity ratings taken at different points in time. In the systematic review of the PONV research, Carlisle (2006) commented on the difficulty of measuring and monitoring the severity of an 'internal symptom' such as nausea.[42] To aid the understanding of how particular measures came to be used in ED-based antiemetic research, a brief history of the measurement scales used to rate subjective symptoms is given here.

4.2 Development and reliability of measurement scales.

A review article by Kersten (2012) gives a succinct history of the types of measurement scales which have been developed and used by researchers for the rating of subjective symptoms.[59] The VAS was first described in the 1920s as a tool to rate strength of emotions in psychology research. Likert, also a psychology researcher, published the first paper formally describing the use of ordinal scales in 1932.[60] These scales were little used in medical research until the 1970s. Research methodology was improving, and the VAS and ordinal scales were seen as a practical way to quantify subjective symptoms, such as pain and dyspnea. A summary of the scales and their approximate origins, as described by Kersten (2012),[59] is provided in Table 4-1. The more recent major papers on the use of measurement scales in medical research, and their conclusions, are described in Table 4-2. This includes the paper by Todd (1996), which defined a 'minimum clinically significant difference' (MCSD) on the VAS for change in pain severity.[61] This was a novel concept at the time. The methods of analysis for comparing change in severity, however, remain somewhat controversial. A summary of the key papers in the debate is given in Table 4-3.

In conclusion, as Hawker (2011) points out, both the VAS and NRS are quick and easy to use.[62] A number of researchers have stated a preference for the VAS, due to its greater sensitivity for detection of change, with Price (2012) providing the most compelling support for the VAS over the NRS. With regard to analysis, the use of non-parametric tests might seem the more conservative course, but type 2 error becomes a risk.[63]

4.3 Implications for future ED-based research.

The VAS, NRS and adjectival scales all appear to be suitable for measuring nausea severity in ED patients. For the measurement and analysis of change in severity, the VAS is preferred and the use of parametric tests seems reasonable. The MCSD may have use as an indicator of treatment effectiveness.

Table 4-1. Measurement scales for subjective symptoms.*

*Adapted from Kersten (2012).[59]

Measure: rating method	Description of scale	Decade of origin
Ordinal adjectival scale: option selected	'none' 'mild' 'moderate' 'severe'	1930s
Ordinal description of relief: option selected	'none' 'slight' 'moderate' 'good' 'complete'	1940s
Ordinal description of change: option selected	'a lot less' 'a little less' 'the same' 'a little more' 'a lot more'	1990s
Visual Analog Scale (line 100 mm long): line marked vertically	_____ No symptom Worst imaginable	1920s
Verbal or Numerical Rating Scale: number selected	0 1 2 3 4 5 6 7 8 9 10 No symptom Worst imaginable	1970s

Table 4-2. A summary of recent developments in the use of measurement scales in medical research.

Author (year)	Finding/description/comment.
Del Favero (1990)[53]	Reported the VAS and NRS to be reliable measures of nausea severity for CINV, but did not explore change in severity.
Todd (1996)[61]	Demonstrated the reliability of the VAS for pain measurement. Patients rated baseline severity on the VAS. At various post-treatment intervals they repeated VAS and ordinal description of change ratings. A novel measure, the 'minimum clinically significant difference' (MCSD) was defined as the mean VAS change when patients described their symptoms as having become either 'a little less', or 'a little more'. Reported the MCSD to be a VAS change of -16 mm.
Boogaerts (2000)[45]	Reported the VAS to be a reliable measure of nausea severity for PONV, with the VAS and the ordinal adjectival scale having high correlation.
Bird (2001)[64]	Reported that for pain measurement, the MCSD (as defined by Todd, 1996) was not a fixed value, but varied with baseline severity.
Holdgate (2003)[65]	Confirmed a high correlation between the VAS and NRS for the measurement and monitoring of pain in ED patients.
Hendey (2005)[66]	Reported the VAS to be reliable for measurement of nausea severity in ED patients, and reported that the MCSD for nausea on the VAS was -15 mm.
Noble (2005)[67]	Presented a historical review of the many scales used in pain research since 1945, noting the rapid increase in use of the adjectival scale, VAS and NRS from this time. In conclusion, the VAS and NRS were recommended as the most valuable tools in analgesia research.
Dorman (2007)[68]	Reviewed scales used for dyspnea, and concluded that multiple studies since the 1990s had validated the use of the VAS and NRS in this setting, and confirmed the correlation between the two.
Meek (2009)[69]	Validated the use of the VAS for measurement of nausea severity in ED patients; confirmed a high correlation between the VAS and the ordinal adjectival scale. Reported that for nausea, the MCSD (as defined by Hendey, 2005) was not a fixed value, but varied with baseline severity.

Table 4-3. A summary of the debate concerning analysis of VAS and NRS data.

Author (year)	Finding/description/comment.
Forrest (1986)[70]	VAS is ordinal and only non-parametric tests should be used. Criticism of researchers doing otherwise.
Philip (1990)[71]	Illustrated VAS data to be 'between' interval and ordinal. Repeated testing of VAS data using parametric tests did not alter rates of type 1 or 2 error, but using non-parametric tests increased risk of type 2 error.
Myles (1999)[72]	VAS does provide interval and ratio data, especially through its mid-sections, only becomes compressed at the extremes.
Noble (2005)[67]	VAS and NRS should both be treated as continuous measures.
Hawker (2011)[62]	Use of VAS in research is superior to ordinal scales as it may be used as a continuous variable.
Kersten (2012)[59]	VAS is ordinal, not continuous. As such, derivation of the MCSD is flawed and its use invalid.
Price (2012)[63]	Lengthy critique of Kersten (2012). Cited substantial evidence for continuous nature of VAS and for use of parametric tests as being valid. VAS and NRS correlate highly, but NRS not so convincingly interval; non-parametric tests recommended for NRS analysis.

CHAPTER 5. ED-based nausea measurement research.

5.1 Introduction.

In contrast to PONV and CINV research where prevention of symptoms is the primary objective, the aim in the ED is for a reduction in nausea severity over a relatively short time-frame. The adjectival scale, the VAS and the NRS may all be used to measure nausea severity in the ED, but the VAS has been the most frequently used rating scale in therapeutic trials.

Two nausea measurement studies involving ED patients, published in 2005 and 2009, validated the use of the VAS for the measurement and monitoring of nausea severity.[66,69] These papers also investigated the clinical significance of different amounts of VAS change.[66,69] The methods drew on those of the ED-based pain measurement research which had been conducted during the previous decade.[61,64] The findings of these two papers are presented here in some detail. This will aid in interpretation of the ED-based antiemetic RCTs, which are described in the following chapter.

5.2 VAS and NRS: Conventions for the measurement and reporting of change in severity for nausea.

5.2.1 VAS:

A plain 100 mm horizontal line is used, labelled only at the left and right-hand extremes. Wording of the labels is not standardized, but severity progresses from none, or minimal, at the left to severe at the right.

Participants are asked to mark the line with a vertical stroke, to indicate symptom severity at that time.

Measurements are taken from the left end, and reported in mm. For group data, some researchers report the median mm, with the interquartile range (IQR). Others report mean mm, with either the standard deviation (SD), or 95% confidence interval (CI).

When there are two measurements at different time-points, amount of change is calculated by subtracting the baseline measure from the repeat measure. This means that if symptoms improve, the change is reported as a negative number. It seems intuitive to associate a negative number with symptom reduction. An example is given in Figure 5-1.

Reporting and analysis of change then depends on the researcher's view as to whether the data is ordinal or interval. Group median (IQR) values might be reported and compared using non-parametric tests. Group mean (95% CI) values might be reported and compared using parametric tests. The former is certainly the more conservative approach, but may increase the risk of type 2 error. The weight of evidence supports the use of parametric tests as being acceptable.[62,63]

5.2.2 NRS:

A horizontal row of numbers, from 0 to 10 (11-point) is usually only labelled at the left and right-hand extremes. There is also no uniform labelling convention, but as with the VAS, the left end is for no, or minimal symptoms, and the right-hand end is for severe symptoms.

Participants are asked to circle the number which indicates their symptom severity at that time. Individual measurements are reported as the circled number.

When there are two measurements at different time-points, the change is calculated by subtracting the baseline measure from the repeat measure. As for the VAS, this means that if symptom severity is reduced, the change is reported as a negative number. An example is given in Figure 5-2.

For group data, most researchers report the change as the median (IQR) value, and compare change between groups using non-parametric tests. The literature debate on the best approach to reporting and analysis of NRS measures has not been as extensive as that for the VAS. The smaller amount of evidence suggests that the more conservative approach of using non-parametric tests is probably preferable.[63]

5.3. First ED-based nausea severity measurement study:

The first ED-based nausea measurement study was published by Hendey (2005).[66] The aim of this study was two-fold. It was partly to validate the use of the VAS as a measure of nausea severity in ED patients, as Del Favero (1990) and Boogaerts (2000) had done for CINV and PONV.[45,53] More importantly, from the authors' point of view, it was to define the MCSD for nausea using the VAS, as had been done by Todd (1996) for ED patients with pain.[61]

The study included a convenience sample of 50 adult patients with nausea as a component of their chief complaint, and an initial VAS rating of 30 mm or more. Participants rated nausea severity on a VAS every 15 minutes, up to four times, regardless of treatment received. At the time of each rating after baseline, the participant also described how their symptoms had changed, using the ordinal description of change scale: 'a lot less', 'a little less', 'no change', 'a little more', 'a lot more'.

Figure 5-1. Calculation of severity and change in severity using the VAS.

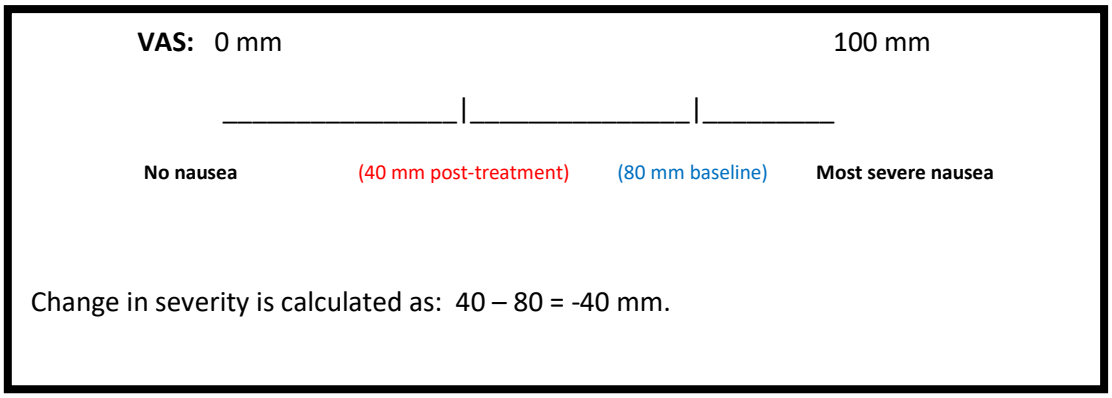
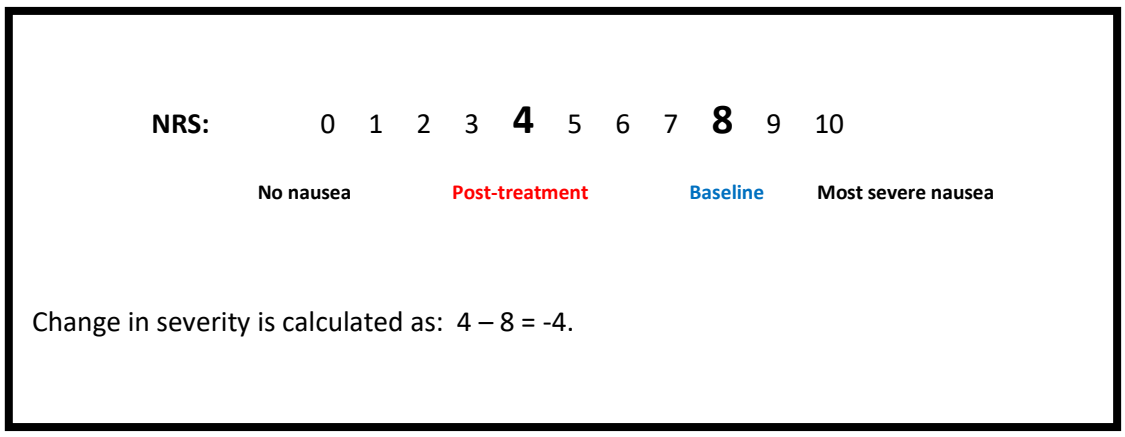


Figure 5-2. Calculation of severity and change in severity using the NRS.



This yielded 83 matched pairs of VAS change and described change. This replicated the methodology used by Todd (1996) for pain measurement in ED patients.[61]

The baseline mean VAS rating for the population was 65 mm (precision not reported). The VAS changes for each description of change category are shown in Table 5-1.

The VAS ranges for each description of change category were shown to be significantly different from each other. This confirmed the reliability of the VAS for detection of symptom change. The MCSD was initially defined as the mean change reported by people whose symptoms were 'a little less' or 'a little more'. It was acknowledged, however, that the number of patients whose symptoms worsen in this setting is small, so their contribution to the MCSD figure is minimal. Also, the aim of antiemetic treatment is symptom reduction, so if the MCSD is to be used as a therapeutic benchmark in any way, it is more logically equated with symptoms becoming 'a little less'.

The study conclusion reads: "In summary, we determined that the minimum clinically significant change in nausea is 15 mm on a visual analog scale. This finding is similar to previous studies of pain assessment and helps in the interpretation of clinical studies reporting changes in nausea. Further studies may determine how the perception and reporting of nausea are affected by severity, race, sex, and etiology."[66]

The recommendation for further research on the effects of initial severity presumably stemmed from some of the ED-based pain research. For example, Bird (2001) had found that when pain was described as being 'a little less', the VAS reductions reported by patients with severe pain, were significantly greater than those reported by patients with moderate or mild pain.[64]

This was acknowledged as a study limitation in the Hendey (2005) paper, but the small sample size precluded any subgroup analysis based on initial severity.

5.4. Second ED-based nausea severity measurement study:

The second ED-based nausea measurement study was published by Meek (2009).[69] The aim of this study was to validate the use of the VAS for nausea severity measurement, and to explore how initial severity influenced the relationship between VAS change and described change.[69]

Hendey (2005) had defined the MCSD for nausea on the VAS as being -15 mm, but acknowledged that this might be influenced by initial severity, as had been demonstrated in pain research.[64] It

seems logical that the clinical implications of a VAS reduction from 100 mm to 85 mm are unlikely to be the same as those of a change from 30 mm to 15 mm.

The study involved 247 patients, each of whom provided a baseline VAS rating, and an initial adjectival severity rating ('mild', 'moderate', severe'). After 30 minutes, and again after 60 minutes, participants provided a second and/or third VAS rating and adjectival severity rating, the latter scale now also including 'none'. At 30 and 60 minutes, a rating on the ordinal description of change scale was obtained. Most patients had some antiemetic treatment, but this was not part of the analysis. There were 693 matched pairs of VAS change and described change available for analysis.

The initial median VAS (IQR) rating for the population was 51 mm (34 – 76). The median VAS ratings (IQR) for the adjectival severity categories of 'none', 'mild', 'moderate' and 'severe', were 2 mm (0 – 6), 23 mm (16 – 33), 53 mm (45 – 63), and 83 mm (75 – 93), respectively. Differences were statistically significant. This was consistent with the findings of Del Favero (1990) and Boogaerts (2000) for patients with CINV and PONV respectively.[45,53,69]

The VAS changes for each description of change category, for both the total population and each initial severity subgroup are shown in Table 5-2. The median MCSD values for the severe, moderate and mild subgroups were -32 mm, -23 mm and -12 mm respectively. The differences were statistically significant. [69] The 'whole population' results for Meek (2009) and Hendey (2005) are shown in Table 5-3. For ease of comparison, the findings for Meek (2009) have been recalculated as mean VAS change.

5.5 Conclusions from both measurement trials.

1) The VAS is a reliable measure of both severity, and change in severity of nausea in adult ED patients. The results of the Meek (2009) study validated the findings of Hendey (2005) with regard to VAS use for nausea measurement and monitoring in ED patients.

2) The Meek (2009) study confirmed that the MCSD on the VAS is not a fixed value, but is influenced by initial severity. Between populations, the MCSD will differ depending on the severity mix within that population.

Table 5-1. VAS changes for each description of change: Hendey (2005).[66]

	Description of change				
	'a lot less' (n = 16)	**'a little less' ("MCSD") (n = 34)**	'the same' (n = 28)	'a little more' (n = 2)	'a lot more' (n = 3)
VAS change: mean mm (95% CI)	-42 mm (-55 to -30)	**-15 mm (-20 to -11)**	0 mm (-6 to 5)	16 (-86 to 118)	24 (-5 to 53)

Table 5-2. VAS changes for each description of change by 'initial' severity subgroup: Meek (2009).[69]

Note: The 'initial' severity from the ordinal adjectival rating scale may refer to either the baseline rating in relation to the 30-minute rating, or the 30-minute rating in relation to the 60-minute rating.

Note: Some column totals appear discrepant because those with a severity of 'none' at 30-minutes are not included.

Population	**'a lot less'**	**'a little less' ("MCSD")**	**'the same'**	**'a little more'**	**'a lot more'**
Whole population: median mm (IQR)	-28 (-52 to -16) (n = 146)	**-20 (-30 to -10) (n = 128)**	-1 (-4 to 1) (n = 132)	16 (9 to 23) (n = 29)	23 (5 to 48) (n = 11)
Initially severe: median mm (IQR)	-65 (-72 to -51) (n = 30)	**-32 (-41 to -26) (n = 28)**	-0.5 (-4 to 6) (n = 22)	-6 (-24 to 12) (n = 2)	n/a (n = 0)
Initially moderate: median mm (IQR)	-41 (-54 to -30) (n = 41)	**-23 (-31 to -12) (n = 51)**	0 (-4 to 3) (n = 44)	16 (-2 to 18) (n = 9)	5 (0.5 to 17) (n = 5)
Initially mild: median mm (IQR)	-20 (-26 to -13) (n = 59)	**-12 (-20 to -9) (n = 46)**	-3 (-6 to 1) (n = 40)	20 (12 to 26) (n = 14)	39 (27 to 45) (n = 4)

Table 5-3. Comparison of whole population mean VAS change per described change: Hendey (2005)[66] **and Meek (2009).**[69]

	Hendey (2005) (n = 83 paired ratings from 50 patients) Baseline mean VAS rating = 64 mm	Meek (2009) (n = 693 paired ratings from 247 patients) Baseline mean VAS rating = 51 mm
Described change	VAS change: mean mm (95% CI)	VAS change: mean mm (95% CI)
'a lot less'	-42 (-55 to -30)	-33 (-37 to -29)
'a little less'	-15 (-20 to -11)	-22 (-24 to -19)
'the same'	0 (-6 to 5)	-1 (-3 to 1)

5.6. Implications for future ED-based antiemetic research.

These studies confirmed the reliability of the VAS for the measurement and monitoring of nausea severity in adult ED patients. Both Hendey (2005) and Meek (2009) attempted to clarify the amount of change on the VAS which was clinically significant.[66,69] With regard to study design and interpretation of results, however, the importance of the MCSD not being a fixed value remained uncertain. Further, it must be remembered that the MCSD represents an amount of change from baseline. This allows inferences to be drawn about the likely clinical significance of reported VAS changes, for either individual patients or for a single treatment group. However, when the VAS changes for two treatment groups both exceed the MCSD, the clinical significance of the resulting between-group difference has never been explored. For example, the mean VAS changes for two treatment groups might be -20 mm and -36 mm, which approximate the amounts of change when symptoms are described as being 'a little less' and 'a lot less' respectively. As such, it may be inferred that the majority in each group are at least 'a little' better, but that relatively more in the latter group are probably 'a lot' better. Exact proportions cannot be determined, however, and the clinical value of the difference is unclear.

CHAPTER 6. A review of therapeutic antiemetic trials conducted in the ED.

6.1 Introduction.

A detailed examination of the ED-based antiemetic literature was undertaken. An initial search was conducted of MEDLINE (OvidSP), the Cochrane Central Register of Controlled Trials, and EMBASE, for the period January 1966 to July 2009. To ensure all relevant literature was obtained during the conduct of the thesis-related research, formal searches were repeated in August 2014, April 2017 and May 2018.

Screening of titles and abstracts of the papers identified to mid-2009 yielded only four ED-based antiemetic RCTs. Information from these trials contributed to the initial planning of the studies undertaken for this thesis. Three additional ED-based RCTs were published between July 2009 and August 2014, all in 2011. The findings of these later studies were also useful in the planning of the later thesis-related research projects, but did not significantly impact on their content or direction. Two additional ED-based antiemetic RCTs were published between August 2014 and May 2018. Both of these papers concern the use of nasally inhaled isopropyl alcohol as an antiemetic agent. The first, published in 2016 compared inhaled isopropyl alcohol with inhaled placebo. The primary outcome measure was change in NRS rating at ten minutes.[73] This was not considered sufficiently similar to the previously identified ED-based studies to warrant inclusion in this chapter. The second, published in early 2018 compared nasally inhaled isopropyl alcohol with oral ondansetron. The primary outcome measure was change in VAS rating at 30-minutes.[74] The findings of this study may be of interest with regard to future research directions in ED nausea management. As its publication followed the completion of the final planned study in this series of research outputs, a detailed review has not been included.

The search strategy and results for MEDLINE, the database with the highest yield are shown in Table 6-1. The increase in the number of papers identified sequentially in 2009, 2014, 2017 and 2018 illustrates the rate at which antiemetic research has increased over this period. A full description of the search strategy for all databases can be found in the Cochrane Systematic Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting.[75] A full copy of this review is included as a related paper in this thesis. (Appendix)

6.2 A brief description of the seven ED-based antiemetic trials: 2000 - 2011.

In order to keep the planned thesis-related research in context, brief summaries of the relevant ED-based RCTs are included here. If required, more detailed critical appraisals of all the studies can be found in the aforementioned Cochrane Systematic Review (Appendix).[75]

Table 6-1. Medline search strategy and results.

Step	Search Terms	Results to July 2009	Results to April 2017	Results to May 2018
1	antiemetics/ or antiemesis.ti,ab. or antiemetic*.ti,ab. or antiemetogenic.ti,ab.	7577	9864	11062
2	nausea/ or vomiting/ or nausea*.ti,ab. or vomit*.ti,ab. or emesis.ti,ab. or emet*.ti,ab. or emergency service, hospital/ or emergency medical services/ or (emergency adj3 (medic* or servic* or ward*)).ti,ab. or (intensive adj3 care).ti,ab.	186445	273418	302940
3	1 and 2	5614	7279	7725
4	1 and 2, limited to: (randomized controlled trial.pt. or randomized.ab. or random*.ti.) not (animals not (humans and animals)).sh.	64	1775	2289

6.2.1 First ED-based antiemetic RCT.

The study of Ernst (2000) was the first completely ED-based antiemetic RCT to be published.[76] A summary of the population, outcome measures and results are shown in Table 6-2.

Table 6-2. Summary of the study by Ernst (2000).

Study setting and population	US ED. Convenience sample of 84 patients.
Inclusion	Nausea secondary to gastroenteritis. No minimum severity, but IV therapy 'required'.
Intervention	**Prochlorperazine 10 mg IV (n = 42)** **Promethazine 25 mg IV (n = 42)**
Blinding	Triple blind.
Outcome measure	Between-group comparison of mean VAS change from baseline to 30 minutes post-treatment.
Baseline severity: mean VAS rating	65 mm for prochlorperazine 73 mm for promethazine
Result: Mean VAS change (precision not reported)	**-45 mm for prochlorperazine** **-27 mm for promethazine**
Definition of clinical significance	Not defined.
Secondary outcome	Use of 'rescue' medication: 4/42 (10%) for prochlorperazine 13/42 (31%) for promethazine

There was no defined minimum severity for inclusion, other than that intravenous hydration and antiemetic administration was "required". An investigator independent to the patient's clinical care prepared the study medication, so blinding was probably satisfactory, but not ideal. Indications for rescue medication were not defined. Clinical significance was not mentioned.

The study conclusion was that prochlorperazine is superior to promethazine.

6.2.2 Second ED-based antiemetic RCT.

The next ED-based RCT published was by Cham (2004).[34] A summary of the population, outcome measures and results are shown in Table 6-3.

Table 6-3. Summary of the study by Cham (2004).

Study setting and population	Australian ED. Convenience sample of 58 patients.
Inclusion	Nausea from any cause. No minimum severity.
Intervention	**Metoclopramide standard dose 10 mg IV (n = 34)** **Metoclopramide intermediate dose 0.4 mg/kg to maximum dose 32 mg IV (n = 24)**
Blinding	Single (Patient only to dose, not drug)
Outcome measure	Between-group comparison of median NRS rating change from baseline to 30 minutes post-treatment. (NRS: 0 to 10)
Baseline severity: median NRS rating	7 for standard dose metoclopramide 7 for intermediate dose metoclopramide
Result	**-4 (IQR: -5 to -3) for standard dose** **-5 (IQR: -6 to -4) for intermediate dose**
Definition of clinical significance	Between-group median NRS difference of 2 or more.
Secondary outcome	Use of 'rescue' medication: 5/34 (15%) versus 3/24 (13%) for standard and intermediate dose respectively.

NRS = Numerical Rating Scale; IQR = Interquartile Range

The rationale for the drug regimens was that higher doses of metoclopramide were reported to be more effective in CINV research. The hypothesis was that this may also be the case for ED patients.

Equating clinical significance with a between-group difference of 2 NRS points was said to be informed from pain research. However, this appears to be a misinterpretation of the defined MCSD for pain using the NRS, which is a reduction of 2 points from baseline at the individual patient level. Indications for rescue medication were not defined, being at 'physician discretion'.

The study conclusion was that the two metoclopramide regimens were equivalent.

6.3.3 Third ED-based antiemetic RCT.

The third study published was by Braude (2006).[35] This was the first ED-based RCT to include a placebo arm. A summary of the population, outcome measures and results are shown in Table 6-4.

Table 6-4. Summary of the study by Braude (2006).

Study setting and population	US ED. Convenience sample of 97 patients.		
Inclusion	Nausea from any cause. Minimum VAS rating of 40 mm.		
Intervention	**Droperidol 1.25 mg IV (n = 22); Metoclopramide 10 mg IV (n = 25); Prochlorperazine 10 mg IV (n = 24); Saline placebo (n = 26).**		
Blinding	Triple blind. Independent pharmacist controlled randomization and concealment.		
Outcome measure	Between-group comparison of mean VAS change, from baseline to 30 minutes post-treatment.		
Baseline severity: Mean VAS rating	70 mm for droperidol; 65 mm for metoclopramide; 72 mm for prochlorperazine; 71 mm for placebo.		
Result: Mean (sd) VAS change	**-55 (18) mm for droperidol; -40 (24) mm for metoclopramide; -41 (24) mm for prochlorperazine; -39 (21) mm for placebo.**		
Definition of clinical significance	Mean change from baseline of -20 mm for each/any group.		
Secondary outcomes	Study drug	Rescue medication	Patient satisfaction
	Droperidol	1/22 (5%)	20/22 (95%)
	Metoclopramide	1/25 (4%)	21/25 (84%)
	Prochlorperazine	6/24 (25%)	20/24 (83%)
	Placebo	4/26 (15%)	22/26 (96%)

sd = standard deviation

The authors criticized previous studies for not including a placebo arm. Blinding and concealment were ensured. The use of rescue medication was at physician discretion. Patient satisfaction with treatment was included as a secondary outcome.

The conclusions were:

1) All treatments, including placebo, were associated with clinically significant symptom improvement.

2) Droperidol was superior to the other three treatments, all of which were equivalent.

The first conclusion was based on the authors' arbitrary definition of clinical significance being a change from baseline in excess of -20 mm. The possible reasons mentioned for the surprisingly good performance of placebo, were: "placebo effect, hydration, relief of nausea after vomiting, general improvement over time, and regression toward the mean".

The second conclusion was based on the difference in mean VAS change between droperidol and the other groups being statistically significant. In line with the reporting of mean change with SD, the analyses used parametric tests.

No justification for use of the VAS as the primary outcome measure was given. The study methods also did not include a justification for a VAS change of -20 mm being deemed clinically significant. The MCSD of -15 mm, as per the recently published Hendey (2005) study,[66] was mentioned in discussion as support for the authors' more "conservative" estimate of clinical significance.

There was no mention of the amount of between-group difference which might be clinically significant. The superiority of droperidol was based solely on statistical significance. In the discussion, the potential merits of droperidol were tempered by mention of its inferior side-effect profile, particularly with regard to akathisia. It was also noted that ED use of droperidol was declining in the wake of the US FDA 'black box' warning of 2001. There was no comment on directions for future research.

6.3.4 Fourth ED-based antiemetic RCT.

The fourth antiemetic RCT was by Braude (2008).[36] The two authors, Braude and Crandall, were two of the six authors of the Braude (2006) study.[35] This was the final ED-based study published prior to 2009, when planning commenced for the series of research projects which comprise this thesis. A summary of the population, outcome measures and results are shown in Table 6-5.

Table 6-5. Summary of the study by Braude (2008).

Study setting and population	US ED. Convenience sample of 120 patients.
Inclusion	Nausea from any cause. Minimum VAS rating of 40 mm.
Intervention	**Ondansetron 4 mg IV (n = 60);** **Promethazine 25 mg IV (n = 60).**
Blinding	Triple blind. Independent pharmacist controlled randomization and concealment.
Outcome measure	Between-group comparison of mean VAS change, from baseline to 30 minutes post-treatment.
Baseline severity: Mean VAS rating	67 mm for ondansetron 69 mm for promethazine
Result: Mean (sd) VAS change	**-36 (28) mm for ondansetron** **-34 (29) mm for promethazine**
Definition of clinical significance	Designed to show non-inferiority of ondansetron; margin of inferiority was 15 mm (between-group mean VAS change)
Secondary outcomes	Rescue medication: 11/60 (18%) for ondansetron 15/60 (25%) for promethazine

sd = standard deviation

The authors chose not to have a placebo arm on this occasion. The reason stated was that since one drug, droperidol, had previously been proven superior to placebo, a placebo group could not be justified. It was also stated that since the Braude (2006) study had found metoclopramide and prochlorperazine to be equivalent to placebo,[35] there was no point in studying them further. For this reason, it was decided to trial ondansetron against promethazine. The inclusion of ondansetron, which was relatively new to the ED, seems reasonable. However, the choice of the older drug, promethazine, seems surprising. Ernst (2000)[76] had already reported promethazine to be inferior to prochlorperazine, although that study was restricted to patients with presumed gastroenteritis.

The primary outcome measure was comparison of mean VAS change between groups, taken at 30 minutes post-treatment. The study was designed as a non-inferiority trial. The stated reason for setting the margin of inferiority at 15 mm, was that this was the MCSD as defined by Hendey (2005).[66] However, this is a misinterpretation of the MCSD, which is a change from baseline and not a between-group difference. The use of rescue medication was at physician discretion.

Study conclusion: drugs were similarly effective; ondansetron was non-inferior.

The authors referred to this finding as 'surprising', since ondansetron had been shown to be effective in CINV research and in some recent ED-based paediatric gastroenteritis trials. It was also mentioned that Braude (2006) had found prochlorperazine to be similar to placebo,[35] while Ernst (2000) had reported prochlorperazine to be superior to promethazine.[76] It was noted as a study limitation that the ondansetron dose of 4 mg may have been insufficient, since doses of up to 32 mg had been used in CINV research. Directions for further research were not suggested.

6.3.5 Fifth ED-based antiemetic RCT.

The fifth ED-based antiemetic RCT published was by Patka (2011).[38] A summary of the population, outcome measures and results are shown in Table 6-6.

Table 6-6. Summary of the study by Patka (2011).

Study setting and population	US ED. Convenience sample of 64 patients.
Inclusion	Nausea from any cause. No minimum VAS rating stated.
Intervention	**Ondansetron 4 mg IV (n = 32);** **Prochlorperazine 10 mg IV (n = 32).**
Blinding	Reported as double blind, but methods for this not described.
Outcome measure	Between-group comparison of mean VAS change, from baseline to 30 minutes post-treatment.
Baseline severity: Mean VAS rating	72 mm for ondansetron 79 mm for prochlorperazine
Result: Mean VAS change **(No measures of precision given)**	**-22 mm for ondansetron** **-31 mm for prochlorperazine**
Definition of clinical significance	None included
Secondary outcome	Rescue medication: 5/32 (16%) for ondansetron 1/32 (3%) for prochlorperazine

Number of vomits and resolution of vomiting at 30 minutes post-treatment were included as primary outcomes, but these proved to be of little value. The most frequent number of vomits per patient was one, and active vomiting was only present in 38% and 19% of the prochlorperazine and ondansetron groups respectively. As a consequence, results were too imprecise for any conclusions to be drawn. No rationale was given for the choice of these outcome measures. Mean VAS change was included as a secondary outcome measure.

The conclusion from the between-group comparisons of mean VAS change was that prochlorperazine and ondansetron were equivalent. Consideration of placebo was not mentioned, and clinical significance was not addressed. Overall, the paper was not well written, which left the rigour of its conduct in doubt.

6.3.6 Sixth ED-based antiemetic RCT.

The sixth ED-based antiemetic RCT published was by Chae (2011).[39] A summary of the population, outcome measures and results are shown in Table 6-7.

Table 6-7. Summary of the study by Chae (2011).

Study setting and population	Australian ED. Convenience sample of 100 patients.
Inclusion	Nausea from any cause. No minimum VAS rating stated.
Intervention	**Tropisetron 4 mg IV (n = 50); Metoclopramide 10 mg IV (n = 50).**
Blinding	Triple blind.
Outcome measure	Between-group comparison of mean VAS change, from baseline to 30 minutes post-treatment.
Baseline severity: Mean VAS rating	59 mm for tropisetron 52 mm for metoclopramide
Result: Mean (sd) VAS change	**-25 (25) mm for ondansetron** **-26 (20) mm for metoclopramide**
Definition of clinical significance	MCSD noted as a desired amount of change for each/either group
Secondary outcome	Rescue medication: 5/50 (10%) for tropisetron; 13/50 (26%) for metoclopramide

sd = standard deviation

The primary outcome measure reported was the 'vomiting rate'. This was defined as number of vomits per person-hour observation, for up to three hours. Sample size was based on expected superiority for tropisetron, with expected rates of persistent vomiting given as 10% for tropisetron and 40% for metoclopramide. No evidence was given to support either the validity of the outcome measure, or the figures chosen for the demonstration of superiority. Mean VAS change per group at 30-minutes post-treatment was compared as a secondary outcome.

Despite active vomiting being uncommon and the number of vomits being much lower than anticipated, the 'vomiting rate' of 0.02 for tropisetron was statistically significantly lower than the 0.16 for metoclopramide. The clinical significance of this, however, is completely obscure. The study conclusion was that tropisetron demonstrated superior "control of vomiting", and as such, looked promising for ED use. The lack of difference in the secondary outcomes was noted.

6.3.7 Seventh ED-based antiemetic RCT.

The seventh ED-based antiemetic RCT published was by Barrett (2011).[37] This was the second ED-based study to include a placebo arm. A summary of the population, outcome measures and results are shown in Table 6-8.

Table 6-8. Summary of the study by Barrett (2011).

Study setting and population	US ED. Convenience sample of 171 patients.
Inclusion	Nausea from any cause. Minimum VAS rating of 40 mm.
Intervention	**Ondansetron 4 mg IV (n = 42); Metoclopramide 10 mg IV (n = 43); Promethazine 12.5 mg IV (n = 45); Saline placebo (n = 41)**
Blinding	Triple blind.
Outcome measure	Between-group comparison of median VAS change, from baseline to 30 minutes post-treatment.
Baseline severity: Mean VAS rating	69 mm for ondansetron; 64 mm for metoclopramide; 68 mm for promethazine; 64 mm for saline placebo.
Result: Median (IQR) VAS change	-22 (-43 to -8) mm for ondansetron -30 (-44 to -20) mm for metoclopramide -29 (-47 to -10) mm for promethazine -16 (-45 to -2) mm for saline placebo
Definition of clinical significance	12 mm difference between ondansetron and any other group to demonstrate superiority for ondansetron
Secondary outcome	Rescue medication: 19/42 (48%) for ondansetron; 9/43 (22%) for metoclopramide; 19/45 (44%) for promethazine; 23/41 (59%) for saline placebo.

IQR = Interquartile Range

This was designed as a superiority study, with the expectation that ondansetron 4 mg IV would prove superior to metoclopramide 10 mg IV, promethazine 12.5 mg IV, and placebo. Given that other studies had shown metoclopramide to be equivalent to placebo,[35] and ondansetron 4 mg IV to be equivalent to promethazine 25 mg IV,[36] the hypothesis seems reasonable.

The level of superiority for ondansetron was arbitrarily defined as being a 12 mm greater reduction in median VAS, in comparison with the other groups. This choice was said to be related to the previously defined MCSD of -15 mm,[66] with -12 mm representing a more conservative estimate with regard to sample size. While it is true that the required sample would be made larger by the choice of -12 mm over -15 mm, this is a less conservative between-group difference. Regardless of this, using the MCSD in this way is incorrect. The MCSD is a change from baseline and does not pertain to between-group differences in VAS change. This was the same error which had been made by both Cham (2004) and Braude (2008) in earlier studies. [34,35]

The planned sample size for the study was 600, and the planned study period was eighteen months. After this period, only 171 patients had been recruited, with 40 to 45 in each group. To determine if continuation was worthwhile, an unplanned interim analysis was conducted. This found that there was no realistic prospect of proving superiority for ondansetron, so the study was terminated. Although the possibility of type 2 error with regard to some comparisons was acknowledged, the conclusion was that all groups were equivalent.

6.3 Comparison of study design for the seven ED-based antiemetic RCTs.

The seven ED-based antiemetic trials had some common elements, and some differences. All studies recruited a convenience sample of patients.[34–39,76] Ernst (2000) only included patients with presumed gastroenteritis,[76] while the other six recruited patients with nausea and/or vomiting from any underlying cause.[34–39] The studies of Braude (2006), Braude (2008) and Barrett (2011) required patients to have a minimum VAS rating of 40 mm for recruitment;[35–37] the other four studies only required that the attending doctor believed IV antiemetic treatment to be indicated.[34,38,39,76] Despite these differences, the baseline VAS ratings were fairly similar in all studies. Randomization and blinding were not ideal in the studies of Ernst (2000), Cham (2004), Chae (2011) and possibly Patka (2011);[34,38,39,76] triple blinding was guaranteed in the Braude (2006), Braude (2008) and Barrett (2011) studies.[35–37] Comparisons of VAS change were undertaken in six studies, with only Cham (2004) using the NRS. Between-group comparisons were performed using parametric tests by Braude (2006), Braude (2008), Chae (2011) and Patka (2011);[35,36,38,39] Ernst (2000), Cham (2004) and Barrett (2011) used non-parametric tests.[34,37,76]

Ernst (2000) did not mention the issue of clinical significance.[76] Braude (2006) arbitrarily defined clinical significance as a group mean VAS change from baseline of -20 mm.[35] It was acknowledged that there was no literature support from nausea-related research for this decision. Although the study of Braude (2006) was published after the measurement study of Hendey (2005), it had been designed and conducted prior to 2005.[35,66] Cham (2004) defined a between-group difference of -2 on the NRS as being clinically significant, based on the MCSD from pain research.[34] Braude (2008) and Barrett (2011) both defined between-group limits for non-inferiority and superiority respectively, based on the MCSD reported by Hendey (2005).[36,37,66] By definition, however, the MCSD, is a change from baseline. It does not refer to the possible clinical significance of between-group differences, so there is no research support for this approach. The alternate primary outcome measures used by Patka (2011) and Chae (2011),[38,39] were based on number of active vomiting episodes. Although Chae (2011) defined an amount of change in the vomiting rate which would indicate superiority, there was no literature to support the validity of the measure;[39] Patka did not define a clinically significant amount of change.[38]

All seven studies used rescue medication as a secondary outcome, but results were discussed little in the published papers. The indications for use of additional medication were not defined in any study, with this being at physician discretion. The inference is that rescue medication is a proxy measure for treatment failure, but this assumption has not been validated. There is no way of knowing why patients did, or did not, receive additional medication. The only other secondary outcome measure used was patient satisfaction, in the study of Braude (2006).[35] Satisfaction with treatment was most frequently reported in the placebo group. It is difficult to interpret the significance of this; it may be that side-effects detracted from satisfaction in the active treatment groups.

Only two studies, that of Braude (2006) and Barrett (2011) included a placebo arm.[35,37] Of the other five studies,[34,36,38,39,76] only Braude (2008) included some justification for non-inclusion of a placebo group.[36] In the introduction of the Braude (2006) paper, the authors criticized previous researchers in the field for not having a placebo arm.[35] In the Braude (2008) paper, the stated reason for not including a placebo group was that since droperidol had previously been proven superior to placebo, a placebo group could not be justified.[36] This seems illogical for two reasons. Since the Braude (2008) study was comparing ondansetron with promethazine, the findings of the earlier study with regard to droperidol are irrelevant. The assertion also fails to appreciate that while the difference in mean VAS change between the droperidol and placebo groups in the Braude (2006) study may have been statistically significant,[35] the clinical significance of the difference was unknown.

6.4 Summary of study results.

Key aspects of study design and the main results are summarized in Table 6-9; mean or median post-treatment VAS changes for each drug regimen across the different studies are illustrated in Figure 6-1.

Two studies did conclude that one study regimen was superior to another. Ernst (2000) reported superiority for prochlorperazine over promethazine as the difference between the respective group mean VAS changes of -45 mm and -27 mm was statistically significant. Braude (2006) concluded that droperidol was superior to metoclopramide, prochlorperazine and placebo, as differences between the mean VAS change for droperidol (-55 mm) and the other groups (-40 mm, -41 mm and -39 mm respectively) were statistically significant. Equivalence between all other treatment regimens in the remaining studies was assumed on the basis of between-group comparisons in mean VAS change not being statistically significant.

Individually, each study conclusion might seem reasonable, but some between-study inconsistencies are difficult to explain. For example: 1) Ernst (2000) reported that prochlorperazine was superior to promethazine;[76] 2) Braude (2006) reported that prochlorperazine and placebo were equivalent;[35] 3) Braude (2008) reported that promethazine and ondansetron were equivalent.[36] This suggests that ondansetron and promethazine should be inferior to placebo. However, Barrett (2011) reported that ondansetron and promethazine were equivalent to placebo.[37]

Interpreting these between-study comparisons is further complicated by the variation in mean VAS changes reported in different studies for the same drug regimens.(Figure 6-1) For example, the post-treatment VAS changes reported for metoclopramide by Braude (2006) and Chae (2011) were -40 mm and -26 mm respectively.[35,39] Braude (2006) and Barrett (2011) reported mean VAS changes following placebo administration of -39 mm and -16 mm respectively.[35,37] This is despite all studies having reasonably matched baseline VAS ratings (Table 6-9) and broadly similar patient populations.[34–39,76]

The meaning of these apparent differences and inconsistencies is clouded by the uncertainty regarding their clinical significance. The difference between droperidol and the other groups in the Braude (2006) study[35] may have been statistically significant, but the mean VAS changes for all treatment groups exceed that reported when symptoms become 'a lot less'.[66,69] Given this, it is difficult to know what additional clinical benefits may have been experienced by patients in the droperidol group. The importance of the between-study variation in mean VAS changes for the

Table 6-9. Key VAS figures and conclusions from ED-based antiemetic trials.

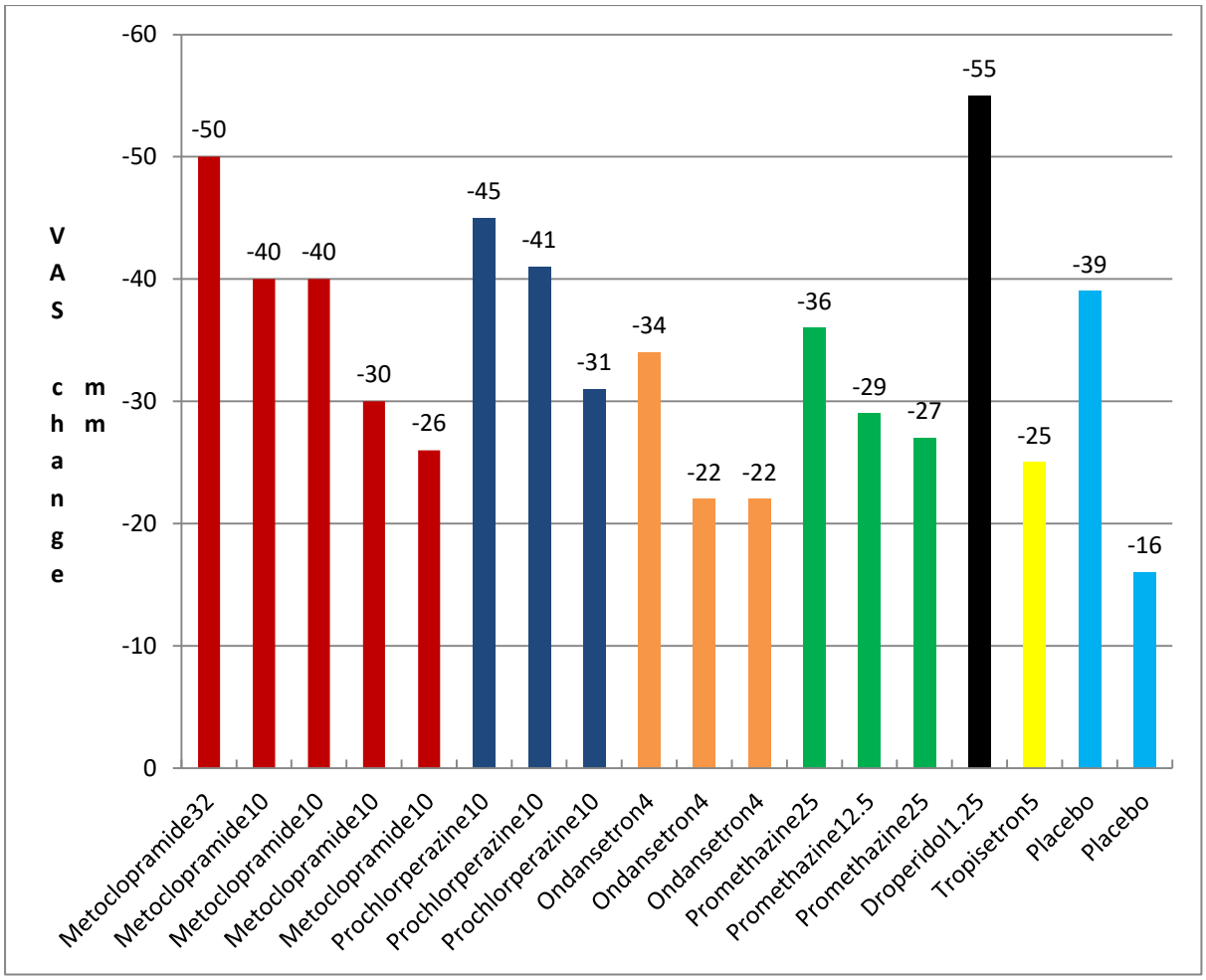
Study interventions	Initial VAS rating per group	VAS changes per groups (sd or IQR)	Stated clinically significant VAS change	Conclusion
Ernst 2000: Prochlorperazine 10 mg Promethazine 25 mg	 65 mm 73 mm	 -45 mm -27 mm (no sd given)	Nil	Prochlorperazine superior to promethazine
Cham 2004: Metoclopramide 10 mg Metoclopramide 0.4 mg/kg (max 32 mg)	 70† 70	 -40 (-30 to -50) -50 (-40 to -60)	 -20 (between groups)	Metoclopramide dosages equivalent
Braude 2006: Droperidol 1.25 mg Metoclopramide 10 mg Prochlorperazine 10 mg Placebo	 70 mm 65 mm 72 mm 71 mm	 -55 (sd 18) mm -40 (sd 24) mm -41 (sd 24) mm -39 (sd 21) mm	 -20 mm (from baseline)	Droperidol superior to all other groups; metoclopramide, prochlorperazine and placebo all equivalent
Braude 2008: Promethazine 25 mg vs Ondansetron 4 mg	 67 mm 69 mm	 -36 (sd 28) mm -34 (sd 29) mm	 -15 mm (between groups)	Ondansetron and promethazine equivalent
Patka 2011: Prochlorperazine 10 mg Ondansetron 4 mg	 79 mm 72 mm	 -31 mm -22 mm (no sd given)	Nil	Ondansetron and prochlorperazine equivalent
Chae 2011: Metoclopramide 10 mg vs Tropisetron 5 mg	 52 mm 59 mm	 -26 (sd 25) mm -25 (sd 20) mm	 -20 mm (from baseline)	Tropisetron and metoclopramide equivalent
Barrett 2011: Ondansetron 4 mg Metoclopramide 10 mg Promethazine 12.5 mg Placebo	 69 mm 64 mm 68 mm 64 mm	 -22 (-43 to -8) mm -30 (-44 to -20) mm -29 (-47 to -10) mm -16 (-45 to -2) mm	 -12 mm (between groups)	Ondansetron, metoclopramide, promethazine and placebo all equivalent

† NRS x 10 for ease of comparison, including IQR for change

IQR = Interquartile Range; sd = standard deviation.

Figure 6-1. VAS changes per drug regimen in different studies.

Note: VAS changes may be mean or median, depending on the study. The source study is readily identifiable from the VAS change per group column in Table 6-9.



same drug regimens is also uncertain. Since all reported mean VAS changes are still greater than the MCSD,[66,69] these differences may be of little clinical consequence.

6.5 Implications for future ED-based antiemetic research.

In summary, however, the collection of ED-based studies do not convincingly support that antiemetic drugs are effective for ED patients with nausea. Given the positive results from the PONV and CINV research,[42,54,58] this might remain difficult to accept until the clinical significance of the ED-based findings can be more clearly understood. Hence, there appears to be a need for research to determine outcome measures which ensure that study results can be presented in a more clinically meaningful and readily understandable way.

CHAPTER 7. Related papers: (1) Drug treatment of adults with nausea and vomiting in primary care. (2) Drugs for the treatment of nausea and vomiting in adults in the ED setting (Cochrane Systematic Review).

7.1 Introduction.

In 2009, at the time of planning the research outputs for this thesis, the number of ED-based antiemetic RCTs [34–36,76] was insufficient to consider performing and publishing a formal systematic review of this literature. Following the publication of the three additional ED-based antiemetic studies in 2011,[37–39] and the first RCT in this series of research in 2014,[40] this was no longer the case. Hence, a Cochrane Systematic Review on the effectiveness of antiemetic drugs for the treatment of adult ED patients with nausea was undertaken at this time. During the writing of the systematic review, an approach was received from the Therapeutics Section Editor of the British Medical Journal, requesting a review article on antiemetic drug use in primary care.

While my contribution to both projects was significant, they are not part of the investigation to identify and develop improved outcome measures for use in ED-based therapeutic trials. As such, they are included here as related publications, since they do advance the general understanding of nausea management in the ED.

7.2 Citations of papers (1) and (2).

(1) Furyk JS; Meek R; McKenzie S. Drug treatment of adults with nausea and vomiting in primary care. BMJ. 2014; 349:g4714.

(2) Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD010106. DOI: 10.1002/14651858.CD010106.pub

FULL PAPERS ARE ATTACHED AS AN APPENDIX TO THIS THESIS

7.3 Brief summary and conclusion for paper (1).

This article was framed in the format required for the Therapeutics section of the British Medical Journal. The general recommendation was that since antiemetic drug efficacy remained largely unproven in this setting, patient preference, drug cost and side-effect profile should all be considered in therapeutic decision making.

7.4 Brief summary and conclusions from paper (2) [Systematic Review].

The initial search yielded 6,799 studies which were checked against the inclusion criteria. This yielded a final 13 studies for full review, of which eight RCTs were ultimately suitable for inclusion. Seven of these have been summarized in Chapter Six of this thesis.[34–39,76] More detailed critical appraisals may be found in the Systematic Review.[75] The eighth paper included is the first RCT in this series of research (Chapter Ten).[40] No previously undetected papers were found during the conduct of the review.

The Authors' conclusions paragraph of the Systematic Review is reproduced here:

"In an ED population, there is no definite evidence to support the superiority of any one drug over any other drug, or the superiority of any drug over placebo. Participants receiving placebo often reported clinically significant improvement in nausea, implying general supportive treatment such as intravenous fluids may be sufficient for the majority of people. If a drug is considered necessary, choice of drug may be dictated by other considerations such as a person's preference, adverse-effect profile and cost. The review was limited by the paucity of clinical trials in this setting. Future research should include the use of placebo and consider focusing on specific diagnostic groups and controlling for factors such as intravenous fluid administered."

CHAPTER 8. Planning of thesis research outputs.

8.1 Introduction.

Nausea and vomiting are common symptoms which occur in many different clinical settings. The distress experienced by patients,[4,7,9] the potential for direct medical complications,[14,18,20,24] and the economic burden imposed by these symptoms,[8,25,29] all make effective treatment desirable. Interest in antiemetic drug research began in the 1960s, as attempts were made to improve the management of patients with PONV.[43,44] Interest in the development of more effective antiemetic drugs increased in the late 1970s, after the discovery and introduction of new, but highly emetogenic chemotherapeutic agents.[49,50] Research for CINV has continued to grow since that time. From the 1960s to the present time, the majority of antiemetic drug research has been conducted in these two fields.

Nausea is also a common problem for emergency department (ED) patients, in whom the symptoms may accompany a wide variety of underlying conditions.[5] Effective treatment is desired in this setting, for the same reasons as it is in oncology and post-operative patients. In comparison with PONV and CINV, however, the clinical circumstances and the objective of antiemetic therapy are different for ED patients. As a consequence, the way in which treatment success is measured must also be different. The primary aim of antiemetic treatment in PONV and CINV is the post-treatment prevention of nausea and/or vomiting. For ED patients, it is the rapid and clinically significant reduction in symptom severity. The contrasts between these research fields are summarized in Table 8-1.

8.2 The primary outcome measure traditionally used in ED-based antiemetic research.

For unstated reasons, in the first ED-based antiemetic trial, Ernst (2000)[76] chose to measure symptom improvement by using VAS ratings and calculating the mean VAS change for each treatment group.[76] At the time, the VAS had not been validated as a reliable tool for the measurement of nausea severity in the ED setting, but there was support for its use from CINV,[53] PONV [45] and ED-based pain research.[61] Perhaps because the Ernst (2000) study was able to demonstrate an apparently positive finding,[76] the same outcome measure was chosen for the first ED-based, placebo-controlled trial, designed and conducted by Braude (2006).[35] Another positive result based on the statistical significance of a between-group comparison probably reinforced the

Table 8-1. Difference in research approach for patients with PONV and CINV compared with ED patients with nausea.

Study characteristic	Antiemetic research for PONV and CINV	ED-based antiemetic research
Initial status	Patient with no nausea is to be administered an emetogenic stimulus.	Patient has nausea associated with an underlying problem.
Aim of antiemetic treatment	Prevention of nausea and vomiting.	Clinically significant reduction in nausea severity during the ED episode of care.
'Study drug' administration (comparison of active drugs +/- placebo)	'Study drug' administered prior to or concurrently with the emetogenic stimulus.	'Study drug' administered for already-present nausea during the ED episode of care.
Traditional outcome measure	Binary: Between-group comparison of number (%) with post-treatment nausea.	Continuous: Between-group comparison of post-treatment mean VAS change from baseline.

belief that VAS change was a suitable primary outcome measure. The ensuing studies of Hendey (2005) and Meek (2009), which validated the use of the VAS for measurement and monitoring of nausea severity in ED patients,[66,69] are likely to have strengthened this support. Known advantages of the VAS included: ease of use for sick patients;[62] reliable correlation with ordinal scales for describing baseline severity and change over time;[66,69] ability to analyze rating change as a continuous variable;[62,63,72] and high sensitivity for detection of change.[63] As such, it does not seem surprising that between-group comparisons of VAS change remained as the primary outcome measure in the ED-based antiemetic studies which followed. The approach is simple: patients rate severity on the VAS, the VAS changes for individual patients are combined and the mean VAS change for each treatment group is calculated. Effectiveness is assumed if the group mean VAS change exceeds the MCSD.[66,69] A conclusion of superiority or equivalence is made depending on whether or not the between-group comparison of mean VAS change is statistically significant.[35–37,76]

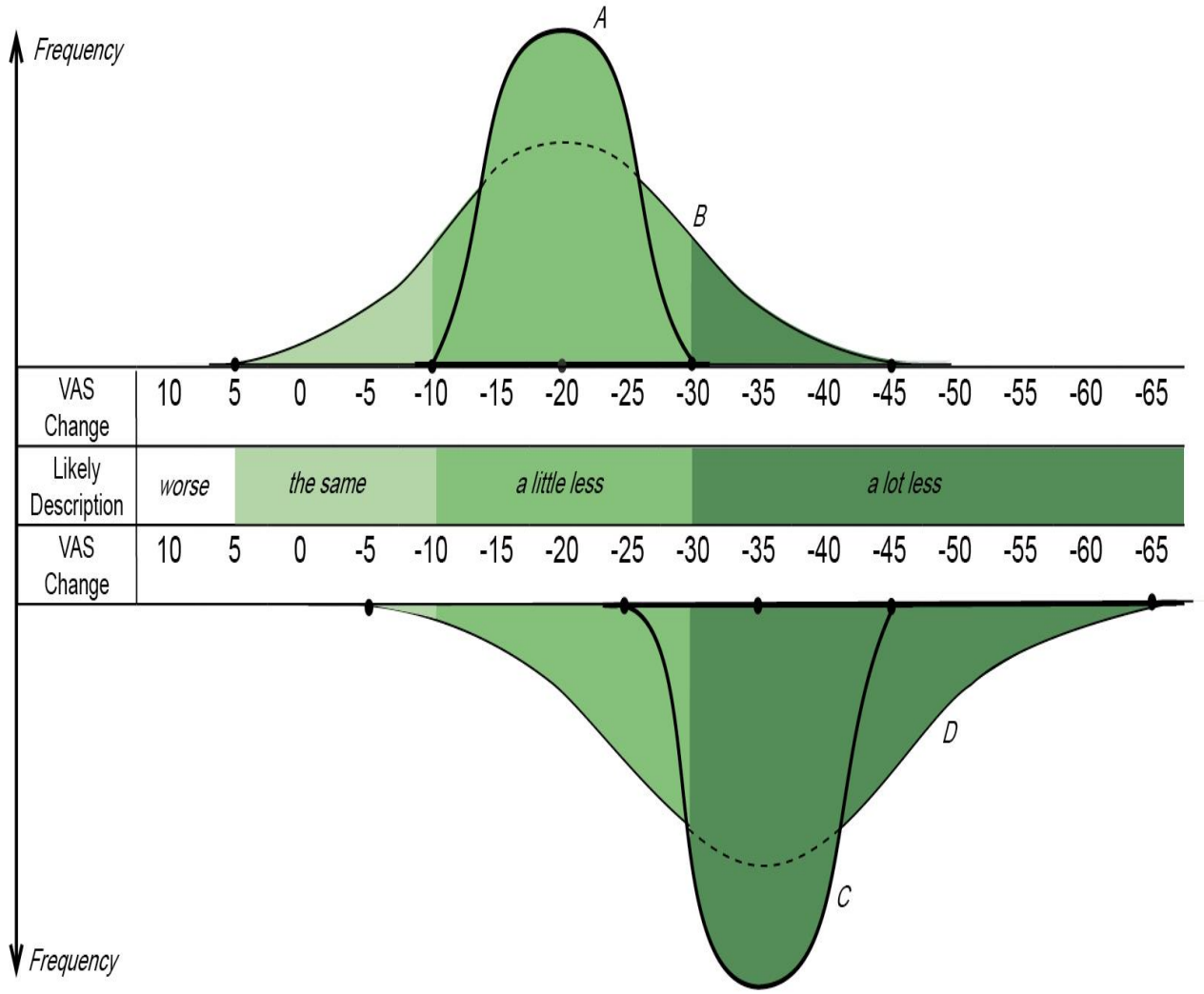
8.3 Limitations of mean VAS change as a primary outcome measure.

Reliance on mean VAS change, however, has two major limitations with regard to interpretation of study findings. Firstly, the mean VAS change for a single treatment group does not give any specific information on the number of patients who experienced symptom improvement. Secondly, the clinical significance of between-group differences in mean VAS change is unknown. Although the MCSD was intended to clarify the issue of clinical significance,[66] its use as an aid in interpreting group mean VAS change is not straightforward.

The difficulties of interpreting group mean VAS change can be illustrated using an example. Figure 8-1 shows four hypothetical treatment groups, A, B, C and D. The mean VAS change for groups A and B is identical at -20 mm. Despite this, they are surprisingly dissimilar with regard to the number of improved patients. The same is the case for groups C and D, which both have a group mean VAS change of -35 mm. This type of difference in the VAS distribution occurs when the severity mix of the populations is not the same.[69] Perhaps more importantly, Figure 8-1 also shows that the difference in mean VAS change of -15 mm between groups A and C is likely to be statistically significant, even though all patients in both groups are improved to some degree. By contrast, the identical -15 mm difference between groups B and D will not be statistically significant, although clearly more patients in group B are unimproved.

Figure 8-1. Difficulties of determining clinical meaning from group mean VAS change and between-group differences in VAS change.

Groups A and B have identical mean VAS changes of about -20 mm; groups C and D have identical mean VAS changes of about -35 mm.



8.4 The required relationship between the primary treatment objective and the primary outcome measure.

For ED patients with nausea, the primary treatment objective is clinically significant symptom improvement. A primary outcome measure should provide the best evidence with regard to the primary objective. For the demonstrated reasons, group mean VAS change seems unlikely to meet this requirement. A comparison with the approach taken in PONV and CINV research helps illustrate the deficiency in the ED method.

PONV/CINV research:

- Primary treatment objective:
    - Absence of post-treatment nausea and/or vomiting.
- Primary outcome measure/study question:
    - Is post-treatment nausea and/or vomiting absent? Yes or No.

The outcome measure, and the study question which is answered, directly relate to the primary treatment objective. The binary response to the study question gives clear information on relative treatment effectiveness with regard to the primary objective. The results are clinically meaningful and easy to understand. For example, post-treatment nausea might occur in 50% of the patients in one group and 30% in the other. The absolute risk reduction is 20%, and the NNT is five. These effect sizes can then be balanced against other factors, such as drug cost and side-effects, to determine if treatment is likely to be worthwhile.

ED-based research:

- Primary treatment objective:
    - Clinically significant improvement in nausea severity.
- Primary outcome measure, traditional:
    - Mean VAS change per treatment group, with between-group comparisons.
- Primary outcome measure, more direct:
    - Did clinically significant improvement in nausea severity occur? Yes or No.

As previously demonstrated (Figure 8-1), the mean VAS change and between-group differences provide only indirect and imprecise information about the likelihood of clinically significant symptom improvement having occurred.

8.5 Potential solutions.

The relevant information could be obtained by simply asking the patient: Are you improved? Yes or no. This assumes that any amount of improvement is clinically significant, which aligns well enough with the concept of the MCSD. In the negative, undecided patients may allocate 'yes' or 'no' in a way which could introduce a systematic bias. A neutral option could be included, but if researchers allocate these to the 'not improved' group for the final analysis, similar biases might result. Use of the ordinal description of change scale might aid patient decision making, but results would still be dichotomized for patients to be classified as improved or not. Overall, however, use of either direct questioning or ordinal ratings of change would not be unreasonable.

Another consideration, however, is that the rating of at least baseline severity remains important in order to determine how well treatment groups are matched. The description of change scale cannot answer this question, with the VAS remaining ideal for this purpose. For this reason, inclusion of VAS ratings in ED-based studies is of value. In addition, although mean VAS change and between-group differences deliver limited information with regard to the primary treatment objective, they do still provide useful information on relative treatment effectiveness.

Both VAS ratings and ordinal descriptions of change ratings could be obtained, as has been done in the specific nausea measurement studies,[66,69] but this is more cumbersome for sick patients. It would seem ideal if the VAS, given its acknowledged advantages, could be used as the sole rating scale. This would require identification of a method by which VAS change could reliably identify patients with clinically significant symptom improvement. Given the known relationship between VAS change and the ordinal description of change scale, this should be possible. If so, rating severity would remain quick and easy for patients, and the presentation of study results would be as straightforward as it is in PONV and CINV research. For example, two treatments might bring about clinically significant symptom improvement in 90% and 80% of patients respectively. The absolute difference is 10% and the NNT is 10. This is both clinically meaningful and easy to understand.

8.6 Aims and brief rationale.

The primary objective of this series of related research projects is to develop improved outcome measures for ED-based antiemetic trials. The aim is to ensure that the main study results relate directly to the primary treatment objective, and that they are presented in an easily understandable and clinically meaningful way. The utility of previously used secondary outcomes, such as rescue medication[35,37,40] and patient satisfaction[35,40] will also be further explored.

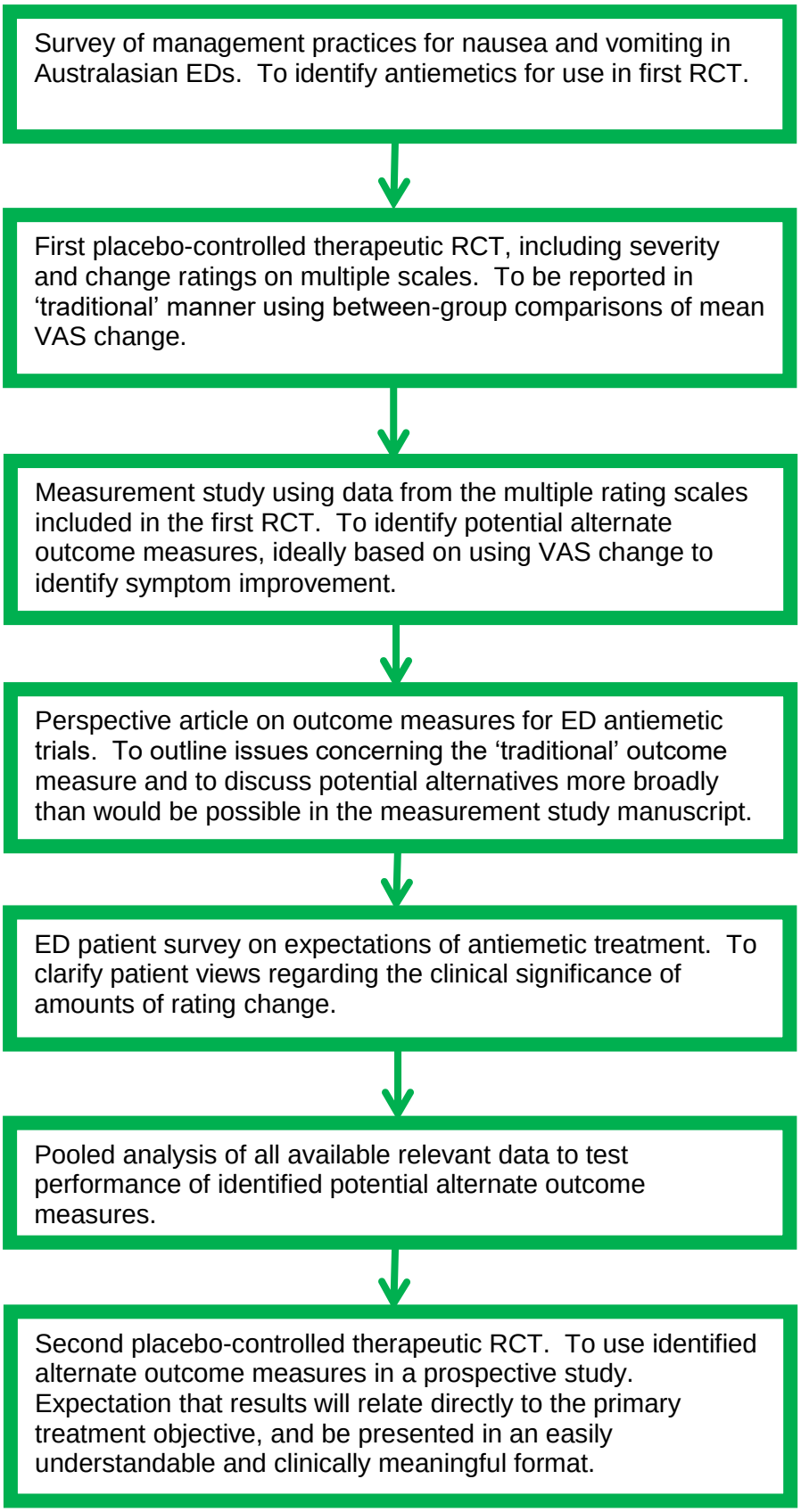
8.7 Method for investigation.

The sequential research plan, including the anticipated aim for each study, is outlined in Figure 8-2.

The first planned study, a survey on ED management practices, was designed to confirm the best choice of drugs for use in an exploratory RCT. As at 2009, three of the four ED-based RCTs had been conducted in the US.[35,36,76] Anecdotally, promethazine and droperidol were rarely used to treat nausea in adult ED patients in Australia. Locally, metoclopramide was thought to be the most frequently used first-line antiemetic agent, but frequency of prochlorperazine and ondansetron use was unknown. The conduct of this study was also an opportunity to explore the ED management of nausea and vomiting more broadly.

The second and third planned studies were a combination therapeutic RCT and measurement study. These were conducted concurrently. At the time of planning, the Braude (2006) study was the only ED-based, placebo-controlled antiemetic RCT to have been published.[35] As a consequence, it seemed important to conduct another placebo-controlled trial, to determine if findings were consistent. In order to do this, the primary outcome measure of the RCT component needed to be a comparison of mean VAS change between treatment groups. In the Australian ED setting, it was most logical to investigate the drugs which were most commonly used in this country.

Figure 8-2. Sequence of planned research: aim and purpose.



For the measurement component of the study, the purpose was to explore the relationship between initial severity, rating scale change and clinical significance in more depth. Planned study measurements included the VAS, NRS, adjectival scales and number of vomiting episodes. Change would be measured directly on these scales, and on the ordinal description of change scale. This would be the most extensive comparison of outcome measures yet undertaken. The previous nausea measurement studies had shown that the VAS ratings for each description of change category were significantly different from each other.[66,69] This supports that an amount of VAS change might equally predict an accompanying description of change, but this had never been explored. If this were possible, amounts of VAS change might enable identification of patients with symptom improvement. This hypothesis is illustrated in Figure 8-3.

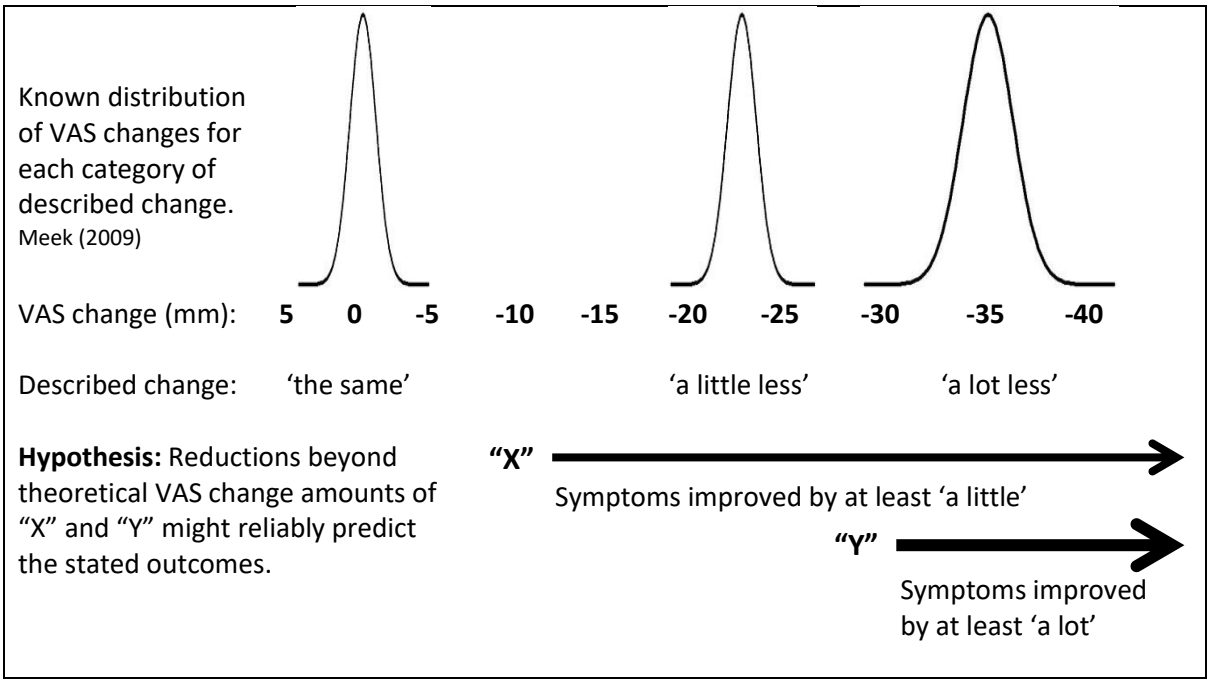
A narrative article was planned to follow publication of the RCT and the measurement study. This would allow a more broad discussion of the findings than would be possible in either published paper. The limitations of the previously used primary outcome measure, proposed alternatives and the potential implications with regard to future ED-based research, could all be discussed.

A patient survey was planned to explore expectations of antiemetic drug treatment. The rationale was that the aim of the measurement study was to explore ways of reliably detecting patients with symptom improvement. In effect, this was equating treatment success with symptom improvement to any degree ('a little less' or 'a lot less'). As a 'beneficial effect', this seems reasonable, but patient views on a 'desired effect' were unknown. The findings of this study were likely to contribute to the final outcome measures chosen for testing in a follow-up RCT.

It was possible that any alternate outcome measures identified could be further examined in a pooled analysis, using similar information from previously published or available data. If this proved possible, it would allow more robust conclusions on the reliability of proposed alternate outcome measures to be drawn. This could further inform the design of a follow-up RCT.

A second ED-based antiemetic RCT was planned as the final study in this series of research. This was to enable testing of any proposed alternate or additional outcome measures, in a properly designed prospective study. This would ensure that the aim of delivering improved outcome measures for use in ED-based antiemetic trials had been met.

Figure 8-3. Hypothesised method for detection of symptom improvement from amounts of VAS change.



CHAPTER 9. Treatment and assessment of emergency department nausea and vomiting in Australasia: a survey of anti-emetic management.

9.1 Brief rationale and aims.

Prior to 2009, the three ED-based RCTs which had compared different antiemetic drugs, were all conducted in US Emergency Departments.[35,36,76] Patterns of ED antiemetic drug use are not necessarily the same in Australia. For example, prochlorperazine, promethazine and droperidol were thought to be infrequently used. In order to identify the most relevant drugs for inclusion in an Australian ED-based antiemetic trial, a survey of current antiemetic drug use was required. This was also an opportunity to more broadly describe the ED management of nausea and vomiting in Australasian ED.

Primary aim: To survey Fellows of the Australasian College for Emergency Medicine in order to describe the current assessment and management of nausea and vomiting in ED patients in Australasia.

Secondary aims: To determine the influence of various factors on drug choice, including perceived drug effectiveness, side effects, cost, pharmacy directives and the extent of use of any ED antiemetic protocols.

9.2 Citation and paper:

Mee MJ, Egerton-Warburton D, Meek R. Treatment and assessment of emergency department nausea and vomiting in Australasia: a survey of anti-emetic management. Emerg Med Australas. 2011; 23(2): 162-8.

PAPER FOLLOWS

EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2011) **23**, 162–168 doi: 10.1111/j.1742-6723.2011.01386.x

ORIGINAL RESEARCH

Treatment and assessment of emergency department nausea and vomiting in Australasia: A survey of anti-emetic management

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Abstract

Objective: To describe the treatment and assessment of emergency department nausea and vomiting (EDNV) in Australasia by Fellows of the Australasian College for Emergency Medicine (FACEM). To determine the influence of various factors on FACEM anti-emetic choice. To compare the influence of drug effectiveness, side effects, cost and pharmacy directives on adult EDNV anti-emetic choice between FACEM choosing the two most common first-line agents.

Methods: A cross-sectional survey of all FACEM practising in Australasian ED was conducted by mail-out in February 2009.

Results: Of all FACEM surveyed 48.7% (532/1092) responded. The most common first-line drugs for adult EDNV were metoclopramide (87.3%, 453/519), 5HT3 antagonists (7.9%, 41/519) and prochlorperazine (2.3%, 12/519). For paediatric EDNV, the most common first-line agents were 5HT3 antagonists (86.2%, 307/356), metoclopramide (6.7%, 24/356) and promethazine (5.1%, 18/356). For most FACEM anti-emetic choice was highly influenced by perceived drug efficacy (96.1%) and side effects (82.5%), and 32.9% of FACEM were highly influenced by drug cost. Few FACEM reported ED anti-emetic protocols for adults (13.0%) or children (16.7%) in their ED. FACEM seldom used scales or tools to measure EDNV severity in adult (2.5%) or paediatric (3.4%) patients.

Conclusions: Fellows of the Australasian College for Emergency Medicine anti-emetic choice in Australasian ED has been described. The main influences on anti-emetic choice were patient age, perceived drug efficacy and drug side-effect profiles.

Key words: *anti-emetics, clinical protocol, emergency medicine, nausea, vomiting.*

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Introduction

Nausea and vomiting are common complaints in patients presenting to the ED.[1] Relief of these symptoms is important for patient comfort and for the prevention of complications, such as dehydration, hypokalaemia and aspiration. Emergency department nausea and vomiting (EDNV) is of diverse aetiology and is often undifferentiated at presentation. Current management practices for EDNV are largely unknown[2–5] and there is a paucity of anti-emetic drug efficacy trials in this setting.[6–10]

There are no published surveys of adult EDNV treatment or assessment in Australasia or overseas. A large US chart review of adult and paediatric EDNV management from 2003 reported that droperidol, promethazine and prochlorperazine were the most commonly used anti-emetics;[1] however, the present study predated the widespread introduction of 5HT3 receptor antagonists, such as ondansetron and granisetron. A recent Australian study investigating nausea severity rating scales incidentally reported almost exclusive use of metoclopramide and ondansetron as first-line anti-emetic agents for adults in the participating ED of Victoria.[11]

Published surveys of paediatric EDNV treatment from Australasia, USA and Italy focus only on paediatric gastroenteritis.[2–5] The Australasian survey from 2005 found that 54% of ED physicians used an anti-emetic for paediatric gastroenteritis, with 60% of these choosing ondansetron and 29% using metoclopramide.[2]

It is difficult to predict current anti-emetic usage in Australasian ED in part because of a lack of evidence for anti-emetic efficacy in the ED setting. Many antiemetics have high-level evidence supporting their use for the prevention of postoperative nausea and vomiting (PONV) as well as chemotherapy- and radiotherapy-induced nausea and vomiting.[12–14] It is not possible to extrapolate this evidence to EDNV because of different patient populations, aetiologies, and given that treatment rather than prevention is usually the aim in the ED setting. Whereas there is evidence for the efficacy of ondansetron in the ED for paediatric gastroenteritis[6] and opioid-induced nausea and vomiting,[7] evidence for anti-emetic efficacy in other areas of EDNV is lacking. An extensive published work search has revealed mostly low-level studies with no systematic reviews, one small randomized placebo-controlled trial and two randomized controlled trials without placebo arm.[8–10]

Cost-effectiveness studies of anti-emetic usage have not been performed for EDNV, in contrast to the fields of PONV and oncology.[15,16] Given that evidence for drug efficacy in EDNV is limited, drug cost might be an important influence on anti-emetic choice.

We aimed to survey Fellows of the Australasian College for Emergency Medicine (FACEM) in order to describe the current treatment and assessment of EDNV in Australasian ED. Additionally, we aimed to determine the influence of various factors on FACEM drug choice, including drug effectiveness, side effects, cost, pharmacy directives and the extent of use of any ED anti-emetic protocols. We sought to compare factors influencing adult EDNV drug choice between FACEM choosing the two most common first-line agents. An understanding of current practice and influence on drug choice might be valuable for determining the approach to future research on anti-emetic drug efficacy and cost-effectiveness in Australasian ED.

Methods

The study was a voluntary, anonymous, cross-sectional survey of all FACEM undertaken in February 2009. The study was approved by the ACEM Scientific Committee and the Southern Health Human Research Ethics Committee. All Fellows registered with ACEM and residing in Australia or New Zealand at the time of the study were mailed the questionnaire with a cover letter explaining the project. Those FACEM residing elsewhere were excluded, as we wanted to clarify current practice in Australasian ED. A reminder letter was sent to non-responders in March 2009. ACEM administrative staff were responsible for distribution and receipt of all documentation. Surveys were coded by a third party at ACEM to ensure anonymity of the respondents.

A published work review of ED nausea and vomiting management was conducted in December 2008 to find previous surveys of EDNV treatment[2–5] and evidence for anti-emetic efficacy in this setting.[6–10] The questionnaire was then designed by the authors and refined using a focused feedback session with ED registrars and consultants at Monash Medical Centre. The survey was pilot tested on a group of ED consultants from Monash Medical Centre and Dandenong Hospital, Dandenong, Australia for face and content validity.

The questionnaire had four main sections. The first section contained five items on FACEM demographics including ED type, annual census, location (by state/country), patient population (adult or paediatric) and ACEM accreditation status. The second section asked FACEM whether their ED had an anti-emetic protocol for adults and children (yes, no, not sure), and if so to

Table 1. FACEM respondents' ED type, size and location (with location of all FACEM for comparison)

Hospital type (n = 532) No. (%)	ED annual census (n = 526) No. (%)	State/country Respondents (n = 532) No. (%, 95% CI)	State/country All FACEM (n = 1096)† No. (%, 95% CI)
Major referral 256 (48.1)	>50 K 224 (42.6)	VIC 156 (29.3, 25.6–33.3)	287 (26.2, 23.7–28.9)
Urban district 160 (30.1)	40–50 K 158 (30.0)	NSW 117 (22.0, 18.7–25.7)	260 (23.7, 21.3–26.3)
Regional 99 (18.6)	30–40 K 94 (17.9)	QLD 85 (16.0, 13.1–19.3)	209 (19.1, 16.8–21.5)
Private 15 (2.8)	20–30 K 35 (6.7)	NZ 67 (12.6, 10.0–15.7)	118 (10.8, 9.0–12.7)
Other 2 (0.4)	10–20 K 13 (2.5)	WA 52 (9.8, 7.5–12.6)	109 (9.9, 8.3–11.8)
	<10 K 2 (0.4)	SA 27 (5.1, 3.5–7.3)	61 (5.6, 4.3–7.0)
		TAS 15 (2.8, 1.7–4.6)	26 (2.4, 1.6–3.4)
		ACT 9 (1.7, 0.8–3.2)	16 (1.5, 0.9–2.3)
		NT 4 (0.8, 0.2–2.0)	10 (0.9, 0.5–1.6)

†*Information supplied by ACEM as of October 2009. ACT, Australian Capital Territory; FACEM, Fellows of the Australasian College for Emergency Medicine; K, 1000 persons; NSW, New South Wales; NT, Northern Territory; NZ, New Zealand; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia.*

name protocol drugs (first-, second- and third-line) and report extent of protocol use (never, sometimes, most of the time, always). The third section asked FACEM to describe their most common first-, second- and third-line drug choices (with dose and route) and other antiemetics or alternate therapies used in the last year. They were then asked to describe the role of various factors (drug effectiveness, side effects, cost and pharmacy directives) on their first-line drug choice (no role, minor role, major role, always), and how their drug choice changed in various clinical situations (pregnancy, chemotherapy/radiotherapy, narcotic induced, vertigo). The final section asked FACEM if they used scales or tools to assess EDNV severity and to describe any used. They were then asked how often they would initiate treatment for patients with isolated nausea, isolated vomiting or nausea with vomiting (never, sometimes, mostly, always). Most questions gave opportunity for respondents to make free-text comments.

All data were entered into Excel spreadsheets (Microsoft Corporation, Redmond, WA, USA). Data were analysed using Stata version 8.0 statistical package (Stata Corporation, College Station, TX, USA). Responses are reported as numbers, fractions (where the denominator is the number of FACEM responding to each questionnaire item) and percentages, with 95% confidence intervals where relevant. Odds ratios with 95% confidence intervals were generated to compare the influence of various factors on FACEM drug choice.

Results

A total of 532 out of 1092 FACEM returned the survey, giving a response rate of 48.7%. Some questionnaires did not contain responses to every item; however, all questionnaires returned were included in the analysis. In total, 75.6% of respondents (402/532) treated both adult and paediatric patients in their primary ED, 22.2% (118/532) treated only adult patients and 2.3% (12/532) treated only paediatric patients. Therefore in total, 520 FACEM treated adults and 414 treated paediatric patients at their primary ED. For 91.7% (488/532) of FACEM their primary ED was accredited. Table 1 shows respondents' primary ED type, annual consensus and location. Most FACEM worked at major referral and urban district hospitals. The proportion of respondents by state/country was similar to the actual FACEM workforce distribution according to information supplied by ACEM from October 2009.

The most common anti-emetic drugs used by FACEM for adult and paediatric EDNV are summarized in Table 2. For adult EDNV 87.3% of respondents preferred metoclopramide first-line. The 5HT3 antagonists were the most used second- and third-line agents, with ondansetron being the preferred 5HT3 antagonist in all categories. Where provided the most common anti-emetic doses were 10 mg for metoclopramide, 4 mg for ondansetron and 12.5 mg for prochlorperazine, and the route of administration was most commonly intravenous (IV).

Of the 414 FACEM treating paediatric patients, 356 reported their preferred first-line anti-emetic. Of these, 307 (86.2%) chose 5HT3 antagonists, usually ondansetron (294/307), and this was most commonly given in wafer form where indicated. Although no section was provided for free-text comments here, five FACEM using metoclopramide noted minimum age requirements for its use, 30 FACEM commented that they rarely or never used drugs for paediatric EDNV

Table 2. Anti-emetic drugs most used (first-, second- and third-line) by FACEM for adult and paediatric EDNV

Adult			Paediatric		
First-line (n = 519) No. (%)	Second-line (n = 510) No. (%)	Third-line (n = 426) No. (%)	First-line (n = 356) No. (%)	Second-line (n = 107) No. (%)	Third-line (n = 18) No. (%)
Metoclopramide 453 (87.3)	5HT3 antagonists 259 (50.8)	5HT3 antagonists 203 (47.7)	5HT3 antagonists 307 (86.2)	5HT3 antagonists 40 (37.4)	Metoclopramide 5 (27.8)
5HT3 antagonists 41 (7.9)	Prochlorperazine 162 (31.8)	Prochlorperazine 98 (23.0)	Metoclopramide 24 (6.7)	Promethazine 38 (35.5)	5HT3 antagonists 4 (22.2)
Prochlorperazine 12 (2.3)	Metoclopramide 40 (7.8)	Droperidol 35 (8.2)	Promethazine 18 (5.1)	Metoclopramide 15 (14.0)	Dexamethasone 2 (11.1)
Other 13 (2.5)	Other 49 (9.6)	Other 90 (21.1)	Other 7 (2.0)	Other 14 (13.1)	Other 7 (38.9)

EDNV, emergency department nausea and vomiting; FACEM, Fellows of the Australasian College for Emergency Medicine.

Table 3. Role of various factors in FACEM respondents' choice of first-line anti-emetic

	Number (%)			
	Drug cost (n = 431)	Drug side effects (n = 530)	Drug effectiveness (n = 532)	Pharmacy directives (n = 531)
No role	18 (4.2)	3 (5.7)	0 (0.0)	164 (30.9)
Minor role	271 (62.9)	90 (17.0)	21 (39.5)	221 (41.6)
Major role	91 (21.1)	279 (52.6)	279 (52.4)	96 (18.1)
Always has role	51 (11.8)	158 (29.8)	232 (43.6)	50 (9.4)

FACEM, Fellows of the Australasian College for Emergency Medicine.

and four respondents stated that IV or nasogastric tube (NGT) hydration was their first-line anti-emetic.

More than three anti-emetic drugs had been used in the last year by 349 (67.1%) of the 520 FACEM responding to this questionnaire item, and 16.1% (83/516) of respondents had used 'non-pharmacological' or 'alternate' therapies. The most common 'alternate' therapies included ginger, IV fluid, NGT hydration, acupuncture and acupressure.

Of those respondents treating adults, 13.0% (67/517) were sure their ED had an adult anti-emetic protocol, and of these 66 (98.5%) reported metoclopramide as the first-line protocol drug. Of those respondents treating paediatric patients, 16.7% (67/401) were sure their ED had a paediatric anti-emetic protocol, and of these 64 (95.5%) reported a 5HT3 antagonist as the first-line protocol drug. Most FACEM used their ED protocol 'some of the time' or 'most of the time' in the case of both adult (76.1%, 51/67) and paediatric (77.3%, 51/66) protocols.

Table 3 describes the role of various factors in FACEM choice of first-line anti-emetic drug. Drug effectiveness was reported as having a 'major' role or 'always' having a role by 96.1% of respondents. Drug side effects had a 'major' role or 'always' had a role for 82.5% of Fellows. In contrast, for both pharmacy directives and drug cost, less than one-third of respondents felt these factors had a 'major' role or 'always' had a role.

First-line antiemetics for EDNV differed in some clinical subgroups. For patients undergoing chemotherapy or radiotherapy, 5HT3 antagonists were preferred as first-line by 336 (67.1%) of the 501 FACEM responding to this question. For EDNV associated with vertigo, 80.3% (416/518) of respondents used prochlorperazine. Several FACEM commented that this choice was based on personal experience rather than evidence in the published work. For nausea and vomiting in pregnancy, 83.9% (427/509) of respondents used metoclopramide first-line. Narcotic-induced EDNV was treated with metoclopramide by 82.8% (419/506) of respondents.

Scales or tools to measure adult EDNV severity were used by 2.5% (13/519) of respondents. For paediatric patients scales or tools were used by 3.4% (14/412) of respondents. The most common scale or tool used was number of vomiting episodes for both adult (4/14) and paediatric (5/16) patients. Nausea with vomiting was 'mostly' or 'always' treated by 93.6% (497/531) of respondents, whereas isolated nausea was 'mostly' or 'always' treated by 49.4% (262/530).

Table 4 compares the influence of various factors on first-line anti-emetic choice for adult EDNV between FACEM choosing metoclopramide and FACEM choosing 5HT3 receptor antagonists. Metoclopramide users were more than twice as likely compared with 5HT3 antagonists users to report drug cost as having a 'major' role or 'always' having a role, and this difference was significant. There were no significant differences between metoclopramide and 5HT3 antagonist users for the other influencing factors considered.

Discussion

We found that metoclopramide was the most commonly used first-line anti-emetic for adult EDNV among FACEM, followed by the 5HT3 receptor antagonists. The predominant use of these drugs is consistent with the limited existing evidence of current anti-emetic practice in Australasia.[11] FACEM preference towards 5HT3 receptor antagonists for pharmacological management of paediatric EDNV parallels current management practice in Australasia for the clinical subgroup of ED paediatric gastroenteritis[2] and might also reflect evidence showing its marginal efficacy in this group of patients.[6] The less common use of metoclopramide by FACEM for paediatric EDNV might be the result of concerns regarding safety of metoclopramide in this population. Decreased reporting of second- and third-line agents for paediatric EDNV not only suggests decreased breadth of anti-emetic use, but might also reflect decreased frequency of anti-emetic administration for paediatric patients.

Anti-emetic protocols for adult or paediatric EDNV were uncommon in Australasia, which might reflect the lack of evidence for anti-emetic efficacy in this setting. For both adult and paediatric EDNV, first-line protocol antiemetics mirrored the first-line agents preferred by FACEM overall regardless of protocol.

For most respondents, drug effectiveness and side effects highly influenced their first-line anti-emetic choice. This is interesting given the lack of evidence for EDNV anti-emetic efficacy in the published work. The 'best' evidence in the published work for anti-emetic efficacy in adult EDNV consists of a small randomized placebo-controlled trial which suggests that droperidol is superior to placebo and fails to demonstrate efficacy of metoclopramide or prochlorperazine over placebo.[8] Two small trials without placebo control suggest that prochlorperazine has greater efficacy than promethazine[9] and ondansetron has equivalent efficacy to promethazine.[1] It is also interesting that metoclopramide users and ondansetron users were similarly influenced by drug side-effect profiles given existing knowledge of metoclopramide's common extrapyramidal side effects.[17] It is perhaps less surprising that metoclopramide users were significantly more likely to be highly influenced by cost. At the time of the survey mail-out, given the brands available at our institution the cost of a 4 mg ampoule of IV ondansetron was $2.90 compared with $0.30 for a 10 mg ampoule of IV metoclopramide.

Presumed aetiology of EDNV has an important role in respondents' choice of anti-emetic. The predominant use of 5HT3 antagonists for chemotherapy- or radiotherapy-induced EDNV is consistent with current evidence supporting the use of these agents in high dose for such patients.[13,14] Evidence guiding anti-emetic use in EDNV with vertigo is lacking; however, the predominant use of prochlorperazine by FACEM is consistent with recommendations in Therapeutic Guidelines[18] and might also reflect expert opinion favouring drugs with antihistamine or anticholinergic action.[19,20] The preference towards metoclopramide for pregnant patients with EDNV might reflect its category A safety rating.[17] The use of metoclopramide as most common first-line for narcotic-induced nausea or vomiting seems surprising given that the limited evidence available supports the use of ondansetron in such cases.[7]

Less than half of FACEM treated isolated nausea compared with almost all FACEM treating nausea with vomiting, and scales to measure nausea or vomiting severity were seldom used. Given extensive evidence that lack of measurement of pain reduces the likelihood of receiving analgesia, it is possible that there is a similar association between lack of measurement and treatment of nausea in the ED.[21,22]

There were several limitations to the present study. Whereas the response rate was reasonable and comparable with that of other recent surveys of FACEM,[23,24] it is possible that the practices of those who did not respond were significantly different from those who did. We believe the respondent group was reasonably representative of the total FACEM population given their locations by state/country were similar to the workforce distribution of all FACEM at the time of the survey, and given the ratio of FACEM working in regional versus metropolitan ED was comparable with another recent survey.[25] Although we believe the clarity, face, content and construct validity of the questionnaire were reasonable, the validity of our survey as a tool to elicit the information we desired cannot be guaranteed. We believe the provisions made for anonymity should have

Table 4. Influences on FACEM first-line drug choice for adult EDNV: metoclopramide versus 5HT3 antagonist users

Influencing factors	Metoclopramide users highly influenced† by each factor (n = 453) No. (%, 95% CI)	5HT3 antagonist users highly influenced† by each factor (n = 41) No. (%, 95% CI)	Odds ratio (95% CI) in favour of metoclopramide as first-line drug	P-value (χ^2)
Drug cost	129 (28.5,24.3–32.6)	5 (12.2, 2.2–22.2)	2.87 (1.09–9.55)	0.03
Drug side effect	369 (81.5,77.7–84.8)	35 (85.4,72.0–93.9)	0.75 (0.25–1.89)	0.53
Drug efficacy	433 (95.6,93.4–97.2)	41 (100, 91.4–100)	0‡ (0.00–1.77)	0.17
Pharmacy directives	132 (29.1,25.1–33.5)	9 (22.0,11.3–36.5)	1.47 (0.66–3.58)	0.33

†*High level of influence is defined as either of the individual responses: 'major role' or 'always has a role'.* ‡*Conditional maximum likelihood estimate used given zero cell value.*
EDNV, emergency department nausea and vomiting; FACEM, Fellows of the Australasian College for Emergency Medicine.

limited potential responder bias as there seems no reason why respondents would record practices or opinions which they did not follow. Another limitation is that the findings of the present study represent FACEM practice at one point in time, and practice patterns might constantly evolve. Furthermore, FACEM practice does not necessarily reflect the practice of more junior staff, so our findings might not accurately represent current management of EDNV in Australasian ED as a whole.

Conclusions

We have described for the first time the assessment and treatment of adult and paediatric EDNV in Australasia among FACEM. The most commonly used agents have limited evidence of efficacy in this setting as demonstrated by our published work review. Despite this lack of evidence, most FACEM reported that drug effectiveness and side effects highly influenced their choice of drug, whereas drug cost and pharmacy directives did not. Randomized placebo-controlled anti-emetic efficacy trials are needed in the ED setting and our survey results suggest such trials for adult EDNV treatment in Australasia should focus on metoclopramide, 5HT3 antagonists and prochlorperazine. The use of scales to guide EDNV treatment was rare for both adult and paediatric patients and might be encouraged by ongoing research in the field. Further anti-emetic research might also guide the development of protocols or guidelines for anti-emetic use in the ED.

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Author contributions

MJM: published work search, questionnaire design, data collation and entry, data interpretation, data analysis, manuscript preparation. DE-W: published work search, questionnaire design, data interpretation, data analysis, manuscript preparation. RM: data interpretation, data analysis, manuscript preparation.

Competing interests

DE-W is a Section Editor for *Emergency Medicine Australasia*. None declared for the other authors.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Copy of questionnaire.
Appendix S2. Extra tables for electronic version of journal article.
Appendix S3. Search strategies for literature review December 2008.

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9.3 Brief summary of results and implications for further ED-based research.

The study confirmed that metoclopramide, at a usual dose of 10 mg IV, was by far the most common first-line antiemetic drug used for adult ED patients with nausea. Ondensetron, at a usual dose of 4 mg IV, was the second most commonly used first-line agent, and the most frequently used second-line agent. Prochlorperazine was uncommonly prescribed, and the use of any other antiemetic drug was rare.

One of the more noteworthy secondary findings was that 94% of doctors said they routinely prescribed antiemetic drugs for patients with active vomiting, but only 49% did so when nausea alone was present. This suggested that prescription of antiemetic drugs in the ED was influenced by the perceived severity of the symptoms, and that use might not be as common as previously assumed.

The study findings confirmed that the most logical comparisons for an Australian ED-based RCT were between metoclopramide, ondansetron and placebo.

CHAPTER 10. A randomized placebo controlled trial of antiemetic agents in adult emergency department patients with nausea or vomiting.

10.1 Brief rationale and statement of aims.

This study comprised the concurrent conduct of two separate investigations. This first published component was a therapeutic RCT. Further exploration of the additional measurement scales was published in a second paper. The therapeutic trial was designed to compare metoclopramide 20 mg IV and ondansetron 4 mg IV, with placebo. The 20 mg dosage of metoclopramide was chosen for two reasons. Firstly, the more standard 10 mg dose was reported as being equivalent to placebo by Braude (2006).[35] Secondly, Cham (2004) found that an 'intermediate' dose of metoclopramide was somewhat more effective than the standard dose, although the difference was not statistically significant.[34] Although Braude (2008) had found the standard ondansetron dose of 4 mg IV to be equivalent to promethazine 25 mg,[36] it had not been tested against placebo.

At the time of planning and commencing this RCT, the study of Braude (2006) was the only other ED-based, placebo-controlled antiemetic trial.[35] As such, it was felt important that a second placebo-controlled study be conducted and reported in the same way, in order to determine if results were consistent. Secondly, there was no literature yet available to support the use of any outcome measure other than the previously used between-group comparison of mean VAS change. Treatment effectiveness was to be assumed if the VAS reduction from baseline exceeded -20 mm for a particular treatment group, as per the previously defined MCSD.[69]

10.2 Citation and paper.

Egerton-Warburton D, Meek R, Mee MJ, Braitberg G. Antiemetic use for nausea and vomiting in adult emergency department patients: Randomised controlled trial comparing ondansetron, metoclopramide, and placebo. Annals of Emergency Medicine. 2014; 64(5):526-532.e1.

PAPER FOLLOWS

Antiemetic Use for Nausea and Vomiting in Adult Emergency Department Patients: Randomized Controlled Trial Comparing Ondansetron, Metoclopramide, and Placebo

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Study objective: We compare efficacy of ondansetron and metoclopramide with placebo for adults with undifferentiated emergency department (ED) nausea and vomiting.

Methods: A prospective, randomized, double-blind, placebo-controlled trial was conducted in 2 metropolitan EDs in Melbourne, Australia. Eligible patients with ED nausea and vomiting were randomized to receive 4 mg intravenous ondansetron, 20 mg intravenous metoclopramide, or saline solution placebo. Primary outcome was mean change in visual analog scale (VAS) rating of nausea severity from enrollment to 30 minutes after study drug administration. Secondary outcomes included patient satisfaction, need for rescue antiemetic treatment, and adverse events.

Results: Of 270 recruited patients, 258 (95.6%) were available for analysis. Of these patients, 87 (33.7%) received ondansetron; 88 (34.1%), metoclopramide; and 83 (32.2%), placebo. Baseline characteristics between treatment groups and recruitment site were similar. Mean decrease in VAS score was 27 mm (95% confidence interval [CI] 22 to 33 mm) for ondansetron, 28 mm (95% CI 22 to 34 mm) for metoclopramide, and 23 mm (95% CI 16 to 30 mm) for placebo. Satisfaction with treatment was reported by 54.1% (95% CI 43.5% to 64.5%), 61.6% (95% CI 51.0% to 71.4%), and 59.5% (95% CI 48.4% to 69.9%) for ondansetron, metoclopramide, and placebo, respectively; rescue medication was required by 34.5% (95% CI 25.0% to 45.1%), 17.9% (95% CI 10.8% to 27.2%), and 36.3% (95% CI 26.3% to 47.2%), respectively. Nine minor adverse events were reported.

Conclusion: Reductions in nausea severity for this adult ED nausea and vomiting population were similar for 4 mg intravenous ondansetron, 20 mg intravenous metoclopramide, and placebo. There was a trend toward greater reductions in VAS ratings and a lesser requirement for rescue medication in the antiemetic drug groups, but differences from the placebo group did not reach significance. The majority of patients in all groups were satisfied with treatment. [Ann Emerg Med. 2014;64:526-532.]

Please see page 527 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Nausea and vomiting are common problems for patients in emergency departments (EDs).[1] Treatment of these symptoms is considered desirable to improve patient comfort and prevent complications such as dehydration, hypokalemia, and aspiration.

Evidence for antiemetic drug efficacy in oncology[2] and postoperative nausea and vomiting[3] has been extrapolated to support ED use, but research on undifferentiated ED nausea and vomiting has been limited. Although the 4 trials to date demonstrate that a number of antiemetic drugs appear to lead to a reduction in nausea severity, the 2 placebo-controlled trials suggest that drugs confer little additional benefit in comparison with the control group in the ED setting.[4-7] A summary of the primary outcome measures of these studies is shown in Appendix E1 (available online at http://www.annemergmed.com).

The aim of this study is to compare metoclopramide and ondansetron with placebo, these drugs being chosen because they are the 2 most commonly used antiemetic drugs in Australasia.[1] Findings are expected to inform on the value of routine antiemetic drug use for ED nausea and vomiting and to allow a more reasoned approach to benefit versus risk considerations.

MATERIALS AND METHODS

Study Design and Setting

A multicenter randomized controlled trial was conducted in the ED of Monash Medical Centre (tertiary referral; ED annual

Editor's Capsule Summary

What is already known on this topic

Metoclopramide and ondansetron are commonly used antiemetics; however, little evidence exists to support either agent over placebo.

What question this study addressed

This 270-patient, multicenter, randomized controlled trial compared metoclopramide, ondansetron, and placebo among adults presenting to the emergency department (ED) with nausea unrelated to chemotherapy or radiotherapy. The primary outcome was the change in nausea severity rating at 30 minutes.

What this study adds to our knowledge

No differences were noted between the study arms at 30 minutes. A majority of subjects were satisfied with care, though roughly 1 in 5 required rescue medications. Few subjects reported adverse effects.

How this is relevant to clinical practice

In the early ED care of nausea unrelated to chemotherapy or radiotherapy, routine antiemetic therapy may not be warranted.

census 70,000) and Dandenong Hospital (urban district; ED annual census 57,000). Conduct of the study was approved by the Monash Health Human Research and Ethics Committee and was registered with the Australian Clinical Trials Registry (ACTRN 12609000549224). Patient recruitment took place at Monash Medical Centre from September 2009 to April 2010 and at Dandenong Hospital from January 2010 to April 2010.

Selection of Participants

Patients were eligible for inclusion if they were aged 18 years or older and had nausea or vomiting during their ED episode of care for which the attending physician recommended intravenous antiemetic medication. Patients were excluded for any of the following: hemodynamic instability or primary diagnosis requiring time critical intervention (such as transfer to the angiography suite for myocardial infarction), pregnancy or lactation, Parkinson's disease or restless leg syndrome, use of any antiemetic drug in the previous 8 hours or previous delivery of intravenous fluids during the ED episode of care, ED nausea and vomiting that was motion related or associated with vertigo, currently undergoing chemotherapy or radiotherapy, inability to understand study explanation or outcome measures (any reason), and known allergy or previous adverse reaction to metoclopramide or ondansetron.

All emergency physicians and nurses received study training through circulated electronic materials and group interactive sessions. When intravenous antiemetic was being recommended, an eligibility checklist was completed by the attending physician. If there were no exclusion criteria, written informed consent was obtained and baseline information, including initial nausea severity ratings, was recorded. The need for identification and enrollment of participants by staff with conflicting work pressures resulted in recruitment of a convenience sample of patients.

Interventions

The study drugs used were metoclopramide (Maxolon 10 mg/2 mL; Valeant Pharmaceuticals Australasia Pty Ltd, Rhodes, New South Wales, Australia) and ondansetron (Zofran 4 mg/2 mL; Aspen Pharmacare Australia Pty Ltd, St Leonards, New South Wales, Australia).

The study drugs were prepared for administration under sterile conditions by a pharmacist independent to the study. Each study pack contained 2 2-mL syringes, each containing identically appearing clear fluid. These were (1) 2 2-mL syringes each containing 10 mg of metoclopramide, for a total dose of 20 mg; (2) 1 2-mL syringe of 0.9% saline solution and 1 2-mL syringe containing 4 mg of ondansetron (prevention of premixing ensured an equivalent shelf life of 28 days for all study packs); and (3) 2 2-mL syringes each containing 0.9% saline solution (placebo). Because of the light sensitivity of ondansetron, all study packs were sealed in black plastic bags, which were stored in the ED drug refrigerator. The pharmacist monitored pack numbers and prepared new packs to maintain a minimum availability of 10 at any one time.

Packs were numbered by the independent pharmacist, who used a computer-generated random number sequence to assign treatment allocations. The permute block method, with block sizes of 6, was used at each site. The allocation list was kept by the pharmacist, who could be contacted in the event of an unexpected serious adverse event.

After enrollment and recording of baseline information, the next numbered study pack was obtained, and the 2 2-mL syringes of study medication were administered as a pushed dose. The initial intention had been to administer the study drug during 10 minutes because of concerns around the potential for higher akathisia rates from pushed doses of metoclopramide, but this was not pursued for practical reasons because use of slower infusions for metoclopramide was not standard nursing practice at the time. Infusion of 0.9% saline solution at a standard rate of 250 mL/hour was commenced concurrently. Treatment for underlying conditions was at the discretion of the attending emergency physician. Thirty minutes after study drug administration, repeated nausea severity ratings, number of episodes of vomiting, description of change, and patient satisfaction ratings were obtained. At this time, the need for use of the nominated antiemetic rescue medication (ondansetron 8 mg intravenously) was determined on discussion between the patient and the attending physician. This decision was not linked to any specific severity outcome measure.

To maintain blinding, treatment allocations were revealed only after study completion, when all outcome measurements had been performed and recorded by the investigators in the study database.

Methods of Measurement

Nausea severity was self-rated on a visual analog scale (VAS) on enrollment and 30 minutes after administration of the study drug. The VAS was a standard 100-mm line marked "no nausea" at the left end and "worst nausea imaginable" at the right end. Reported measures were in millimeters from the left end, with change to the left recorded as positive (reduced severity). All measurements were initially performed and recorded by one of the investigators (M.J.M.), with a random sample of 10% being checked for accuracy by one other investigator (D.E.-W.). Use of the VAS for measurement of nausea severity and change has been validated.[8,9] The minimum clinically significant difference was defined for this study as 20 mm.[9]

Severity was also self-rated on a numeric rating scale at enrollment and 30 minutes after administration of the study drug. The numeric rating scale was numbered 0 to 10 and labeled "no nausea" at the left end and "worst nausea imaginable" at the right end.

Severity change at 30 minutes after study drug administration was self-reported and described as "a lot less," "a little less," "the same," "a little more," "a lot more."

Number of vomiting episodes in the 30 minutes before drug administration and during the 30-minute study period was self-reported by the patient. Numeric difference was recorded as positive for reductions.

Patient satisfaction was self-reported and recorded as "satisfied," "not satisfied," or "no opinion."

Outcome Measures

The primary outcome was mean change in severity rating on the VAS 30 minutes after administration of the study drug.

Secondary outcomes were median change in severity on the numeric rating scale, adjectival description of change, change in number of vomiting episodes, need for rescue medication, patient satisfaction, and adverse events.

Primary Data Analysis

An intention-to-treat analysis was planned, and participant flow is reported with the Consolidated Standards of Reporting Trials (CONSORT) methodology.[10] Baseline data are presented as mean or median, number, and percentage and compared with the appropriate statistical tests as required.

For the primary outcome, individual VAS severity ratings are reported as median with interquartile range (IQR). Change in rating is reported as mean because distribution approximated normal. Comparison of mean change between groups used 1-way ANOVA.

The secondary outcomes of adjectival description of change and numeric score are described. Analysis of correlation between scales is being reported separately. Change in number of vomiting episodes is reported as median with IQR; patient satisfaction and need for rescue medication are reported as number and percentage with 95% confidence intervals (CIs).

Sample size was based on estimated change in primary outcome from baseline in each group, with a specified degree of precision. The limited relevant literature suggested that most drugs and placebo lead to VAS score reductions of at least 30 mm, with SDs of up to 30 mm.[4-7] If these results were reproduced, a sample of 80 patients per group would be sufficient to demonstrate this level of change, with the lower limit of the 95% CI still exceeding the defined minimum clinically significant difference. This was the approach previously taken by Braude et al.[4] To allow some margin of error, it was decided that 90 patients per group would be recruited.

Case report forms were entered into a secure study database (Microsoft Access 2007, version 12.0.6211.1000; Microsoft, Mountain View, CA) by one investigator (M.J.M.). An audit of 10% of entries was conducted to ensure accuracy. Data were subsequently analyzed with Stata (version 8.0; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Subjects

During the study period, 744 patients had eligibility criteria checked before administration of intravenous antiemetics. Of these, 270 patients (36.3%) were enrolled in the study. Twelve patients (4.4%) were excluded from the final analysis because of lack of recording of one or both of the VAS severity ratings, so a modified intention-to-treat analysis was conducted, with the 258 patients with complete outcome data being analyzed in the groups to which they were randomized. Of these, 187 patients (72.5%) were recruited at Monash Medical Centre and 71 (27.5%) at Dandenong Hospital. Ondansetron, metoclopramide, and placebo were received by 87 (33.7%), 88 (34.1%), and 83 (32.2%) patients, respectively. Full details of participant flow are shown in Figure 1. Differences in baseline patient characteristics between patients recruited at different sites were not statistically significant. Baseline information between treatment groups is compared in Table 1, and the most common underlying conditions are shown in Table 2.

Main Results

Median time between initial severity rating and administration of study drug was 2.5 minutes (IQR 0 to 5 minutes), both times having been recorded for 240 (93.0%) of 258 patients. Median time from study drug to second severity rating was 35 minutes (IQR 30 to 40 minutes), both times having been recorded for 224 (86.8%) of 258 patients.

The median VAS severity measures at enrollment for ondansetron, metoclopramide, and placebo were 52 mm (IQR 35 to 75 mm), 50 mm (IQR 36.5 to 63.5 mm), and 52 mm (IQR 38 to 75 mm), respectively. The median posttreatment ratings were 19 mm (IQR 7 to 43 mm), 18 mm (IQR 1 to

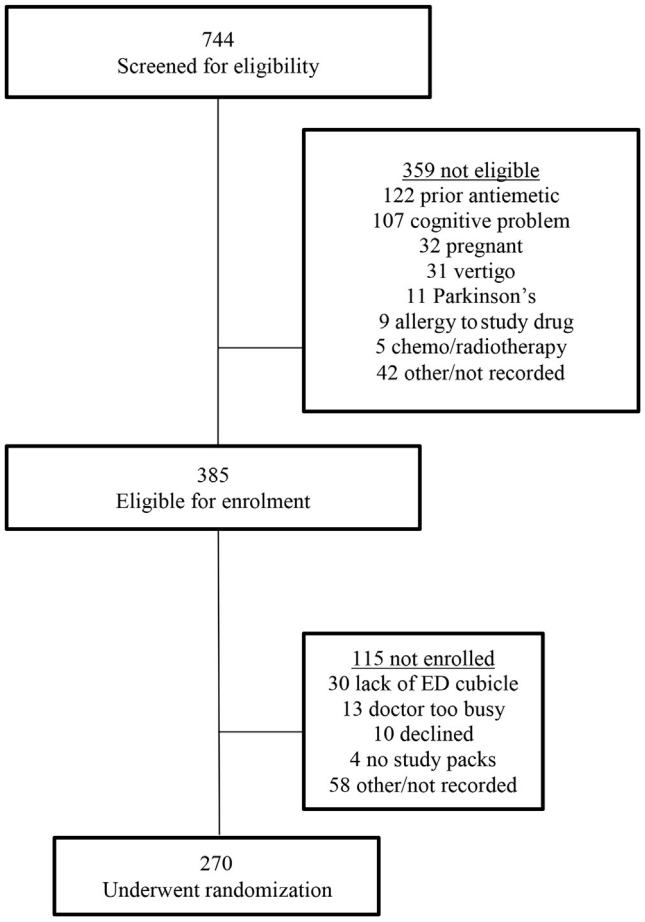

Figure 1. CONSORT diagram of patient flow.

44 mm), and 27 mm (IQR 7 to 54 mm), respectively. These are illustrated in Figure 2. The change in ratings for each patient in each study group is illustrated in Figure 3. Patients whose symptom severity worsened and those who received rescue medication are highlighted.

The differences in mean VAS score change for ondansetron, metoclopramide, and placebo of 27 mm (95% CI 22 to 33 mm), 28 mm (95% CI 22 to 34 mm), and 23 mm (95% CI 16 to 30 mm), respectively, were not statistically significant between the 3 groups.

Secondary outcome measures are summarized in Table 3. Change in severity on the numeric rating scale, adjectival descriptions of change, reduction in number of vomiting episodes, and patient satisfaction were all similar between treatment groups. Differences in the percentage receiving rescue medication for ondansetron, metoclopramide, and placebo, being 29 of 84 (34.5%; 95% CI 25.0% to 45.1%), 15 of 84 (17.9%; 95% CI 10.8% to 27.2%), and 29 of 80 (36.3%; 95% CI 26.3% to 47.2%), respectively, were significant. This is illustrated with the individual patient ratings in Figure 3. Distribution of adjectival descriptions of change for each group is illustrated in Figure 4.

An adverse event was recorded for 9 (3.5%) of the 258 patients. Six of these were in patients who had received metoclopramide: 2 had akathisia, 2 had restlessness, 1 had muscle twitching, and 1 had sweatiness. Two patients had received ondansetron: 1 had dizziness and 1 had stinging at the injection site. One patient who had received placebo was noted as having "shaking/restlessness."

LIMITATIONS

A number of study limitations warrant discussion. Selection bias may be an issue. It is unlikely that only 744 patients, or about 3 per day, received intravenous antiemetics during the study period. Because we have no information on the total number of patients who might have been eligible, the representativeness of this convenience sample is uncertain. Given the sample size, however, and the range of underlying conditions included, it seems unlikely that this would result in any systematic bias. From patients recruited, attrition bias was minimal, with lack of primary outcome measure recording in only 12 (4%) of 270. Performance bias should have been minimized by the randomization and masking. There had been some concern that occurrence of extrapyramidal adverse effects would suggest that metoclopramide had been given, but it happened that such reactions were identified too infrequently for there to have been any potential effect on results. Although no

Table 1. Patient characteristics for each treatment group.

Patient-related Variable	Ondansetron (n=87)	Metoclopramide (n=88)	Placebo (n=83)
Age, median (IQR), y	42 (27–61)	42 (27–67)	42 (28–62)
Female sex, No. (%)	56 (64.4)	58 (65.9)	55 (66.3)
[95% CI]	[53.9–73.9]	[55.6–75.2]	[55.6–75.8]
Main clinical causes, No. (%) [95 CI]			
Opioid induced	23/72 (31.9)	19/65 (29.2)	16/63 (25.4)
	[22.0–43.4]	(19.2–41.1)	(15.8–37.2)
Gastroenteritis	19/72 (26.4)	10/65 (15.4)	14/63 (22.2)
	[17.2–37.5]	[8.1–25.7]	[13.2–33.7]
Fluid administered during the 30-min period, median (IQR), mL	180 (125–250)	200 (125–300)	200 (125–250)
Initial VAS score, median (IQR), mm	52 (35–75)	50 (36.5–63.5)	52 (38–75)
Number of vomiting episodes preceding 30 min, median (IQR)	0 (0–1)	1 (0–2)	1 (0–2)

Table 2. Presumed underlying conditions.*

Diagnostic Group	Frequency, No. (%)
Opioid induced	58 (29.0)
Gastroenteritis	43 (21.5)
Other infective illness	15 (7.5)
Renal colic	11 (5.5)
Acute musculoskeletal pain/injury	10 (5.0)
Ethanol related	9 (4.5)
Appendicitis	8 (4.0)
Headache	7 (3.5)
Other	39 (19.5)

*Recorded for 200 of 258 patients. Reported where frequency greater than 4.

study patients received intravenous fluids before study enrollment, no data were collected on other treatments, such as opioids, steroids, or sedative agents, which may have either influenced severity ratings directly or affected secondary outcomes such as satisfaction with treatment.

Measurement bias was minimized because of the patients' self-reporting of outcomes, and use of the VAS as a measure in this setting has been validated.[8,9] Timing the second measurement at about 30 minutes is consistent with previous literature, and delaying additional treatments beyond that period was not thought to be clinically supportable. The individual drug doses of 20 mg for metoclopramide and 4 mg for ondansetron could be debated. Other studies have used 10 mg of metoclopramide or 8 mg of ondansetron,[4-7] but evidence for superiority of either regimen or for sequential dosing during a period for ED nausea and vomiting is lacking.

The secondary outcomes of satisfaction with antiemetic treatment, need for rescue medication, and number of vomiting episodes were all problematic. Perceived satisfaction may have been influenced by receipt of other ancillary treatments, and what constitutes satisfaction may be quite variable. For example, although 72%, 78%, and 64% of patients in the ondansetron, metoclopramide, and placebo groups, respectively, reported

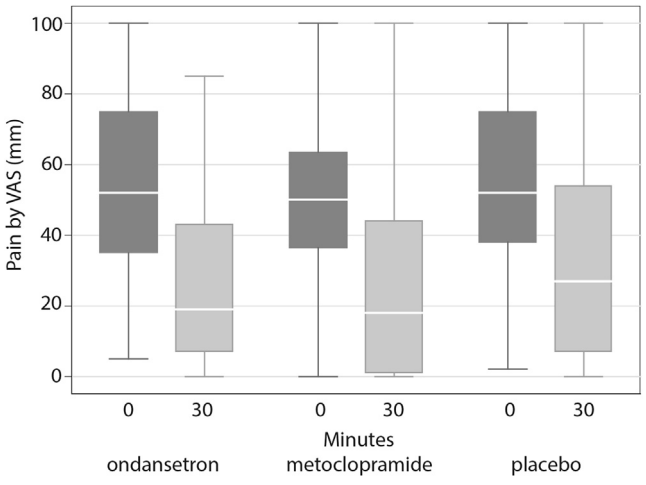

Figure 2. Box and whisker plot of enrollment (VAS1) and 30-minute (VAS2) severity ratings for each treatment group.

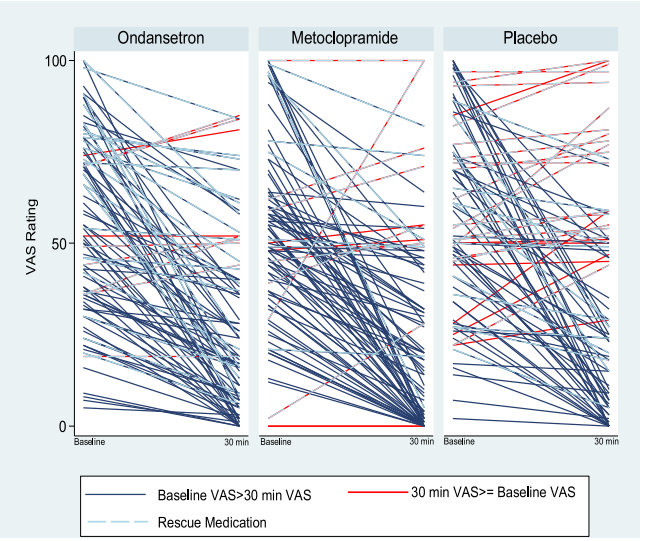

Figure 3. Change in rating from baseline to 30 minutes for all patients in each treatment group. Patients with increased severity ratings and who received rescue antiemetic are highlighted.

symptom improvement on an adjectival scale, only 54%, 62%, and 60% claimed to be satisfied, so it is difficult to interpret this finding in isolation. Self-reported number of vomiting episodes may also be complicated by differing interpretations of the spectrum between expulsion of stomach contents, retching with reflux, and retching with no regurgitation. It happened that reported numbers of vomiting episodes were so small that analysis of this outcome measure was uninformative. Findings for delivery of rescue medication appeared to be inconsistent with the results for symptom severity reduction and patient satisfaction, particularly in the metoclopramide group. The lack of standardization about rescue medication and lack of recording reasons for its use or nonuse limited the value of this secondary outcome.

The choice of change in symptom severity 30 minutes after a single dose of medication as the best primary outcome measure

Table 3. Comparison of secondary outcome measures between treatment groups.*

Outcome	Ondansetron (n=87)	Metoclopramide (n=88)	Placebo (n=83)
Reduction in numeric scale rating, median (IQR)	2 (1–3)	2 (1–4)	1 (0–4)
Symptoms improved ("a lot" or "a little"), No. (%) [95% CI]	62/86 (72.1) [61.9–80.8]	69/88 (78.1) [68.9–86.1]	52/81 (64.2) [53.3–74.1]
Reduction in number of vomiting episodes, median (IQR)	0 (0–1)	0 (0–2)	0 (0–1)
Satisfied, No. (%) [95% CI]	46/85 (54.1) [43.5–64.5]	53/86 (61.6) [51.0–71.4]	47/79 (59.5) [48.4–69.9]
Rescue medication, No. (%) [95% CI]	29/84 (34.5) [25.0–45.1]	15/84 (17.9) [10.8–27.2]	29/80 (36.3) [26.3–47.2]

*Recording of some measures was incomplete, so individual sample sizes are shown.

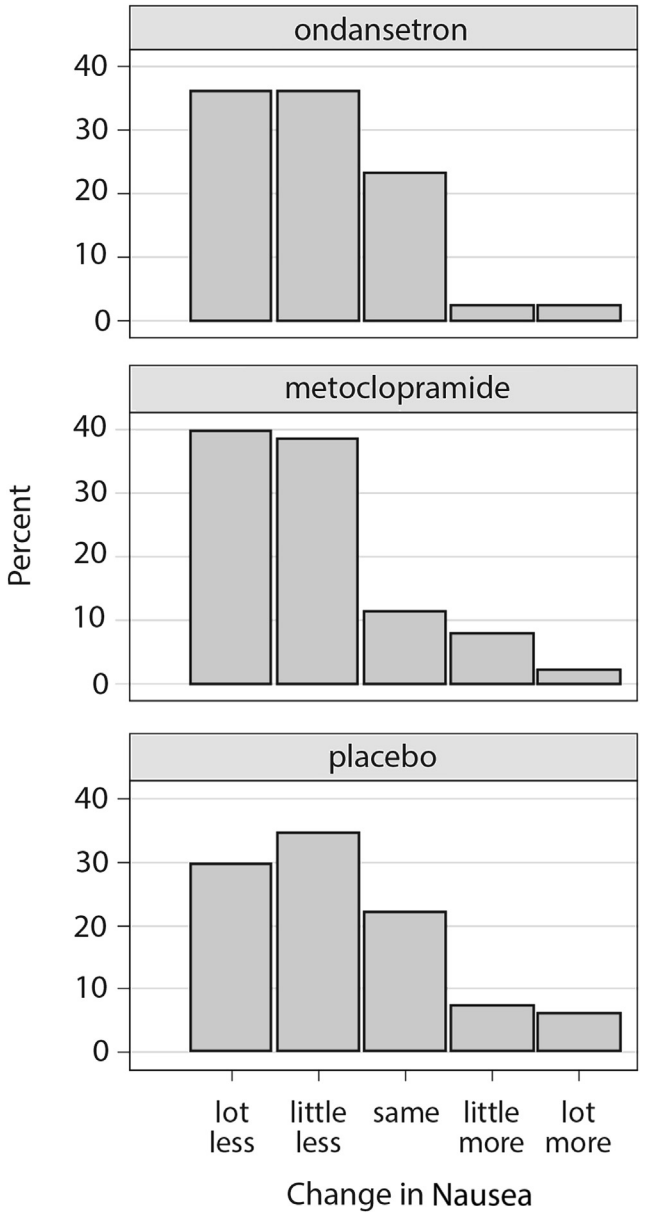

Figure 4. Distribution of change in severity descriptions from enrollment to 30 minutes for each treatment group. 1="a lot less," 2="a little less," 3="the same," 4="a little more," and 5="a lot more."

could also be debated. Although all previous ED studies have used this primary outcome, it could be argued that while this is important within the ED episode of care, patients may consider other outcomes such as need for hospital admission, total symptom duration and return to work to be more important than the rapidity of their initial response.

DISCUSSION

This study found that in a convenience sample of adult ED patients with nausea and vomiting from a variety of causes, similar VAS score reductions of 27, 28, and 23 mm were reported at 30 minutes by patients who had received 4 mg intravenous ondansetron, 20 mg intravenous metoclopramide, or saline solution placebo, respectively. These results are consistent with the 2 ED nausea and vomiting randomized placebo-controlled trials to date, by Braude et al[4] and Barrett et al,[5] the latter being published after commencement of this study. Braude et al,[4] with about 25 patients per group, found similar mean VAS score reductions of 40 mm (SD 24), 41 mm (SD 24), and 39 mm (SD 21) for 20 mg intravenous metoclopramide, 10 mg intravenous prochlorperazine, and saline solution placebo, respectively.[4] Barrett et al,[5] with about 40 patients per group, reported similar median VAS score reductions of 40 mm (IQR 23 to 63 mm), 32 mm (IQR 20 to 47 mm), 35 mm (IQR 22 to 59 mm), and 37 mm (IQR 23 to 56 mm) for 4 mg intravenous ondansetron, 10 mg intravenous metoclopramide, 12.5 mg intravenous promethazine, and saline solution placebo, respectively. The sole exception to the pattern was the finding by Braude et al[4] that the mean VAS score reduction of 55 mm (SD 18) for 1.25 mg intravenous droperidol was statistically significantly greater than that demonstrated in the metoclopramide, prochlorperazine, and placebo groups.[4] However, the clinical significance of this difference is uncertain.

An inconsistency between the findings of this study and those of Braude et al[4] and Barrett et al[5] is the lesser reduction in VAS ratings detected. Seven different treatment arms in the former studies yielded mean VAS score reductions between 35 and 41 mm in comparison with the 23 to 28 mm detected in the present study. Of the 2 nonplacebo-controlled ED nausea and vomiting studies, one reported mean VAS score reductions at 30 minutes for ondansetron and promethazine of 34 and 36 mm, respectively,[6] whereas the other reported reductions of 25 and 26 mm for tropisetron and metoclopramide, respectively.[7] This variability is most likely due to minor differences in study methods. For example, the enrollment VAS score and amount of intravenous fluid administered by Braude et al[4] were approximately 70 mm and 800 mL, respectively; by Barrett et al,[5] approximately 65 mm and 500 mL, respectively.[4,5] This is in comparison with the enrollment VAS score of about 50 mm and the delivery of 250 mL of intravenous fluid in this study. Differences in the wording of the VAS score endpoints between studies may also lead to differences in interpretation and ratings by patients. Whatever the reason, the somewhat less-than-expected reductions in this study led to the possibility of type 2 error in that the lower limit of the 95% CI of 16 mm for the placebo arm did fall below our defined minimum clinically significant difference level of 20 mm, in comparison with the 22 mm lower limits for both drug arms. It may also be the case that one minimum clinically significant difference level may not be strictly applicable to all ED nausea and vomiting study populations.[8,9]

Taken together, however, this small but increasing body of evidence does suggest that antiemetic drugs do not significantly contribute to early ED nausea and vomiting management, beyond other measures for the primary condition and provision

of intravenous fluids. This seems at odds with the oncology[2] and postoperative nausea and vomiting[3] research, which supports the use of antiemetic drugs, but there may be several reasons for this. In such research, patients with no nausea concurrently receive an antiemetic drug and an emetogenic stimulus (anesthetic drugs, chemotherapy, radiotherapy), with the study outcome being severity of the ensuing symptoms during various lengths of time.[2,3] In the ED-based studies, the symptoms are already present and the outcome measure is early reduction in severity after administration of a single dose of an antiemetic drug.[4-7] Although nausea and vomiting are largely mediated through the same pathways,[11,12] it may be that these different clinical settings are not comparable and that ED nausea and vomiting caused by different underlying causes may not be comparable either.

In summary, this study found that although 20 mg intravenous metoclopramide and 4 mg intravenous ondansetron resulted in slightly greater VAS score reductions than saline solution placebo, differences did not reach significance. Comparable majorities in each group also reported symptom improvement and satisfaction with treatment. This supports the findings of the other placebo- and nonplacebo-controlled studies, which also suggest that all antiemetic drugs, with the possible exception of droperidol, are similar.[4-7] Reported adverse events in this study were uncommon, and those associated with most antiemetic drugs are generally considered to be fairly mild and self-limited, but some such as severe akathisia and oculogyric crisis can be distressing.[13] This adds weight to a recommendation that drug use not be routine and that condition-specific treatments, where possible, and other supportive measures, such as provision of intravenous fluids, be undertaken in the first instance. Research investigating effectiveness of different amounts of intravenous fluid and drug use for specific conditions appears warranted. It may also be that the effect of either a combination of drugs, as commonly occurs in the oncology setting, or sequential drug administration during a longer period is different from that of a single drug dose, but evidence of this is yet to be demonstrated. Exploration of different treatment regimens in relation to other clinically significant outcomes would also be worthwhile.

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Author contributions: DE-W and RM conceived the study. All authors designed the trial, jointly drafted the article, and contributed substantially to its revision. DE-W, MJM, and GB obtained research funding and ethics approval. DE-W, RM, and MJM supervised the conduct of the trial and data collection, undertook recruitment of patients, and managed data, including quality control. MJM recorded data on electronic database. RM provided statistical advice on study design and analyzed the data. RM takes responsibility for the paper as a whole.

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APPENDIX E1.

Summary of primary outcome measures from studies to date on ED patients with undifferentiated nausea and vomiting.

Study	Drug/Dose (Sample Size)	30-Minute Reduction: Mean mm on VAS (Precision Variably Reported)
Braude, 2006[4]	Droperidol 1.25 mg (n=22)	55 (SD 18)
	Metoclopramide 10 mg (n=25)	40 (SD 24)
	Prochlorperazine 10 mg (n=24)	41 (SD 24)
	Saline solution placebo, 10-mL bolus (n=26)	39 (SD 21)
Barrett, 2011[5]	Ondansetron 4 mg (n=42)	40 (IQR 23–63)
	Metoclopramide 10 mg (n=43)	32 (IQR 20–47)
	Promethazine 12.5 mg (n=45)	35 (IQR 22–59)
	Placebo, 2-mL bolus (n=41)	37 (IQR 23–56)
Braude, 2008[6]	Ondansetron 4 mg (n=60)	34 (SD 29)
	Promethazine 25 mg (n=60)	36 (SD 28)
Chae, 2011[7]	Tropisetron 5 mg (n=50)	25 (SD 25)
	Metoclopramide 10 mg (n=50)	26 (SD 20)

10.3 Brief statement of main results.

Of the 258 patients, 87 received ondansetron, 88 metoclopramide and 83 placebo. This was the largest ED-based antiemetic trial to date. All treatments were deemed effective, since the mean VAS change for each group exceeded the MCSD. Between-group differences were not statistically significant, leading to the conclusion that ondansetron and metoclopramide were equivalent to placebo.

10.4 Implications for further ED-based research.

With the initial paper by Braude (2006), and the subsequently published study of Barrett (2011),[35,37] this was now the third ED-based placebo-controlled antiemetic trial. Findings of these three studies are summarized and compared in Table 10-1.

Together, these appear to support that commonly used antiemetic drugs are no more effective than placebo for ED patients with nausea. Interpreting between-study differences, however, remained difficult. For example, the mean VAS change for metoclopramide in this study was -27 mm, with the baseline and post-treatment mean VAS ratings having been 50 mm and 23 mm. Although the mean VAS change for metoclopramide in the Barrett (2011) study is a similar appearing -30 mm.[37,40] it results from a baseline to post-treatment change in mean VAS ratings from 69 mm to 39 mm.[37,40] Nausea measurement research suggests that 'on average', these would equate with changes in severity from 'moderate' to 'mild', and 'severe' to 'moderate' respectively.[69] As has been outlined in Chapter 8 of this thesis, the clinical significance of this type of difference is unclear. This further reinforces the importance of finding ways to present study results in an easily understandable format which relates directly to the primary treatment objective.

As it happened, this RCT did create some interest in the literature. It was published in Annals of Emergency Medicine, the highest impact emergency medicine journal, and was one of the top dozen papers accessed on-line that year. Soon after its publication, the findings were discussed in an issue of the American College of Physicians Journal Club, which is published in Annals of Internal Medicine. The review by Pitts (2014) pointed out that despite the demonstration of equivalence, real differences might still exist. This was based on the secondary outcome of rescue medication favoring metoclopramide over placebo. Since study rigor appeared satisfactory, however, the lack of difference in the primary outcome was said to be difficult to explain.[77] Interestingly, the choice and nature of the primary outcome measure itself was not identified as an issue.

Table 10-1. Summary of VAS changes from the three ED-based, placebo controlled trials.[35,37,40]

Study	Metoclopramide (10mg a & b, 20mg c)	Ondansetron (4 mg)	Placebo	Other
Braude (2006): mean VAS change (+/- SD)	-40 mm (+/- 24) [Baseline 65 mm]	n/a	-39 mm (+/- 21) [Baseline 71 mm]	Droperidol (1.25mg) -55 mm (+/- 18) [Baseline 70 mm] Prochlorperazine (10mg) -41 mm (+/- 24) [Baseline 72 mm]
Barrett: mean VAS change (95% CI)	-30 mm (-44 to -20) [Baseline 69 mm]	-22 mm (-43 to -8) [Baseline 64 mm]	-16 mm (-45 to -2) [Baseline 64 mm]	Promethazine (10mg) -29 mm (-47 to -10) [Baseline 68 mm]
Current RCT: mean VAS change (95% CI)*	-27 mm (-33 to -22) [Baseline 50 mm]	-28 mm (-34 to -22) [Baseline 52 mm]	-23 mm (-30 to -16) [Baseline 50 mm]	n/a

SD, Standard Deviation; CI, Confidence Interval;
*Note: in contrast to the median values of the published paper, mean VAS change is shown here in order to aid direct comparisons.

CHAPTER 11. Measurement and monitoring of nausea severity in emergency department patients: A comparison of scales and exploration of treatment efficacy outcome measures.

11.1 Introduction.

From previous nausea measurement studies in CINV, PONV and in the ED, the correlation between the VAS and the ordinal adjectival scale of severity had been established.[45,53,69] The two ED measurement studies had confirmed the relationship between the VAS and the ordinal description of change scale, and provided information on the MCSD.[66,69] It had been demonstrated that the MCSD differed significantly depending on whether baseline nausea was described as being 'mild', 'moderate' or 'severe'. [69]

The inclusion of all known measurement scales within the one study, allowed a more extensive exploration of the relationships between the different scales, and between scale change and described improvement.

11.2 Specific aims.

The study included severity ratings on the adjectival scale, the VAS, the NRS and number of vomiting episodes. Change in severity was calculated from each scale, and referenced against the ordinal description of change scale. Use of rescue medication and patient satisfaction with treatment were also included.

In particular, the study would be the first to explore whether or not some amount of VAS change could be used to identify patients with symptom improvement.

11.3 Citation and paper.

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PAPER FOLLOWS

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ORIGINAL CONTRIBUTION

Measurement and Monitoring of Nausea Severity in Emergency Department Patients: A Comparison of Scales and Exploration of Treatment Efficacy Outcome Measures

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Abstract

Objectives: The objective was to investigate the correlation of the visual analog scale (VAS) and numeric rating scale (NRS) for nausea severity measurement and to explore options for improved reporting of antiemetic efficacy trial results.

Methods: This was a multicenter observational study of adult emergency department (ED) patients with nausea. Participants rated severity at enrollment and 30 minutes posttreatment using an adjectival scale, a VAS, and an NRS. Posttreatment, patients described symptom change and rated satisfaction.

Results: Ratings were performed by 258 patients. Both the VAS (0 to 100 mm) and the NRS (0 to 10) discriminated between adjectival severity categories. Median ratings with interquartile ranges (IQRs) were "severe" VAS 90.5 (IQR = 79 to 97) and NRS 9 (IQR = 8 to 9), "moderate" VAS 59 (IQR = 48 to 71) and NRS 6 (IQR = 5 to 7), "mild" VAS 34 (IQR = 25 to 49) and NRS 4 (IQR = 3 to 5), and "none" VAS 5 (IQR = 0 to 9) and NRS 0 (IQR = 0 to 1). Correlation between the VAS and NRS was high (0.83, Spearman). For the VAS, median mm (IQR) reductions for posttreatment change were "a lot less" –42 (IQR = –26 to –58.5), "a little less" –20.5 (IQR = –11 to –33), "the same" –2 (IQR = –8 to 3.5), "a little more" 14 (IQR = –2 to 22), and "a lot more" 17 (IQR = 6 to 23) and for satisfaction were "very satisfied" –45 (IQR = –27 to 63), "satisfied" –27 (IQR = –13 to 46), "unsure" –15 (IQR = –3 to –24), "dissatisfied" 4.5 (IQR = –5.5 to 13.5), and "very dissatisfied" 8.5 (IQR = 0 to 23). A VAS cutoff of ≥–5 mm detected symptom improvement with sensitivity 91.6% (95% CI = 86.7% to 95.1%), specificity 72.1% (95% CI = 59.9% to 82.3%), and positive predictive value 90.2% (95% CI = 85.1% to 94.0%).

Conclusions: The VAS and NRS correlate highly. A VAS cutoff level of ≥–5 mm was a good predictor of symptom improvement, suggesting that its inclusion as an outcome measure would enhance reporting in antiemetic efficacy trials.

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Nausea and vomiting is a common and frequently treated symptom in emergency department (ED) patients.[1] Rating symptom severity and monitoring change with time is important for the assessment of antiemetic treatment efficacy. Tools such as the visual analog scale (VAS), numeric rating scale

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(NRS), and adjectival scales are available for the rating and monitoring of subjective symptoms, and their ease of use for ED patients has been shown.[2]

Two studies, from 2005 and 2009, report that for nausea in ED patients, repeat VAS ratings reliably reflect change in severity, and figures for the "minimum clinically significant difference" (MCSD), the mean amount of VAS change that corresponds to symptoms being "a little less," have been proposed as proxy measures for antiemetic treatment efficacy.[3,4] This followed the more long-standing approach taken in research of pain management in ED patients, where use of an MCSD figure was first proposed for use in analgesia efficacy studies in 1996.[5]

Although the four most recent ED-based antiemetic studies all used the VAS to measure change in symptom severity, primary outcome definitions and use of the MCSD varied.[6–9] This suggests that the best way of interpreting and reporting VAS change to reflect treatment efficacy remains unclear. It has also been demonstrated in the more extensive ED-based pain research that the VAS and NRS correlate highly with each other,[10,11] and the use of patient satisfaction as a primary outcome has been explored.[12–15] The NRS was used in one older ED-based antiemetic efficacy trial,[16] but its correlation with the VAS has not been demonstrated for nausea, and use of patient satisfaction as a potential primary outcome measure has not yet been considered in antiemetic research.

To clarify the relationship between ratings scales for nausea, and to explore ways in which primary outcome measures might best reflect treatment efficacy, the objectives of this study were to investigate correlation between the VAS and NRS for rating nausea severity, to determine VAS and NRS changes for different descriptions of symptom change, to investigate patient satisfaction as an efficacy outcome measure, and to explore ways in which defined levels of VAS change, other than the MCSD, might also reflect treatment efficacy. The purpose was to inform on the reliability of the different scales for nausea monitoring and to suggest ways in which outcome reporting from ED-based antiemetic efficacy studies might be improved.

METHODS

Study Design

This was a multicenter observational study. Study conduct, covering both the concurrent randomized controlled trial (RCT) from which we drew the patients for this study, and this separate examination of the rating scales, was approved by the Monash Health Human Research and Ethics Committee. Written consent was obtained in all cases.

Study Setting and Population

The study was conducted with a convenience sample of ED patients with nausea in Melbourne, Australia. The study took place in the ED at Monash Clayton (tertiary referral, annual ED census 42,000 patients) and Monash Dandenong (urban district, annual ED census 49,000 patients) between September 2009 and April 2010.

The participants in this study were those recruited to a concurrent RCT comparing the efficacy of ondansetron and metoclopramide with placebo.[6] Eligible participants were patients 18 years or older who presented to the ED with nausea (with or without vomiting) for which intravenous (IV) antiemetic medication was recommended. Exclusion criteria for this study were required to be those of the concurrent RCT, which included hemodynamic instability; pregnancy or lactation; Parkinson's disease or restless leg syndrome; regular dopamine antagonist medication; nausea associated with vertigo, chemotherapy, or radiotherapy; cognitive impairment; and known allergy to metoclopramide or ondansetron.

Study Protocol

Recruitment to the RCT was performed at any time by the attending emergency physician (EP). Participants rated nausea severity on the three different measurement scales (VAS, NRS, and adjectival) at enrollment and 30 minutes after treatment as per the concurrent RCT (ondansetron 4 mg IV, metoclopramide 20 mg IV, or 0.9% saline 10 ml IV).[6] Each participant received an infusion of 0.9% saline at 250 mL/hr. Other treatments for the patient's primary condition were at the discretion of the attending EP, who recorded baseline patient information and ensured that all ratings were obtained at the appropriate times. The three scales were presented in the same order on each of two pages for the baseline rating and the 30-minute posttreatment rating. The second page also included the descriptions of change in severity from baseline and the options for rating satisfaction with antiemetic treatment. At the time of the second rating, patients could look at their initial ratings if they wished. All ratings were being used as outcome measures and reported per treatment group for the therapeutic RCT[6] and were not separately required for the purposes of this study.

The rating scales used were: 1) VAS—marking a standard 100-mm line labeled "no nausea" at the left and "unbearable nausea" at the right, with ratings recorded as millimeters from the left and change to the left or right being recorded as negative or positive, respectively; 2) NRS—circling a number between "0" (labeled "no nausea") and "10" (labeled "unbearable nausea"), with unit change to left or right recorded as negative or positive, respectively; and 3) adjectival scale—circling one of "none," "mild," "moderate," or "severe." Thirty minutes after treatment, patients rated nausea severity using the same three scales, nominated a description of change by circling one of "a lot less," "a little less," "the same," "a little more," or "a lot more" and rated satisfaction with their antiemetic treatment by circling one of "very satisfied," "satisfied," "unsure," "dissatisfied," or "very dissatisfied." Patient characteristics and all study measurements were recorded in to a secure database (Microsoft Access 2007) by one investigator (MM).

Data Analysis

Baseline patient characteristics of age, sex, symptoms, and the initial VAS, NRS, and adjectival ratings are reported as median with interquartile range (IQR) and number and percentage, and compared between study

sites using the Mann-Whitney, Fisher's exact, and Kruskal-Wallis tests, as appropriate. Measures of the VAS and NRS for each adjectival rating are reported as median with IQR and examined for correlation using the Spearman rank correlation coefficient. Severity, change in severity, and satisfaction ratings were compared between scales using the Kruskal-Wallis test. Diagnostic performance of VAS cutoff levels for predicting patient improvement are illustrated in standard two-by-two tables, for which the sensitivity, specificity, and positive predictive values (PPVs) for symptom improvement are calculated with 95% confidence intervals (CIs; exact binomial method). Analyses were performed using Stata, Version 12.0. A significance level of 0.05 was chosen for all comparisons, with no adjustment for multiple comparisons.

Sample Size. For this study, the sample size was fixed at the 270 being sought for the concurrent RCT. The only relevant information from the limited previous literature was the VAS changes for each description of change category.[3,4] These were approximately –35 mm (SD ± 25 mm) for symptoms being "a lot less," –22 mm (SD ± 15 mm) for "a little less," –1 mm (SD ± 15 mm) for "the same," 16 mm (SD ± 15 mm) for "a little more," and 30 mm (SD ± 30) for "a lot more," in populations where about 30% of the study population reported each of "a lot less," "a little less," and "the same," with the remaining minority reporting worsening of symptoms. Should these distributions of change categories and amounts of VAS change for each category be replicated, a sample of 270 was sufficient to detect differences between categories at the 0.05 level. To our knowledge, there was no previous literature to inform on sample size for other study analyses.

RESULTS

A total of 744 adult patients received IV antiemetic drugs during the study period, of whom 270 (36.3%) were recruited to the concurrent antiemetic RCT.[6] The 258 (95.6%) patients with complete recording of severity ratings on all three scales were included in this study. Reasons for nonrecruitment and patient flow for the RCT are shown in Data Supplement S1 (available as supporting information in the online version of this paper). Of the 258 participants, 187 (72.5%) were recruited at Monash Clayton and 71 (27.5%) at Monash Dandenong. There were no significant differences in patient characteristics between sites (Table 1). Clinical reason for nausea and/or vomiting was recorded for 200 (77.5%) patients. Seven diagnostic groups accounted for 161 (80.5%) of these: opioid-induced (n = 58, 29.0%), gastroenteritis (n = 43, 21.5%), other infection (n = 15, 7.5%), renal colic (n = 11, 5.5%), "pain" (n = 10, 5.0%), alcohol-related (n = 9, 4.5%), appendicitis (n = 8, 4.0%), and headache (n = 7, 3.5%). Thirty-three different infrequent diagnoses were recorded for the remaining 39 participants.

The relationship between adjectival descriptions of severity, the VAS, and the NRS was examined using the baseline ratings provided by the 258 patients. For the 42 "severe" nausea ratings, the median VAS and NRS measures were 90.5 mm (IQR = 79 to 97 mm) and 9 (IQR = 8 to 9), respectively; for the 116 "moderate" ratings, VAS was 59 mm (IQR = 48 to 71 mm) and NRS was 6 (IQR = 5 to 7); for the 93 "mild" ratings, VAS was 34 mm (IQR = 25 to 49 mm) and NRS was 4 (IQR = 3 to 5); and for the 7 "none" ratings, VAS was 5 mm (IQR = 0 to 9 mm) and NRS was 0 (IQR = 0 to 1). Differences between each severity category were statistically significant for both the VAS and the NRS (each $p = 0.0001$, Kruskal-Wallis; Figure 1). The VAS ranges for each NRS response are illustrated in Figure 2. The Spearman rank correlation coefficient between the VAS and the NRS was 0.83 ($p < 0.0001$).

Posttreatment change in VAS and NRS ratings. Baseline and posttreatment median severity ratings on the VAS were 51.5 mm (IQR = 36 to 73 mm) and 20.5 mm (IQR = 4 to 49 mm), and on the NRS were 5 (IQR = 4 to 7) and 3 (IQR = 1 to 5), respectively. Median changes in VAS and NRS ratings for the total population were –22 mm

Table 1
Baseline Patient Characteristics for Each Study Site

Characteristic	Total Sample	Monash Clayton	Monash Dandenong	p-value
Age (yr)	42 (27–62)	42.5 (27–63)	42 (28–55)	0.31*
Female	169 (65.5) [59.5–71.1]	121 (64.7) [57.7–71.3]	48 (67.6) [56.1–77.7]	0.77†
Nausea without vomiting	119/253 (47.0) [40.9–53.2]	87/183 (47.5) [40.4–54.8]	32/70 (45.7) [34.3–57.4]	0.89†
Initial VAS rating	51.5 (36–73)	51 (37–73)	52 (32–71)	0.67*
Initial NRS rating	5 (4–7)	5 (4–7)	5 (4–7)	0.98*
Initial adjectival rating				
None	7/258 (2.7) [1.1–5.5]	4/187 (2.1) [0.6–5.4]	3/71 (4.2) [1.1–11.1]	0.94‡
Mild	93/258 (36.0) [30.2–42.2]	67/187 (35.8) [29.0–43.2]	26/71 (36.6) [26.1–48.3]	
Moderate	116/258 (45.0) [38.8–51.3]	88/187 (47.1) [39.7–54.5]	28/71 (39.4) [28.6–51.1]	
Severe	42/258 (16.3) [12.0–21.4]	28/187 (15.0) [10.2–20.9]	14/71 (19.7) [11.7–30.2]	

Data are reported as median (IQR) or n (%) [95% CI].
Note: Total sample = 258; Monash Clayton, n = 187; Monash Dandenong, n = 71, unless otherwise specified.
IQR = interquartile range.
*Mann-Whitney
†Fisher's exact.
‡Kruskal-Wallis.

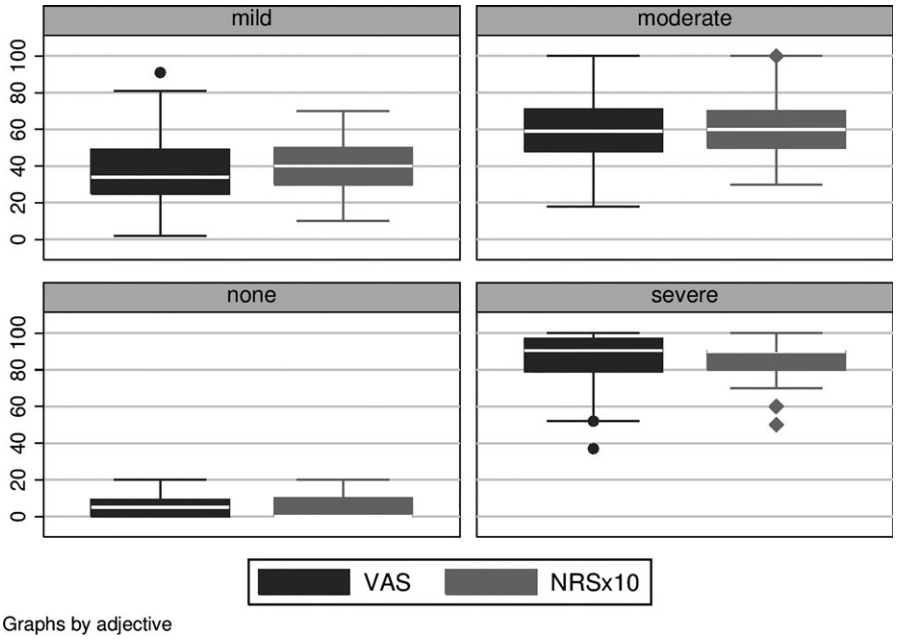

Figure 1. Box plot of VAS and numeric rating scale ratings for each severity descriptor. Note: VAS and NRS baseline ratings, NRS values × 10 for ease of visualization. NRS = numeric rating scale; VAS = visual analog scale.

(IQR = –4 to –44 mm) and –2 (IQR = –1 to –4), respectively. Of the 258 patients, 87 (33.7%) received ondansetron, 88 (34.1%) metoclopramide, and 83 (32.2%) saline placebo. In brief, the main result of the RCT, published elsewhere in detail, was of no significant difference in median VAS change or patient satisfaction between groups.[6]

Relationship between description of change and patient satisfaction. For the 258 participants, posttreatment change was described as being "a lot less" by 96 (37.2%), "a little less" by 94 (36.4%), "the same" by 48 (18.6%), "a little more" by 15 (5.8%), and "a lot more" by five (1.9%) patients. Of the 258, a total of 250 (96.9%) recorded satisfaction, this being "very satisfied" by 49 (19.6%), "satisfied" 97 (38.8%), "unsure" by 66 (26.4%), "dissatisfied" by 32 (12.8%), and "very dissatisfied" by six (2.4%) patients. The median VAS and NRS ratings for each description of change and satisfaction category are shown in Table 2. Differences in ratings between categories, for both change in severity and satisfaction, were statistically significant for both the VAS and the NRS (all $p < 0.0001$, Kruskal-Wallis). VAS distributions per category for change and satisfaction are illustrated in Figures 3 and 4. For the 250 participants who recorded both change in severity and satisfaction, satisfaction ratings for each severity change category are shown in Table 3 and illustrated in Figure 5.

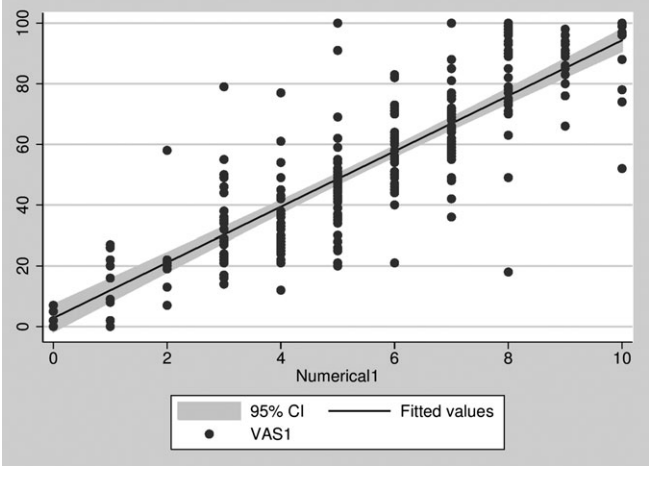

Figure 2. Scatterplot of VAS ratings for each NRS rating, showing median visual analog scale values. VAS1 and numerical1 = baseline VAS and NRS ratings. NRS = numeric rating scale; VAS = visual analog scale.

Influence of initial severity on VAS change. For the whole sample, when symptoms were "a little less," the median values for the VAS and NRS were –20.5 mm (IQR = –33 to –11 mm) and –2 (IQR = –3 to –1), respectively. Median changes in VAS rating for each initial severity subgroup are shown in Table 4. Within each initial severity subgroup, the VAS changes for each description of change category were significantly different from each other ($p < 0.001$, Kruskal-Wallis). When description of change was either "a lot less" or "a little less," the VAS changes were significantly different between initial severity subgroups ($p = 0.0001$ and $p = 0.0004$, respectively, Kruskal-Wallis). When severity was "the same," "a little more," or "a lot more," the differences in VAS change between initial severity subgroups were not significant ($p = 0.08$, $p = 0.28$, and $p = 0.17$, respectively by Kruskal-Wallis).

Performance of defined VAS cutoff levels for predicting symptom improvement. Of the 258 patients, 190 (73.6%, 95% CI = 67.8% to 78.9%) reported symptom improvement ("a lot less" or "a little less"). For the initially "severe," "moderate," and "mild" subgroups,

Table 2
Changes in Visual Analog Scale and Numerical Rating Scale for Each Description of Change and Satisfaction Category

Rating Instrument	Description of Change				
	A lot less (n = 96)	A little less (n = 94)	The same (n = 48)	A Little more (n = 15)	A Lot More (n = 5)
VAS	–42 (–26 to –58.5)	–20.5 (–11 to –33)	–2 (–8 to 3.5)	14 (–2 to 22)	17 (6 to 23)
NRS	–4 (–3 to –5)	–2 (–1 to –3)	0 (–1 to 0)	1 (0 to 2)	3 (3 to 3)
	Patient Satisfaction				
	Very Satisfied (n = 49)	Satisfied (n = 97)	Unsure (n = 66)	Dissatisfied (n = 32)	Very Dissatisfied (n = 6)
VAS	–45 (–27 to –63)	–27 (–13 to –46)	–15 (–3 to –24)	4.5 (–5.5 to 13.5)	8.5 (0 to 23)
NRS	–5 (–3 to –6)	–2 (–1 to –4)	–1.5 (–2 to 0)	0 (0 to 1)	1.5 (0 to 3)

All data reported as median (interquartile range).
NRS = numeric rating scale.
VAS is measured in mm.
VAS = visual analog scale.

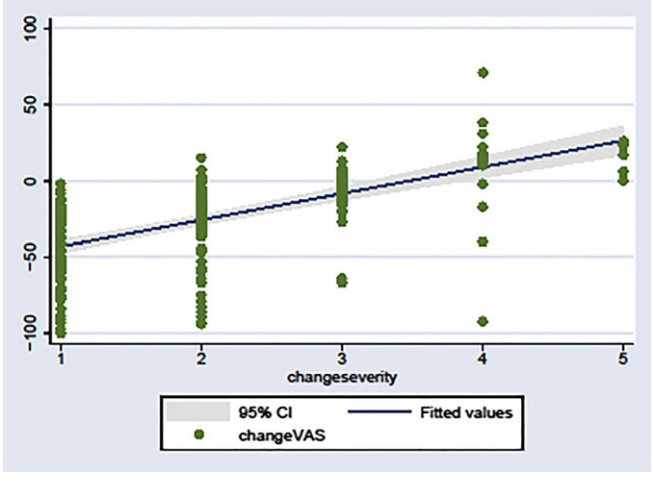

Figure 3. Scatter plot of VAS responses for each description of change category. 1 = "a lot less," 2 = "a little less," 3 = "the same," 4 = "a little worse," 5 = "a lot worse." VAS = visual analog scale.

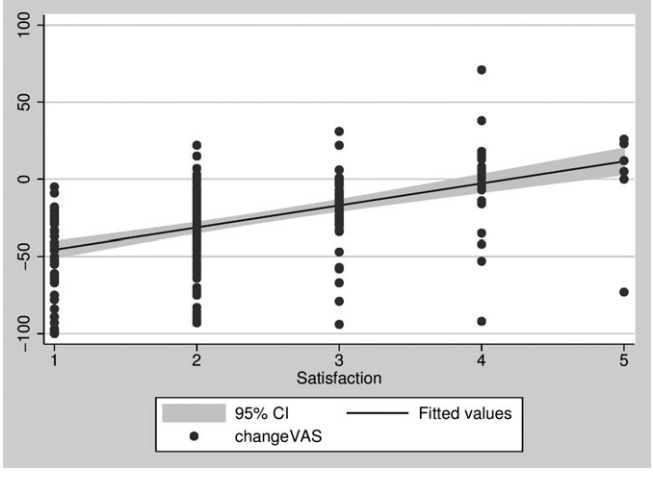

Figure 4. Scatter plot of VAS responses for each satisfaction category. 1 = "very satisfied," 2 = "satisfied," 3 = "unsure," 4 = "dissatisfied," 5 = "very dissatisfied." VAS = visual analog scale.

symptom improvement was reported by 31 of 42 (73.8%, 95% CI = 58.0% to 86.1%), 89 of 116 (76.7%, 95% CI = 68.0% to 84.1%), and 67 of 93 (72.0%, 95% CI = 61.8% to 80.9%), respectively. The diagnostic performance of the VAS cutoff levels of ≥–5, ≥–10, and ≥–20 mm for predicting symptom improvement are shown in Table 5, along with that of the ≥–5 mm cutoff for each initial severity subgroup. Sensitivity, specificity, and PPVs are shown. For the ≥–5 mm cutoff level, the sensitivity and PPV were not significantly different between the initial severity subgroups.

DISCUSSION

This study found that for a sample of adult ED patients with nausea and/or vomiting for a variety of reasons, the VAS and NRS both discriminate between adjectival descriptors of severity and that the VAS and NRS correlate highly with each other (Spearman rank correlation coefficient = 0.83). When people described their nausea as "severe," VAS and NRS ratings were about 90 mm and 9, respectively; for "moderate," they were about VAS 59 mm and NRS 6; and for "mild" nausea, they were about VAS 34 mm and NRS 4. These findings with regard to the VAS are consistent with those from previous studies on nausea severity,[3,17] and the strength of the correlation between the VAS and NRS, reported for the first time here for nausea, is consistent with that previously reported in pain research.[10,11] This supports that the VAS and NRS can both be used to reliably rate nausea severity.

For the descriptions of change, we found that the amount of change on both the VAS and the NRS discriminated between categories. For example, when change was described as "a little less," VAS and NRS changes were about –20 mm and –2, respectively; for nausea being "the same," they were about VAS –2 mm and NRS 0. For the VAS, this was consistent with the findings of the two previous ED-based studies on nausea,[3,4] but the similar findings for the NRS had not previously been demonstrated. For this sample, the MCSD, defined as the amount of VAS change reported by those whose symptoms are "a little less," was −20.5 mm. This is generally consistent with the −15 and

Table 3
Levels of Satisfaction for Each Description of Change

Description	Very Satisfied (n = 49)	Satisfied (n = 97)	Unsure (n = 66)	Dissatisfied (n = 32)	Very Dissatisfied (n = 6)
A lot less (n = 90)	43 (47.8) [37.1–58.6]	41 (45.6) [35.0–56.4]	3 (3.3) [0.7–9.4]	2 (2.2) [0.3–7.8]	1 (1.1) [0.03–6.0]
A little less (n = 94)	2 (2.1) [0.3–7.5]	48 (51.1) [40.5–61.5]	41 (43.6) [33.4–54.2]	3 (3.2) [0.7–9.0]	0 (0) [0–3.8]
The same (n = 47)	4 (8.5) [2.4–20.4]	5 (10.6) [3.5–23.1]	20 (42.6) [28.3–57.8]	17 (36.2) [22.7–51.5]	1 (2.1) [0.05–11.3]
A little more (n = 14)	0 (0) [0–23.2]	3 (21.4) [4.7–50.8]	2 (14.3) [1.8–42.8]	8 (57.1) [28.9–82.3]	1 (7.1) [0.2–33.9]
A lot more (n = 5)	0 (0) [0–52.2]	0 (0) [0–52.2]	0 (0) [0–52.2]	2 (40.0) [5.3–85.3]	3 (60.0) [14.7–94.7]

Data are reported as n (%) [95% CI].

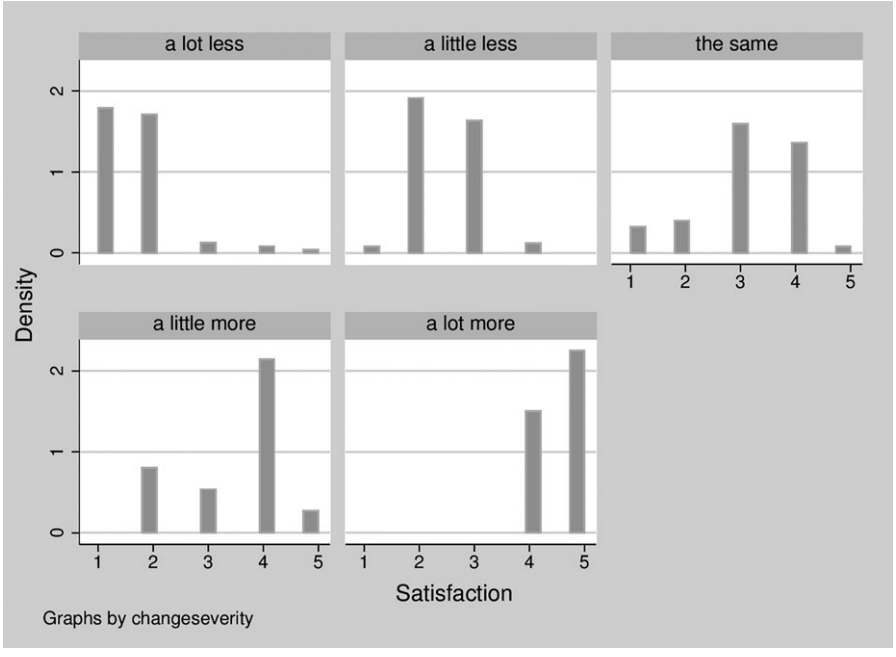

Figure 5. Frequency of satisfaction responses for each description of change. 1 = very satisfied, 2 = satisfied, 3 = unsure, 4 = dissatisfied, 5 = very dissatisfied. Samples sizes for "a lot less," "a little less," "the same," "a little more," and "a lot more" are 90, 94, 47, 14, and 5. respectively

–22 mm previously reported.[3,4] Similar variability in the MCSD between populations has also been found for both the VAS and the NRS in pain research.[10,11,18–21] Reasons for this have not been discussed in the literature, but may relate to variation in initial nausea severity between patients in any given population. Both this study and one previous ED-based study on nausea rating[3] found that the MCSD is quite different between initial severity subgroups. In this population, the MCSD estimates for the initially "severe," "moderate," and "mild" subgroups were –45.5, –20, and –17.5 mm, respectively. Hence, the MCSD for any population must differ, depending on its initial severity mix. This same variability in MCSD estimates has also been reported in pain research,[10,11,18–21] presumably for similar reasons. This may create difficulties in research planning, because a predefined MCSD might not prove to be correct for the recruited population, although the extent to which this might affect result interpretation is unknown.

For patient satisfaction, this study found that the amount of change on both the VAS and the NRS discriminated between satisfaction categories. For example, when people were "satisfied," change in VAS and NRS ratings was –27 mm and –2; when "unsure," they were –15 mm and –1.5. Three of the last four ED-based antiemetic efficacy trials reported patient satisfaction as a secondary outcome,[6–8] and while use of satisfaction as a primary outcome measure has been debated in pain research,[12–15] this has not been explored for nausea. Although the amounts of change in the VAS and NRS ratings were significantly different between satisfaction categories, we found that for each description of change, the corresponding satisfaction ratings were fairly evenly split between two adjacent categories. For example, when severity was "a little less," approximately equal numbers were "satisfied" as were "unsure." This may reflect that a number of different factors, such as other therapeutic measures and general treatment expectations, contribute to satisfaction ratings, while the choice of whether nausea severity is "the same," "a little less," or "a lot less" may be more straightforward. Regardless of the reasons, these findings suggest that

Table 4
Visual Analog Scale Change for Each Description of Change Category, for the Whole Sample and Each Initial Severity Subgroup

Change rating	Whole Sample	Initially "Severe"	Initially "Moderate"	Initially "Mild"
A lot less (n = 96: severe = 15, moderate = 42, mild = 39)	–42 (–58.5 to –26)	–61 (–91 to –47)	–50 (–64 to –34)	–26 (–37 to –19)
A little less (n = 94: severe = 16, moderate = 47, mild = 28, none = 3)	–20.5 (–33 to –11)	–45.5 (–71 to –25.5)	–20 (–26 to –11)	–17.5 (–33.5 to –11)
The same (n = 48: severe = 8, moderate = 20, mild = 17, none = 3)	–2 (–8 to 3.5)	–6 (–15.5 to 0.5)	0 (–2.5 to 5.5)	–3 (–9 to 1)
A little more (n = 15: severe = 1, moderate = 6, mild = 7, none = 1)	14 (–2 to 22)	n/a	15 (12 to 18)	16 (10 to 31)
A lot more (n = 5: severe = 2, moderate = 1, mild = 2)	17 (6 to 23)	n/a	n/a	n/a

Data are reported as median, mm (IQR).
Note: Not reported for the seven patients who recorded initial severity as "none" or for subgroups where $n < 3$ (n/a).

Table 5
Performance of Visual Analog Scale Cutoff Levels for Predicting Symptom Improvement

VAS Reduction	Improved	Not Improved	Total	Performance Measure, n/N (%) [95% CI]*
≥–5 mm	174	19	193	Sensitivity: 174/190 (91.6) [86.7–95.1]
<–5 mm	16	49	65	Specificity: 49/68 (72.1) [59.9–82.3]
Total	190	68	258	PPV: 174/193 (90.2) [85.1–94.0]
≥–10 mm	166	13	179	Sensitivity: 166/190 (87.4) [81.8–91.7]
<–10 mm	24	55	79	Specificity: 55/68 (80.9) [69.5–89.4]
Total	190	68	258	PPV: 166/179 (92.7) [87.9–96.1]
≥–20 mm	133	7	140	Sensitivity: 133/190 (70.0) [62.9–76.4]
<–20 mm	57	61	118	Specificity: 61/68 (89.7) [79.9–95.8]
Total	190	68	258	PPV: 133/140 (95.0) [90.0–98.0]
Initial severity description "severe" (n = 42)				
≥–5 mm	30	6	36	Sensitivity: 30/31 (96.8) [83.3–99.9]
<–5 mm	1	5	6	Specificity: 5/11 (45.5) [16.7–76.6]
Total	31	11	42	PPV: 30/36 (83.3) [67.2–93.6]
Initial severity description "moderate" (n = 116)				
≥–5 mm	81	4	85	Sensitivity: 81/89 (91.0) [83.1–96.0]
<–5 mm	8	23	31	Specificity: 23/27 (85.2) [66.3–95.8]
Total	89	27	116	PPV: 81/85 (95.3) [88.4–98.7]
Initial severity description "mild" (n = 93)				
≥–5 mm	62	7	69	Sensitivity: 62/67 (92.5) [83.4–97.5]
<–5 mm	5	19	24	Specificity: 19/26 (73.1) [52.2–88.4]
Total	67	26	93	PPV: 62/69 (89.9) [80.2–95.8]

Improved = "a lot less" or "a little less;" not improved = "the same", "worse," or "a lot worse."
PPV = positive predictive value; VAS = visual analog scale.
*CI by exact binomial method.

level of satisfaction may be less useful as a primary outcome measure. It also seems reasonable to argue, as was done with the development of the MCSD concept, that the main therapeutic aim is to reduce symptoms by at least "a little," even though only half the patients may be satisfied with this degree of improvement.

The VAS change had been used to define the primary outcome measure in the four most recent ED-based antiemetic efficacy trials.[6–9] This seems reasonable, given its greater sensitivity for the detection of change, in comparison with ordinal scales such as the NRS or the description of change categories. All four studies reported VAS reductions and compared these between groups, but differed in their approach to equating differences with clinical significance. Two studies were superiority trials,[8,9] which stated that superiority would be demonstrated if the VAS reduction for the study drug was at least –12 mm,[9] or –15 mm,[8] greater than that of either an active control or placebo. The inference is that greater VAS reductions equate with increased patient benefit, and while this might seem intuitive, there is no evidence to either support or quantify this view. The other two studies were described as noninferiority trials, with both predefining the MCSD as –20 mm.[6,7] The inferences were that provided VAS reductions all reached this level, no treatment would be inferior to any other, and all would have had clinically significant effects. The issue of MCSD variability between populations has already been discussed, but it is also the case that even if the reported amount of VAS change approximates the nominated MCSD, it is not immediately evident how many patients in each group might have improved. To explore this, we examined the diagnostic performance of a number of VAS cutoff levels for prediction of symptom improvement. While an MCSD-based cutoff of ≥–20 mm did have a high PPV of 95% (133 of 140 patients with this level of change were improved), the sensitivity was poor at 70% (detected only 133 of 190 improved patients). This is not surprising, since by definition, those with VAS reductions beyond the MCSD will comprise half whose symptoms are "a little less," most with "a lot less," and fairly few who are "the same" or worse. Hence, it seems more logical to approach detection of symptom improvement

from the viewpoint that symptoms should no longer be "the same." In the two previous ED-based studies on use of the VAS in nausea,[3,4] the VAS changes when nausea remained "the same" were –0.4 mm (95% CI = –5.6 to 4.8 mm)[4] and –1 mm (IQR = –4 to –1 mm),[3] and in this study it was –2 mm (IQR = –8 to 3.5 mm). This suggests that almost all patients reporting VAS reductions in excess of about –5 mm should have improved symptoms, since the group would comprise almost all reporting symptoms to be "a lot less" or "a little less" and very few who are still "the same" or worse. In this population, the ≥–5 mm cutoff had a PPV of 90% (174 of 193 patients with this level of change were improved) and a sensitivity of 92% (detected 174 of 190 improved patients). Incorporation of this cutoff in defining outcome measures may also have an advantage in study planning. Unlike the MCSD, the VAS change for symptoms being "the same" does not differ significantly between initial severity subgroups, so the ≥–5 mm cutoff should perform equally well, regardless of the severity mix of the population. So use of VAS reduction of ≥–5 mm as a proxy measure for symptom improvement, particularly in superiority studies, would also allow this comparison between treatment groups and enable calculation of the useful number needed to treat figure. We believe that this information, in addition to the VAS change per group and how this relates to the MCSD, would enhance result reporting in antiemetic efficacy trials.

LIMITATIONS

How well the findings from these patients recruited to a therapeutic RCT can be generalized to other ED populations is not known. The RCT participants were only a minority of the ED patients with nausea, and the exclusion criteria eliminated some common clinical groups. Although VAS change and satisfaction were similar between treatment groups in the RCT, it is possible that the study drugs, or other therapies for primary conditions, may have influenced ratings in this study in some way. Potential influence on patient responses by ED staff is likely to have been minimized by the masking associated with the RCT. For this study, rather than a more ideal presentation of the rating scales in different orders on different pages, they were printed in the same order on one page for each time point, to aid smooth conduct of the RCT. This may have led to some "lining up" of responses, which could exaggerate the degree of correlation between scales.

CONCLUSIONS

We found that for this population of ED patients with nausea, the visual analog scale and the numeric rating scale reliably differentiated between initial severity categories, change in severity, and patient satisfaction categories and correlated highly with each other. The spread of satisfaction ratings for each change in severity category appeared to limit the usefulness of patient satisfaction as a primary outcome measure in antiemetic efficacy trials. The cutoff level of visual analog scale reduction of ≥–5 mm performed well as a proxy measure of symptom improvement. We suggest that the current method of reporting antiemetic trials by comparing group change in visual analog scale ratings and equating this with the minimum clinically significant difference, would be enhanced by comparing the percentage of patients per group who exceed a visual analog scale cutoff level of ≥–5 mm, from which the useful number needed to treat could also be calculated per group. Further research to validate the use of visual analog scale cutoffs and to explore other methods of equating the change with clinical effect appears to be warranted

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Consort diagram of patient flow for the concurrent antiemetic RCT.

11.4. Discussion of results.

The relationship between the VAS and the adjectival scale, and the VAS and the ordinal description of change scale was consistent with previous research.[66,69] The high correlation between the VAS and the NRS had previously been demonstrated in pain research,[65] but not for nausea measurement. The exploration of reduction in vomiting confirmed this to be of little use. As with the studies of Patka (2011) and Chae (2011), the proportion of people with nausea who had active vomiting was relatively small, and the low number of vomits when present, combined to limit the usefulness of this as an outcome measure.[38,39]

With regard to the primary treatment objective, this study suggested that measured VAS change could reliably identify patients with symptom improvement. As hypothesized in the introduction to this series of research projects (Figure 8-3), this related to the amount of VAS change beyond which symptoms were no longer 'the same'. The accuracy of the VAS change cut-off tested is not surprising, given that VAS change when symptoms remain 'the same' is known to be tightly concentrated around zero, regardless of initial severity.[66,69]

11.5 Implications for ongoing ED-based research.

The study identified and tested, to a degree, a potential binary outcome measure based on the ability of VAS change to discriminate between improved and non-improved patients. At this time, it was only possible to report the findings within the framework of an original research manuscript. On the assumption that alternate outcome measures were identified, it was planned to discuss the potential importance of these more broadly in a narrative perspective article. The study findings suggested that this was warranted.

Equating treatment effectiveness with symptoms no longer being 'the same', does assume that symptom improvement to any degree is clinically significant. Since symptom improvement may be viewed as beneficial, this seems reasonable. However, this study also found that not all those with symptom improvement were satisfied with treatment. As a consequence, the survey which was planned to explore patient views on clinical significance remained important.

The findings with regard to the apparent accuracy of a VAS change cut-off level were based on the data from a moderate number of patients from one study. The conduct of ROC curve analyses on a larger population, combining similarly collected data from previously published studies, also remained important. This was likely to yield more robust findings with regard to the reliability of VAS change for detection of symptom improvement, and better identify the most accurate VAS change cut-off point.

CHAPTER 12. Do antiemetic drugs benefit adult emergency department patients with nausea? The literature says no, but is it right?

12.1 Rationale and aims.

Based on the RCTs published to 2014, the Cochrane Systematic Review concluded that there was no convincing evidence that antiemetic drugs were superior to placebo for the treatment of adult ED patients with nausea.[75] This series of research projects was undertaken due to the recognition that group mean VAS change may not be providing the best evidence with regard to the primary treatment objective. Symptom improvement is the marker of treatment success, and this was not being directly compared between study groups. Symptom improvement rates cannot be derived from group mean VAS change and the clinical significance of between-group differences in mean VAS change is unknown.

The primary intent of this article was not to suggest, as Pitts (2014)[77] had done, that an alternate outcome measure might uncover real treatment differences which had not previously been detectable. It seemed reasonable, however, to exploit this doubt in order to promote interest in the topic.

12.2 Citation and paper.

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PAPER FOLLOWS

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PERSPECTIVE

Do antiemetic drugs benefit adult emergency department patients with nausea? The literature says no, but is it right?

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Abstract

Nausea is a common problem in ED patients. Antiemetic drugs have been used in the ED for decades, but a recent Cochrane review found no convincing evidence for the benefit of antiemetic drugs over placebo. This was largely based on three placebo-controlled trials, which found mean Visual Analog Scale (VAS) changes for various drugs and placebo, to be similar. However, reliance on mean VAS change as the primary outcome measure has probably been a mistake. It does not give information on the number of improved patients, so these cannot be compared between groups. Alternative primary outcome measures warrant further exploration. Use of a VAS cut-off level indicative of clinically significant symptom improvement would allow comparison of numbers of patients with improved nausea ratings. This is proposed as the best option currently available. Preliminary testing of this outcome measure suggests that the conclusions of past studies may be misleading, and that the question of antiemetic efficacy for ED patients is not yet answered.

Key words: *antiemetics, clinical effectiveness, ED, nausea, Visual Analog Scale.*

Background: 'Proven' lack of benefit for antiemetic drugs, or not?

Nausea is a common problem in ED patients,[1] for which antiemetic drugs have been used for many decades. Surveys have shown that ED patients with nausea expect to be given antiemetic drugs, and that doctors commonly prescribe them.[1,2] For many years, there was no reason to doubt the anecdotal impression that most ED patients' nausea improved after they received drug treatment. The ED community has been surprised, however, by the findings of three ED-based, placebo-controlled antiemetic randomised controlled trials (RCTs).[3,4]

Braude *et al.* reported the superiority of droperidol over metoclopramide, prochlorperazine and placebo in matched patient cohorts.[5] Barrett *et al.* found no difference between ondansetron, metoclopramide, promethazine and placebo.[6] Similarly, Egerton-Warburton *et al.* found no difference between ondansetron, metoclopramide and placebo.[7] A summary of these study results is shown in Table 1. Largely based on these three studies, a 2015 Cochrane review on antiemetic treatment of adult ED patients concluded that there was no convincing evidence for the superiority of any drug over placebo.[8] Although the impact of these negative studies on practice is uncertain, many ED doctors probably remain reluctant to accept that prescribed drugs make no contribution to witnessed beneficial effects.

A number of explanations for the failure to show benefit have been offered. First, drug doses used in ED research may be too low.[2] Second, that the primary outcome measure used in the trials may not be well suited to demonstrate relative efficacy. To quote from the Encyclopedia of Biostatistics, the primary outcome must be a 'measure capable of providing the best evidence directly related to the primary objective'.[9] For ED-based antiemetic drug trials, the primary objective is clinically significant symptom improvement.

Current primary outcome measure: Evolution and issues

Hendey *et al.* addressed the issue of clinical significance, by determining the minimum clinically significant difference (MCSD) for nausea, using the Visual Analog Scale (VAS).[10] The VAS used in that study was a 100 mm line, labelled 'least severe nausea' at the left, and 'most severe nausea' at the right. Patients were asked to mark the line to indicate baseline severity. They marked the line again post-treatment and described their degree of symptom change. Change to the left is reported as negative. The MCSD was defined as the mean VAS change for those reporting symptoms to be 'a little less'. For the derivation study sample, the MCSD was −15 mm.[10] This clarification of clinical

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TABLE 1. *Summary of VAS changes from the ED-based, placebo-controlled randomised controlled trials*

Study	Primary outcome	Metoclopramide (10 mg a & b, 20 mg c)	Ondansetron (4 mg)	Placebo	Other
(a) Braude *et al.*[5]	VAS change: mean (±SD)	–40 mm (±24)	N/A	–39 mm (±21)	Droperidol (1.25 mg) –55 mm (±18)
(b) Barrett *et al.*[6]	VAS change: mean (95% CI)	–30 mm (–44 to –20)	–22 mm (–43 to –8)	–16 mm (–45 to –2)	Promethazine (10 mg) –29 mm (–47 to –10)
(c) Egerton-Warburton *et al.*[7]	VAS change: median (IQR)	–28 mm (–34 to –22)	–27 mm (–33 to –22)	–23 mm (–30 to –16)	N/A

CI, confidence interval; IQR, interquartile range; SD, standard deviation; VAS, Visual Analog Scale.

significance was welcomed, because many researchers favoured use of the VAS in nausea research. It is easy to use, and sensitive for detection of change. Henceforth, ED-based antiemetic research compared mean or median VAS change between groups as the primary outcome, with efficacy being inferred if the previously defined MCSD was exceeded.[5–7]

However, Meek *et al.* reported that the MCSD for nausea varies with initial severity.[11] For 'severe', 'moderate' and 'mild' nausea, the mean VAS change for people whose nausea becomes 'a little less', is –32, –23 and –12 mm, respectively.[11] It makes sense that if symptoms are 'a little less', the VAS mark will not be shifted by the same amount from a pre-treatment rating of 30 mm, as it is from an initial rating of 90 mm. As ED-based placebo-controlled trials to date have excluded people with mild nausea, the MCSD for a mixed population with moderate or severe nausea will not be –15 mm, but some value between –23 and –32 mm. Using the results of Barrett *et al.* as an example, the mean VAS reductions for all groups, of between –16 and –30 mm,[6] suggest that efficacy may have been borderline at best.

Besides the variable MCSD, interpreting differences in mean VAS change between groups is another limitation of the currently published ED antiemetic trials. Braude *et al.* concluded that droperidol was a superior antinausea agent, because the difference in mean VAS change in comparison to the other groups, was statistically significant.[5] However, the clinical significance of differences in mean VAS change beyond the MCSD are not known. Barrett *et al.* attempted to address this, by arbitrarily defining superiority as a difference in mean VAS change between groups of more than –12 mm.[6] There is no literature support for this figure. The persisting lack of certainty about clinical significance highlights the major problem with this primary outcome measure. The mean VAS change does not tell us how many people in each treatment group improved, so this cannot be compared, and a Number Needed to Treat (NNT) cannot be calculated. This is illustrated in Figure 1. Consequently, the continued reliance on mean VAS change has been a methodological mistake.

Possible alternate primary outcome measures

How might patients with clinically significant improvement be best identified? There are a number of options to consider. The most simple would be to ask the patient: Are your symptoms improved? Yes or No. This seems to tell us what we want to know, but it forces a binary response on people who may not be all that sure. An expanded ordinal scale, such as that used in measurement research,[10,11] could also be used. However, responses would still need to be dichotomised (improved or

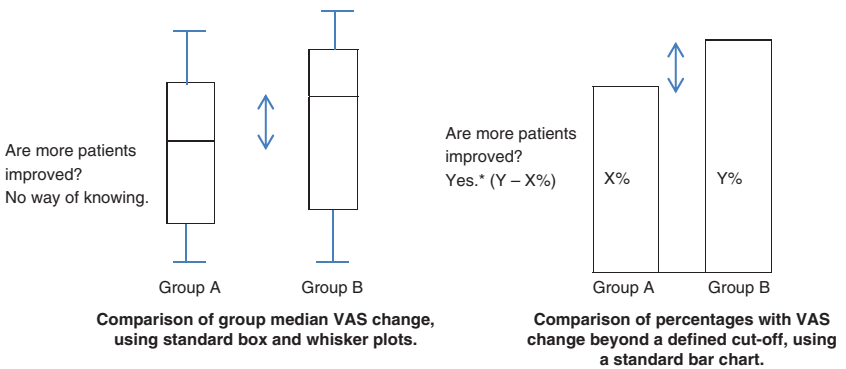

Figure 1. *Interpretation of between-group differences using the 'traditional' versus the proposed outcome measure. *How certain are we that more patients are improved when we compare the percentages of with reductions > –5 mm? More than 90% certain. Why? Because: 90% of patients with a VAS reduction > –5 mm have symptom improvement (positive predictive value) and 92% of patients with symptom improvement have a VAS reduction > –5 mm (sensitivity).*

not) for final analysis. This brings us back to consideration of how the VAS might be used to tell us what we want to know.

One possibility is to explore the percentage reduction in VAS rating, when patients report symptoms to be 'a little less'. This would overcome the problem of the variable MCSD, and allow patients with a VAS change in excess of the defined percentage reduction to be classified as 'improved'. The data of Meek *et al.* suggest that for people in each initial severity subgroup, the pre-treatment VAS rating is reduced by about 25 to 35% when symptoms are reported to be 'a little less'.[11] This method may have potential, but further research is required.

Another possibility has been researched more fully. If nausea symptoms have improved, it can be assumed that they are no longer 'the same'. Early measurement research identified two useful facts about the VAS when patients report symptoms to be 'the same'.[10,11] One is that the VAS change is very tightly concentrated around zero, with 95% confidence intervals in the order of ±5 mm. The second is that the VAS ranges for symptoms being 'the same', do not change with initial severity. This is in contrast to the more variable VAS changes when symptoms are 'a little less', or 'a lot less'. It seems reasonable that if symptoms are unchanged, people would place their post-treatment VAS mark very close to the original, regardless of where that was along the scale. Hence, a VAS cut-off level beyond which patients are no longer 'the same' should identify those who are improved.

Meek *et al.* evaluated this outcome measure in detail.[12] VAS reductions in excess of –5 mm had a 90% positive predictive value for symptom improvement ('a little less' or 'a lot less') and a sensitivity of 92% for the detection of patients with improved symptoms. When the cut-off was increased to –10 mm, which still seems a small amount, the sensitivity fell to 87%. This is due to the fact that a number of people with VAS reductions of –5 to –10 mm, still report symptoms to be 'a little less'. Consequently, applying a VAS cut-off level of –5 mm will enable researchers to identify patients with improved nausea ratings, with more than 90% certainty. This allows the desired information to be elicited by use of the VAS alone, without burdening the patient with a question requiring a Yes/No response, to which they may feel ambivalent. Better methods may come to light with further research, but this seems the best option currently available.

Possible impact of this new outcome measure on antiemetic RCT results?

One might wonder if adopting this outcome measure would significantly impact on study results. Using the results of Egerton-Warburton *et al.* as an example, the median VAS changes for ondansetron and placebo were –27 and –23 mm.[7] The conclusion was that the treatments were similar, and the clinical significance of the difference certainly looks doubtful. Reanalysis of the raw data from this study shows that for the ondansetron and placebo groups, VAS reductions in excess of –5 mm were reported by 83% (95% CI: 73–90) and 63% (95% CI: 51–73) of patients, respectively. Results no longer look similar, and the NNT of 5 looks impressive. While it is difficult to draw firm conclusions from a limited post hoc analysis, the example highlights the difficulty of interpreting differences in mean VAS change between treatment groups. The difference in interpretation of study results using these two outcome measures is illustrated in Figure 1.

In conclusion, the mean VAS change is most likely not the best primary outcome measure for ED-based antiemetic trials. It gives no information on numbers of improved patients. Relative differences are difficult to interpret and findings of equivalence may be misleading. Researchers in the field of ED nausea should adopt a VAS change in excess of –5 mm as the cut-off value indicating symptom improvement. Care must still be taken, of course, to ensure that study design is robust, with statistician input being advised. Mean VAS change can be retained as a secondary outcome measure. Further research may yield superior alternatives, but use of this method may help clarify the vexed issue of antiemetic efficacy in ED patients.

Author contributions

RM and AG jointly conceived the idea for this perspective and collaborated on the manuscript. RM takes overall responsibility for the manuscript.

Competing interests

AG is a section editor for *Emergency Medicine Australasia*.

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12.3 Brief discussion and implications for further ED-based research.

The perceived limitations of the mean VAS change as a primary outcome were discussed; reasons for use of a measured VAS change cut-off level were presented. The possibility of using a percentage VAS change cut-off was mentioned, but this required further exploration. A limited post-hoc analysis of data from the RCT was presented, which did support that real between-group differences might exist. This was used to highlight the importance of the ongoing work on outcome measures, and supported that ED-based research on antiemetic drug efficacy should continue.

CHAPTER 13. Antiemetic treatment in the emergency department: Patient opinions and expectations.

13.1 Rationale and aims

The primary outcome measure of any study needs to provide the best evidence relating to the primary objective. The primary objective of antiemetic treatment in the ED is clinically significant symptom improvement during the ED episode of care. Both the MCSD and the proposed VAS change cut-off levels equate clinical significance with any degree of symptom improvement. Since improvement may be viewed as beneficial, this seems reasonable. However, efficacy may also be defined as demonstration of a desired effect. In the initial RCT (Chapter 10), it was found that the patient satisfaction rates were lower than the symptom improvement rates. Reasons for this could not be explored in that study, but it suggested that not all patients were satisfied with their amount of improvement.

Patient surveys in PONV and CINV all show that nausea and vomiting are feared and distressing symptoms, which patients do not want to experience. [4,7–13] Recent CINV research has used 'symptom control' as a secondary outcome. The implication is that development of mild nausea following chemotherapy may be acceptable,[55,56,58] but patient views on this have not been sought. Only one previous ED-based patient survey on nausea could be located. A survey by Singer (2016) reported that the majority of ED patients with moderate or severe nausea want antiemetic drug treatment, but expectations of treatment were not specifically explored.[41]

This survey of ED patients with nausea aimed to clarify patient expectations of antiemetic treatment. This would give insights in to the amount of symptom improvement which patients view as being clinically significant. It was thought possible that the results from such an investigation could contribute to the choice of outcome measures for the planned follow-up RCT.

13.2 Citation and paper.

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ORIGINAL RESEARCH

Antiemetic treatment in the emergency department: Patient opinions and expectations

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Abstract

Objective: To determine patient expectations of antiemetic treatment in the ED.

Methods: Survey of adult ED patients with nausea. Primary outcome: expectation of antiemetic treatment as symptoms being 'totally gone', 'a lot less', 'a little less' and 'the same'. Secondary outcomes: comparison between expectations and symptom change when expectations were met; general views on indications for treatment, treatment satisfaction and reasons for additional medication use.

Results: Of 176 surveyed, treatment expectation was recorded by 165 (94%). These were: 'totally gone', 'a lot less' or 'a little less' for 60 (36%), 84 (51%) and 21 (13%), respectively. This pre-treatment nomination, was matched or exceeded by the reported level of symptom reduction at 30 min, for 43/87 (49%, 95% CI: 39–60) whose expectations were met, and 6/33 (18%, 95% CI: 7–35) whose were not. The majority (117/176, 66%) believed treatment should be reserved for moderate or severe nausea; 158/176 (90%) would accept treatment if offered; 130/165 (79%) expected a treatment effect by 30 min. Treatment satisfaction findings were similar to expectations being met. Further drug treatment at 30 min was desired by 29/120 (24%) who received an antiemetic drug. Most were improved, but believed additional drugs might help more. Of the 91 not wanting more treatment, most were improved and thought no more drugs were necessary.

Conclusion: Most patients expected antiemetic treatment to make symptoms at least 'a lot less'. Most also believe treatment should be reserved for moderate or severe nausea, and should take effect by 30 min.

Key words: *antiemetics, ED, nausea, patient preference, survey.*

Key findings

- Most patients expect antinausea treatment if symptoms are worse than mild.
- Most patients expect antiemetic drugs to be effective by 30 min.
- Most patients expect antiemetic drugs to make their symptoms at least 'a lot less'.

Background

Nausea and vomiting is a common and distressing problem for ED patients.[1] Although antiemetic drugs have been used in the ED for many decades, little ED-based antiemetic research has been conducted. A recent Cochrane systematic review on antiemetic drugs for the treatment of adult ED patients with nausea[2] identified only eight ED-based randomised, controlled trials.[3–10]

The most common outcome measure used in these studies is the comparison of change in mean or median visual analogue scale (VAS) ratings between treatment groups.[4–10] Effectiveness of treatment is inferred if the VAS change exceeds the minimum clinically significant difference (MCSD).[11,12] The MCSD is defined as the mean VAS change reported when symptoms have become 'a little less'.[11,12] This approach has recently been criticised because the mean VAS change yields no information on number of patients per group who are improved.[13]

Use of a VAS cut-off level has been proposed as an alternative.[13] When patients' nausea remains 'the same', reported VAS change has repeatedly been found to be zero, with 95% confidence limits of +/– 5 mm.[11–13] Hence, patients reporting a VAS reduction beyond –5 mm can reasonably be identified as improved, since their symptoms are no longer 'the same'. As with the MCSD, this approach still equates clinical significance with symptom improvement to any degree. However, it is not known if patients believe that symptoms being made 'a little less', is adequate. One US ED survey asked patients with nausea if they expected or wanted drug treatment for nausea,[14] but patient views on the desired effectiveness of antiemetic medication have never been explored.

The primary objective of this study is to determine what degree of symptom relief patients expect from antiemetic drugs. The effect of initial severity on treatment expectations will be examined, along with agreement between post-treatment symptom improvement and pre-treatment

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expectations, when expectations were said to have been met. This will inform on the consistency between what people want, and what they are happy to accept. Other general views on the necessity of antiemetic treatment, the willingness to accept it, expected time to therapeutic effect and the reasons for which further treatment is desired, will also be described. Study findings may enable the inclusion of more patient-centred outcomes in future ED-based antiemetic drug trials.

Methods

Study design, setting and period

An observational study was conducted at Dandenong Hospital (urban district hospital, ED annual census 60 000 patients). A convenience sample of patients was surveyed between 1 February and 30 April 2016. Study conduct was approved by the Monash Health Human Research Ethics Committee.

Participants

Inclusion

Patients aged 18 years or more, with nausea as part of their presenting complaint.

Exclusion

Hemodynamic instability (BP <90 systolic, HR >130/min); condition requiring time critical intervention (e.g. suspected cardiac chest pain); cognitive impairment or inability to understand the study explanation (any reason); antiemetic drug use within the previous 4 h.

Primary outcome

Degree of symptom relief patients expect from antiemetic drug treatment, classified as: totally gone, a lot less, a little less and the same.

Secondary outcomes

(i) Comparison of patient expectations between initial severity subgroups, age and gender; (ii) validation of pre-treatment patient expectations by comparison with post-treatment degree of symptom change, when expectations were said to have been met or not; (iii) pre and post-treatment views on satisfaction with treatment; (iv) pre-treatment patient opinions on need for drug treatment, willingness to accept it and expected time to treatment effect; and (v) post-treatment desire for additional medication and reasons for this.

Materials and measures

A summary of the questionnaire is included as Appendix S1. This shows the response options for all questions, and the specific scales used to describe severity, change in severity, expectations and satisfaction.

Study procedure

Eighteen medical students conducted the survey. Each student performed two different 8 h research shifts during the study period, one being 08:00 to 16:00 hours and the other 16:00 to 24:00 hours. They received training on: participant eligibility, the measurement scales, and interview technique. The student monitored new patient arrivals on the electronic ED tracking system (Symphony Version 2.0, Ascribe, Bolton, UK). Triage entries were checked for those with presenting complaints potentially associated with nausea (e.g. presumed gastroenteritis, abdominal pain, migraine/headache). Potentially eligible patients were approached to determine if nausea or vomiting were present. Verbal consent for the interview to proceed was obtained in all cases. All patients were asked to complete the baseline section of the questionnaire. Those still in the ED after 30 min reported their level of symptom change. Patients who received an antiemetic drug completed the final section on expectations, satisfaction and desire for additional medication. It should be noted that type and dosages of antiemetic drugs used were not recorded. The ED has no guideline for antiemetic use, so treatment is not controlled in any way and no comparisons that related to the prescribed drug regimen were being made. Data were entered in to a Microsoft Excel spreadsheet (version 12, Microsoft, Redmond, WA, USA) by one investigator (SA).

Statistical analysis

Baseline data are presented as number and percent, or median with interquartile range (IQR). In particular, although VAS distributions do approximate normal, there is literature disagreement as to whether VAS data should be presented and compared using parametric or non-parametric tests.[15–17] For this study, the more conservative approach of using Mann–Whitney and Kruskal–Wallis tests was adopted. Also, since some subgroup numbers were relatively small, Fisher's exact test was used for all comparisons of binary variables. For these, presented 95% confidence intervals were calculated using the binomial exact method. Where participants failed to answer a particular question, these were left as missing data, so that the totals for particular responses may be less than the total number surveyed. Analyses were performed using Stata v12.1 statistical software (StataCorp, College Station, TX, USA). There was no literature to inform on sample size. Assuming that 90% of patients might expect symptoms to become at least a little less, a sample of 150 would yield arbitrarily reasonable 95% confidence limits of +/– 5%.

Results

Baseline and primary outcome

A total of 176 participants completed the baseline section of the questionnaire. Median age was 43 years (IQR: 29–61) and 57 (32%) were male. Nausea was reported as being mild, moderate or severe by 48 (28%), 63 (36%) and 65 (37%) patients. The median VAS ratings for those subgroups were 27 mm (IQR: 19–46), 49 mm (IQR: 41–61) and 84 mm (IQR: 76–97), respectively. Of the 176, 165 (94%) recorded their treatment expectation. Of these, 60 (36%) patients expected symptoms to be 'totally gone' after treatment,

TABLE 1. *Level of symptom reduction expected from treatment for each severity subgroup*

	Respondent's nausea rating			
	Mild	Moderate	Severe	Total
Treatment expected to make nausea:				
Totally gone: *n* (%, 95% CI)	20 (47.6%, 32.0–63.6)	15 (25.4%, 15.0–38.4)	25 (39.1%, 27.1–52.1)	60
A lot less: *n* (%, 95% CI)	14 (33.3%, 19.6–49.5)	37 (62.7%, 49.1–75.0)	33 (51.6%, 38.7–64.2)	84
A little less: *n* (%, 95% CI)	8 (19.0%, 8.6–34.1)	7 (11.9%, 4.9–22.9)	6 (9.4%, 3.5–19.3)	21
Total	42 (100%)	59 (100%)	64 (100%)	165

CI, confidence interval (binomial exact method).

84 (51%) expected symptoms to be 'a lot less' and 21 (13%) expected 'a little less' (Table 1).

Secondary outcomes

Influence on treatment expectations of initial severity, age and sex

The response pattern for treatment expectation varied depending on initial severity. The most frequent response for the mild group was 'totally gone' (20/42 [48%, 95% CI: 32–64]), for moderate it was 'a lot less' (37/59 [63%, 95% CI: 49–75]), and for severe it was 'a lot less' (33/64 [52%, 95% CI: 39–64]), $P = 0.04$ (Fisher's exact) (Table 1, Fig. 1). The responses for the expected amounts of symptom relief were similar for men and women ($P = 0.87$, Fisher's exact) and did not differ significantly with age ($P = 0.51$, Kruskal–Wallis).

Comparison of pre-treatment expectations with post-treatment symptom change

Of the 120 patients who received antiemetic drugs, 87 (73%) reported that their expectations were met, 17 (14%) thought not and 16 (13%) were unsure. Expectations were met for similar majorities from each severity subgroup. Of the 120, 107 (89%) had expected treatment to make symptoms at least a lot less ('a lot less' or 'totally gone'), while 13 (11%) had expected symptoms to be made 'a little less'.

The reported amounts of post-treatment symptom change matched, or were greater than, the pre-treatment expected amounts of change, for significantly more who stated expectations had been met, versus not ($P = 0.002$, Fisher's exact). Significantly, more reported a lesser adjectival severity rating when expectations were met, versus not ($P < 0.001$, Fisher's exact). The median VAS reduction was significantly greater for the group whose expectations were met, versus not ($P < 0.001$, Mann–Whitney). Full details of these results are shown in Table 2 and illustrated in Figure 2.

TABLE 2. *Comparison of before and after rating differences for expectations being met or not*

	Expectations met	Expectations not met
Pre-treatment nomination matched or exceeded by reported symptom reduction, *n* (%) [95% CI]	44/87 (51%) [40–61]	6/33 (18%) [7–35]
Less severe adjectival rating, *n* (%) [95% CI]	74/87 (85%) [76–92]	16/33 (48%) (31–66)
VAS change, median (IQR)	–44 mm (–66 to –26)	–20 mm (–42 to –1)

CI, confidence interval (binomial exact method); IQR, interquartile range; VAS, visual analogue scale.

Satisfaction with treatment

For the 166 (94.3%) patients who gave a pre-treatment response, satisfaction was anticipated if symptoms were 'totally gone', 'a lot less' or 'a little less' for 68 (41%), 79 (48%) and 19 (11%), respectively.

Of the 120 patients who received antiemetic drug treatment, 71 (59%) said they were satisfied (22 'very

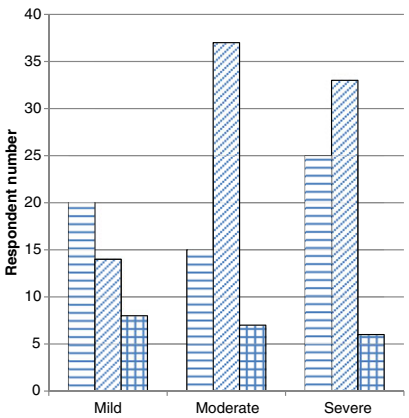

Figure 1. *Frequency of nominated treatment expectations for each severity subgroup. (□), Totally gone; (▨), A lot less; (▦), A little less.*

TABLE 3. *Comparison of before and after rating differences if satisfied or not*

	Satisfied with treatment	Not satisfied with treatment
Pre-treatment nomination matched or exceeded by reported symptom reduction, *n* (%) [95% CI]	35/71 (49%) [37–61]	14/49 (29%) [17–43]
Less severe adjectival rating, *n* (%) [95% CI]	68/71 (96%) [88–99]	30/49 (61%) [46–75]
VAS change, median (IQR)	–52 mm (–66 to –35)	–20 mm (–37 to –1)

CI, confidence interval (binomial exact method); IQR, interquartile range; VAS, visual analog scale.

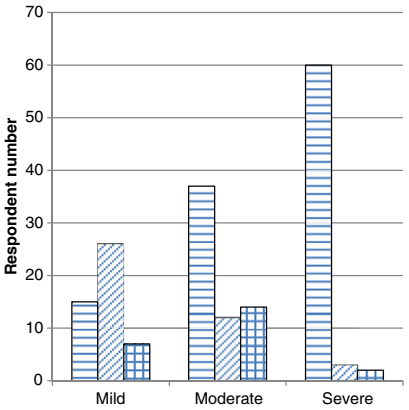

Figure 3. *Perceived need for treatment in each severity subgroup. (▭), Need treatment; (▨), No need for treatment; (▦), Unsure.*

satisfied' and 49 'satisfied'), 17 (15%) were not (8 'dissatisfied' and 9 'very dissatisfied') and 32 (27%) were 'unsure'. Satisfaction with drug treatment was similar between the initial severity subgroups.

The reported amounts of post-treatment symptom change matched, or were greater than, the pre-treatment anticipated amounts of change, for significantly more who were satisfied, versus not ($P = 0.03$, Fisher's exact) (Fig. 2). Significantly more reported a lesser adjectival severity rating if they were satisfied, versus not ($P < 0.001$, Fisher's exact). The median VAS reduction was significantly greater for the group who were satisfied, versus not ($P < 0.001$, Mann–Whitney). Full details of these results are shown in Table 3.

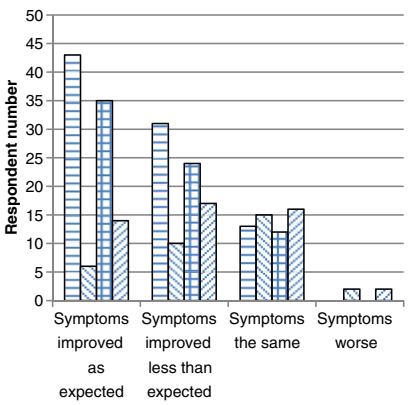

Figure 2. *Comparison of 30 min levels of symptom change with pre-treatment nominations for expectations and satisfaction. (▭), Expectations met; (▧), Expectations not met; (▦), Satisfied; (▨), Not satisfied.*

Other opinions on antiemetic drug treatment

Of all 176, 59 (34%) believed treatment was warranted for nausea of any severity, 74 (42%) for moderate or severe nausea, and 43 (24%) for severe nausea only. This response pattern was similar between the initial severity subgroups.

Of the total, 112 (64%) felt that drug treatment was necessary for them, 41 (23%) thought not and 23 (13%) were unsure. The perceived need for drug treatment differed between initial severity subgroups, being 15 of 48 (31%, 95% CI: 19–46) for mild, 37 of 63 (59%, 95% CI: 46–71) for moderate and 60 of 65 (92%, 95% CI: 83–97) for severe ($P < 0.001$, Fisher's exact) (Fig. 3).

If drug treatment was offered, 158 (90%) said they would accept it (111/112 who felt drug treatment was necessary, 23/23 who had been unsure, 24/41 who had felt it was not). The 18 not wanting drug treatment gave the following reasons: 12 (67%) 'symptoms not bad enough'; 2 'drugs won't work'; 2 'worried about side-effects'; 2 'never take drugs'.

For the 165 (94%) who nominated an expected time to treatment effect, responses of 'by 30 min', '30–60 min' or 'over 60 min', were given by 130 (79%), 25 (15%) and 10 (6%), respectively. Responses were similar between initial severity subgroups.

More drug treatment: perceived need and reasons

Of the 120 who received an antiemetic drug, 29 (24%) wanted further treatment at 30 min. Reasons given: 23 (79%) felt improved but thought further drugs would help more, 6 (21%) felt no better but thought further drugs might help. For the 91 who did not want further drugs, reasons were: 82 (90%) felt improved and thought no more drugs were necessary, 6 (7%) felt improved but doubted more drugs would help, 3 (3%) felt no better and thought more drugs would not help.

Discussion

This is the first paper to describe ED patients' expectations of antiemetic drug treatment. Although there was some variation in response between the initial severity subgroups, we found that over 80% of patients expected that antiemetic drugs should make their nausea at least a lot less. This finding is important, since no ED-based antiemetic drug

trial to date, has been able to take patient expectations in to account, when defining either primary or secondary outcome measures.

In order to validate the finding, we compared the patients' pre-treatment expectations, with their reported post-treatment levels of symptom change. Interestingly, when expectations were said to have been met, these only matched about half the time. It was not uncommon for people to report lesser amounts of symptom change than they had nominated pre-treatment, but still say that their expectations had been met. This suggests that to some degree, people may be willing to accept less than they had hoped for. In contrast, when expectations were met versus not, median VAS changes were –44 mm and –20 mm, respectively. Nausea measurement studies have shown that these levels of VAS change reliably correlate with symptoms being 'a lot less' and 'a little less', respectively.[11–13] It was not possible to specifically explore reasons for this possible inconsistency between the ordinal scale and the VAS in this population. However, since the VAS is considered to have greater sensitivity for detection of change than ordinal scales,[15,16] the findings do generally support that people want symptoms to be made at least 'a lot less'.

This is also the first in-depth exploration of patients' general views on antiemetic drug treatment. We found that most patients believe drug treatment should be reserved for those with at least moderate nausea. Consistent with this, the 64% who felt they needed drug treatment, and the 68% who received it, were predominantly from the moderate and severe groups. These findings are similar to those of a US ED survey of patients, which asked patients with nausea if they expected and/or wanted to receive antiemetic drug treatment. In that study, 51% of patients who wanted an antiemetic drug, and 53% of those who received one, were also from the more severe subgroups.[14] Although we cannot be certain, we suspect that those who did not have drugs were not offered them, since 90% of patients said they would accept any offered treatment. This is supported by the results of an Australasian survey, in which the majority of ED doctors said they did not routinely prescribe antiemetics for mild nausea.[1] We did not specifically examine for influence of age or sex on antiemetic drug provision, but the US survey found no association with these variables.[14]

Patient satisfaction has been used as a secondary outcome measure in some ED-based antiemetic drug trials,[5,9] but its utility has been questioned.[13] We found the overall responses regarding satisfaction, and expectations being met, to be similar. In retrospect, adjacent question placement may have lessened the patient's likelihood of differentiating between these concepts. The need for additional, or 'rescue' medication has also been used in antiemetic trials as a proxy measure for treatment failure.[3–10] However, we found that most wanting additional treatment were improved to some degree, but thought that more drugs might convey more benefit. This, along with the general variability in responses, suggests that the value of 'rescue' medication as an outcome measure may be limited.

Our purpose in examining patient views on antiemetic treatment was their potential to contribute to the design of ED-based antiemetic drug trials. Our findings support the usual approach taken in recent studies, of excluding patients with mild nausea and timing the outcome measure at 30 min.[3–10] Current approaches equate clinical significance with symptoms becoming 'a little less', or no longer being 'the same'.[3–10,13] This degree of change meets the definition for efficacy being a 'beneficial' effect, but efficacy may equally be defined as a 'desired' effect.[18] Our finding is that the patients' desired effect, is for symptoms to be made 'a lot less'.

Reconciling this difference may not be straightforward. Primary outcome could be based on the ordinal description of change scale, but in our population it appeared that the VAS may have better reflected the true degree of change. However, measurement research has shown that the VAS change for symptoms being 'a lot less', varies significantly between initial severity subgroups.[12] Consequently, defining a VAS change indicative of symptoms being 'a lot less', requires further investigation and thought.

Limitations

The generalisability of results from a convenience sample may be uncertain. Not all patients with nausea will have been identified from perusal of the presenting complaint and the triage record. Students did not keep details of eligible patients they were unable to approach for whatever reason, or those who were approached and declined participation. However, the recruited population did represent all severity subgroups, with VAS ranges for these being consistent with previous reports.[11–13] Potential interviewer bias was minimised by having multiple people deliver the questionnaire at different times.

The choice of responses had face validity, and most scales used were validated in previous ED nausea research.[11–13] 'Totally gone' was offered as an expectation option, but not as a description of change response. This limited some direct comparisons but we preferred not to alter the previously validated description of change scale.[11–13] Other aspects of the questionnaire design may have impacted on responses. The adjacent placement of questions concerning treatment expectations and satisfaction with treatment may have lessened appreciation of the difference in these concepts. For time to treatment effect, patients may have preferentially just chosen the shortest time option without having firm views on the number of minutes.

The particular antiemetic drug treatment may have impacted on expectations being met or satisfaction with treatment, in some way other than whatever change in symptom severity had occurred. However, this was not a therapeutic trial, and the study was not designed to examine any differences between

treatment groups. There was no controlling for potential treatment confounders, and so comparison of outcomes when drugs were used versus not, or between different drugs that were used, is likely to be misleading. Some reported secondary outcomes lack precision due to small numbers in some subgroups.

Conclusion

Most people surveyed expected that antiemetic drug treatment should make their symptoms at least a lot less. The majority also believed that antiemetic drugs should be reserved for symptoms of at least moderate severity, and that treatment should be effective by 30 min. The implications of these findings with regard to outcome measures in antiemetic drug trials, and in particular, how primary outcome measures might incorporate patient views, warrants further consideration.

Author contributions

RM and AG jointly conceived the idea for the study. SA supervised the conduct of the study and was responsible for data entry and initial data analysis. RM primarily conducted the study analysis and prepared the initial manuscript. All authors contributed to the final manuscript. RM takes overall responsibility for the manuscript.

Competing interests

None declared.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Appendix S1. Summary of questionnaire.

13.3 Brief discussion and implications for further ED-based research.

The survey findings were helpful in a number of ways with regard to future study design. Most patients felt that mild nausea probably does not warrant drug treatment, and that treatment effects should be evident by 30 minutes. This supports the research approach of excluding those with more mild symptoms and timing the primary outcome at 30 minutes.

Of primary interest, was the fact that most patients expected that drug treatment should make their symptoms at least 'a lot less'. Patients whose expectations had been met, reported VAS reductions which correlated with this level of symptom improvement. This explains why many patients in the RCT who reported their symptoms to be 'a little less', had been 'unsure' about satisfaction with treatment.[40] Also consistent was the fact that most who wanted additional medication had improved 'a little', but hoped that more drugs would deliver the desired effect.

A pooled analysis to further examine the accuracy of VAS change for detection of improved versus non-improved patients (beneficial effect) was still planned. It seemed worthwhile to also explore the ability of VAS change to detect symptoms becoming 'a lot less' (desired effect), since using one measure to detect both outcomes was appealing in its simplicity.

CHAPTER 14. Visual Analog Scale rating change cut-offs for detection of improvement in nausea severity.

14.1 Rationale and aims.

The ability of a measured VAS change cut-off to discriminate between improved and non-improved patients appeared promising, but could only be explored to a limited extent in the published measurement paper.[78] It was important to better evaluate performance in a larger and more varied ED population than that which had been recruited to the initial RCT.[40]

Individual patient ratings on both the VAS and the ordinal description of change scale were available from three published studies. These were the therapeutic RCT[40] and patient survey[79] which form part of this series of research projects, and the earlier measurement study of Meek (2009).[69] Pooling the data from all three populations would strengthen any findings with regard to the ability of VAS change to discriminate between improved and non-improved patients. The possibility of using percentage VAS change, which had been raised in the perspective article (Chapter 12), was also explored as part of this pooled analysis. Detection of delivery of the desired treatment effect, using the proxy measure of symptoms becoming 'a lot less', was also included as a secondary aim.

14.2. Citation and paper:

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Visual Analog Scale rating change cut-offs for detection of improvement in nausea severity.

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VAS change cut-offs reliably detect nausea improvement

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Visual Analog Scale rating change cut-offs for detection of improvement in nausea severity.

Abstract

Objective: To determine accuracy and best cut-off levels in Visual Analog Scale (VAS) rating change for detection of nausea symptom improvement.

Methods: A pooled analysis of individual patient data from three studies which included a baseline VAS severity rating, and both a VAS rating and description of symptom change ('a lot less', 'a little less', 'the same', 'a little more', 'a lot more') at 30 minutes. VAS change was calculated as measured difference in mm, and percentage change from baseline. ROC curve analysis was performed to primarily assess accuracy of VAS change for detection of improvement ('a lot less' or 'a little less'). Detection of symptoms becoming 'a lot less' was included as a secondary outcome.

Results: The analyses included 653 patients. For improvement, areas under the ROC curve were 0.86 (95% CI: 0.83 – 0.90), and 0.87 (95% CI: 0.84 – 0.90) for measured and percentage VAS change respectively. Best VAS change cut-offs were -8mm and -20 percent. For symptoms becoming 'a lot less', areas under the ROC curve were 0.81 (95% CI: 0.77 – 0.84) and 0.85 (95% CI: 0.82 – 0.88*)* respectively. Best VAS change cut-offs were -45mm and -67 percent.

Conclusion: For detection of symptom improvement, accuracy of measured and percentage VAS change is good. Additional use of the best VAS cut-offs to indicate treatment success in reporting ED-based antiemetic trials appears worthwhile. Accuracy for detection of symptoms becoming 'a lot less' was less good, although use of these cut-offs may still be of some value.

Key words

antiemetics, clinical effectiveness, emergency department, nausea, Visual Analog Scale

Visual Analog Scale rating change cut-offs for detection of improvement in nausea severity.

Background

Antiemetic drugs have been used to treat emergency department (ED) patients with nausea and vomiting for many decades. Recently, however, a Cochrane systematic review reported that there is no convincing evidence that antiemetic drugs are effective in the treatment of adult ED patients with nausea.[1] This conclusion was largely based on three ED-based therapeutic trials which failed to demonstrate superiority for antiemetic drugs over placebo.[2–4] As these findings seem counter-intuitive, traditionally used study methods and outcome measures have been reexamined.[5–8]

In all three ED-based, placebo-controlled studies, patients rated nausea severity at baseline and 30-minutes post-treatment on a standard 100 mm Visual Analog Scale (VAS). [2–4] Rating change was measured in mm for each patient and the mean amount of change for each treatment group calculated. Between-group comparisons of mean VAS change were performed, and equivalence was assumed when differences were not statistically significant. [2–4] This has been the standard approach in most of the ED-based antiemetic research conducted over the past two decades.[2–4,9–11] It has recently been pointed out, that uncertainty about the clinical significance of between-group differences in mean VAS change limits the information provided by these results. [7,8]

It has been suggested that ED-based antiemetic trial results would be enhanced if the number of patients with clinically significant improvement could be identified.[7,8] This would allow between-group comparisons of treatment success rates, and enable calculation of a Number Needed to Treat.[7,8] One study has reported that the amount of VAS change appears to reliably predict symptom improvement at the individual patient level, [8] but further validation is required. In addition, it has been hypothesized that percentage VAS change from baseline might also predict symptom improvement,[8] but this has not been formally explored. This approach, which equates treatment effectiveness with any amount of described symptom improvement[7,8] seems reasonable; a recent survey of ED patients with nausea, however, reported that most expect antiemetic treatment to make symptoms at least 'a lot less'.[12] The use of VAS change to detect this greater level of symptom improvement has never been examined.

The primary objective of this study is to investigate the ability of both measured and percentage VAS change to discriminate between improved and non-improved patients. As a secondary aim, the

accuracy of VAS change for detection of symptoms having become 'a lot less' is also assessed. This is done by performing ROC curve analyses, using pooled data from three previously published studies.[4,12,13] Findings should enable more robust recommendations to be made regarding the value of including VAS change cut-off levels as additional outcome measures in future ED-based antiemetic trials.

Methods

Study design

Analysis of pooled individual patient data from previously published studies on nausea measurement was performed. Data were available from three studies which included VAS severity ratings at baseline and after 30 minutes, with matched descriptions of symptom change.[4,12,13]

Summary of methods for each study

The titles given below, which reflect the study type, are used as descriptors throughout this paper.

'Measurement study': This cross-sectional study recruited patients at two hospital EDs in Melbourne, Australia; conduct was approved by the relevant ethics committees. [13] Participants rated nausea severity on the VAS at baseline, 30 and 60 minutes. Symptom change was described on an ordinal scale. (Box 1) The study objective was to validate use of the VAS for measurement of nausea severity. Comparison of treatment was not part of the study; about one-third did not receive an antiemetic drug.

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'Therapeutic RCT': This antiemetic drug trial recruited patients at two hospital EDs in Melbourne, Australia; conduct was approved by the institutional ethics committee.[2] Participants were randomized to receive either intravenous (IV) ondansetron 4 mg, metoclopramide 20 mg IV or 0.9% saline placebo. Nausea severity was rated on the VAS at baseline and 30 minutes post-treatment. Symptom change was also described at 30 minutes. The primary objective was to assess the relative efficacy of the drug treatments.

'Management survey': A survey of ED patients with nausea recruited patients at one hospital ED in Melbourne, Australia; conduct was approved by the institutional ethics committee.[12] Nausea severity was rated on the VAS at baseline and after 30 minutes, when symptom change was also described. The primary objective was to explore patient opinions regarding antiemetic management. Treatment comparisons were not part of the study; about one-third of patients did not receive an antiemetic drug.

Study population for the pooled analysis

Inclusion/Exclusion criteria: All three studies included a convenience sample of adult ED patients with nausea from any cause. Exclusion criteria were similar: time-critical conditions (e.g. ischemic chest pain), clinical instability (e.g. BP < 90 mmHg, HR > 130/min), cognitive impairment (any reason) and specific antiemetic drug allergies.[4,12,13]

All patients with baseline and 30-minute VAS ratings, with matched 30-minute descriptions of change, were included for analysis. The 60-minute ratings from the measurement study were not included. In total, complete data were available for 653 patients. These were 236 (96%) of the 247 patients from the measurement study, 168 (95%) of the 176 patients from the management survey, and 249 (97%) of the 258 patients from the therapeutic RCT. Type of treatment was not considered relevant for these analyses.

Objectives

Primary: To determine the accuracy and best cut-off level of measured and percentage VAS change for the detection of nausea symptom improvement.

Secondary: To determine the accuracy and best cut-off level of measured and percentage VAS change for the detection of symptoms becoming 'a lot less'; to describe VAS changes when symptoms are described as being 'a lot less', 'a little less' or 'the same'.

Measurements and definitions

All included studies used the VAS and the ordinal description of change scale. Measurement methods and scale definitions, including how the ordinal scale was dichotomized for analysis, are detailed in Box 1. An example of the VAS change calculations is illustrated in Box 2.

Statistical analysis

Baseline information on age, sex and initial VAS rating are reported and compared between the three study populations using the Kruskal-Wallis test, Pearson chi square test and one-way ANOVA respectively. Further analyses use combined individual patient data from all studies. As the distribution of change in VAS ratings, both measured and percentage, approximates normal, mean (95% CI) values are reported. ROC curve analysis is performed to determine the ability of VAS change to discriminate between improved versus non-improved patients, and the area under the curve (AUC, 95% CI) is

reported. The best VAS change cut-off is defined as the figure with the highest mean value for sensitivity + specificity. Standard measures of diagnostic performance for each cut-off are presented. To address the potential for overfitting of data, three-fold cross-validation was performed for each outcome. This comprised a pooled analysis for each pair of included studies, with diagnostic performance of the best cut-off being determined for the remaining study population. Sample size was dictated by the populations available from the three studies.

Results

Baseline characteristics

Data from 653 patients were available for analysis: 236 (36%) from the measurement study, 249 (38%) from the therapeutic RCT and 168 (26%) from the management survey. Age, sex and baseline VAS ratings were similar between studies. (Table 1)

Detection of symptom improvement: individual studies and whole pooled sample

Measured VAS change: For the measurement study, therapeutic RCT and management survey respectively, the ROC AUC values were 0.93 (95% CI: 0.89 – 0.96), 0.87 (95% CI: 0.81 – 0.93) and 0.81 (95% CI: 0.74 – 0.88). (Figure 1a) The ROC AUC for the pooled sample was 0.86 (95% CI: 0.83 – 0.90), with a best cut-off level of -8 mm (correct classification rate 85%, 95% CI: 83 – 88).

Percentage VAS change: For the measurement study, therapeutic RCT and management survey respectively, the ROC AUC values were 0.94 (95% CI: 0.90 – 0.97), 0.86 (95% CI: 0.80 – 0.92) and 0.86 (95% CI: 0.80 – 0.92). (Figure 1b) The ROC AUC for the pooled sample was 0.87 (95% CI: 0.84 – 0.90), with a best cut-off level of -20 percent (correct classification rate 86%, 95% CI: 83 – 89).

Three-fold cross-validation of measured and percentage VAS change for detection of symptom improvement

For each combination of two studies, the ROC AUC values for detection of symptom improvement by both measured and percentage VAS change were between 0.83 and 0.90. The best measured and percentage VAS change cut-offs were -8 mm and -20 percent for each pair of studies. Full results for accuracy and diagnostic performance of the cut-offs, from both the three-fold cross-validation and for the whole population are shown in Table 2.

Detection of symptoms being 'a lot less': individual studies and whole pooled sample

Measured VAS change: For the measurement study, therapeutic RCT and management survey respectively, the ROC AUC values were 0.82 (95% CI: 0.76 – 0.87), 0.80 (95% CI: 0.75 – 0.86) and 0.85 (95% CI: 0.79 – 0.91). (Figure 2a) The ROC AUC for the pooled sample was 0.81 (95% CI: 0.77 – 0.84), with a best cut-off level of -45 mm (correct classification rate 76%, 95% CI: 72 – 79).

Percentage VAS change: For the measurement study, therapeutic RCT and management survey respectively, the ROC AUC values were 0.88 (95% CI: 0.82 – 0.93), 0.85 (95% CI: 0.81 – 0.90) and 0.86 (95% CI: 0.81 – 0.91). (Figure 2b) The ROC AUC for the pooled sample was 0.85 (95% CI: 0.82 – 0.88), with a best cut-off level of -67 percent (correct classification rate 80%, 95% CI: 77 – 83).

Three-fold cross-validation of measured and percentage VAS change for detection of symptoms being 'a lot less'

For each combination of two studies, the ROC AUC values for detection of symptoms being 'a lot less' by both measured and percentage VAS change were between 0.81 and 0.86. The best measured and percentage VAS change cut-offs were -45 mm and -67 percent for each pair of studies. Full results for accuracy and diagnostic performance of the cut-offs, from both the three-fold cross-validation and for the whole population are shown in Table 3.

VAS ranges for description of change categories

Of all 653 patients, symptoms were described as being 'a lot less', 'a little less', 'the same', 'a little more' and 'a lot more' by 220 (34%), 229 (35%), 148 (23%), 39 (6%) and 17 (3%) patients respectively. The mean measured VAS changes reported for symptoms being 'a lot less', 'a little less' and 'the same' were -46 mm (95% CI: -49 to -42), -27 mm (95% CI: -30 to -24) and -8 mm (95% CI: -11 to -5) respectively; the mean percentage VAS changes were -78 percent (95% CI: -82 to -74), -50 percent (95% CI: -53 to -46) and -10 percent (95% CI: -18 to -3) respectively. (Figure 3)

Discussion

This analysis found that the ability of VAS change to discriminate between improved and non-improved patients was good. For measured and percentage VAS change, the ROC AUC values were 0.86 (95% CI: 0.83 – 0.90) and 0.87 (95% CI: 0.84 – 0.90) respectively. The best suggested cut-off levels were -8 mm and -20 percent. False positives (VAS change greater than the cut-off but symptoms not improved) and

false negatives (symptoms improved but VAS change less than the cut-off) were relatively few, and fairly well balanced. The sensitivity and PPV for detection of symptom improvement were both about 90%. This supports that the number beyond the cut-off level accurately reflects the true number of improved patients. Three-fold cross-validation confirmed that potential overfitting of the data was not a significant issue. The findings suggest that VAS change cut-offs predict symptom improvement reliably enough to allow their use as an additional outcome measure in ED-based antiemetic trials.

Traditionally, most researchers have reported the mean VAS change per treatment group, with between-group comparisons, as the primary outcome measure.[2–4,10] Treatment effectiveness is assumed if the mean VAS change per group exceeds the 'minimum clinically significant difference' (MCSD).[2,4,13,14] The MCSD is defined as the mean VAS change when patients describe symptoms as being 'a little less'.[13,14] For nausea, it was reported to be -16 mm by Hendey,[14] and -20 mm by Meek.[13] Since the MCSD is influenced by initial severity, minor differences between study populations are expected.[13] Using the MCSD as a benchmark for efficacy seems reasonable, but using it in ED-based antiemetic trials has not proved straightforward.

For example, the mean VAS change for a treatment group might be -16 mm. This approximates the MCSD, but it does not mean that all patients reported symptoms to be 'a little less'. VAS change tends to be normally distributed, so the majority will have reported VAS changes of about -16 mm, and would have described symptoms as being 'a little less'. However, roughly equal proportions will also have reported lesser and greater VAS reductions, with respective symptom changes being either 'the same' or 'a lot less'. So although most of the population will be improved to some degree, the actual treatment success rate is unknown.

A number of authors have further stated that clinical significance can be assumed if the between-group difference exceeds the MCSD.[3,10,15] Two different treatments might result in mean VAS changes of -32 mm and -48 mm, with the between-group difference being -16 mm. This approximates the MCSD but, in this setting, it is clearly not a change from baseline which equates with symptoms being 'a little less'.[13,14] As such, the clinical significance and practical implications of this between-group difference are unclear. In this example, almost all patients in both groups probably experienced symptom improvement to some degree, meaning that treatment success rates are likely to be fairly similar.

The purpose of exploring the use of VAS change cut-off levels was to supplement the information being provided by the mean VAS change. If treatment success rates were known, these could also be directly

compared and a NNT calculated. Given the known properties of the VAS in nausea measurement and monitoring,[7,13,14] the accuracy of the VAS change cut-offs for detecting symptom improvement is not surprising. Nausea management studies have consistently shown that when symptoms remain 'the same', VAS change is tightly concentrated around zero, regardless of initial nausea severity. Since the -8 mm and -20 percent cut-offs correspond to the upper 95% confidence limits for symptoms being 'the same', it follows that people with greater reductions are almost certain to report symptom improvement. In essence, this is just an alternate view of the traditional MCSD, with clinical significance being defined as symptoms being no longer 'the same', rather than having become 'a little less'.

The secondary analysis regarding symptoms having become 'a lot less' stemmed from the findings of a survey of ED patients with nausea.[12] Most reported that the 'desired effect' of antiemetic treatment was for symptoms to become at least 'a lot less'.[12] Although we found performance of VAS change for this outcome to be good, with ROC AUC values in the range of 0.80 to 0.85, it was not as accurate as for the detection of symptom improvement. For the best cut-offs of -45 mm and -67 percent, the sensitivity and PPV values were less than 80% for the whole population and for most of the cross-validation samples; false positives and negatives were both relatively frequent and not so evenly balanced. This is not surprising, given that the VAS change distributions overlap more when symptoms are 'a lot less' or 'a little less', than occurs between other categories and symptoms remaining 'the same'.[7,13,14] Despite the lesser accuracy, additional use of the higher VAS change cut-off may still add some value to antiemetic trial results. Patient satisfaction, for which this is a proxy measure,[12] has been included in some ED-based studies.[2,4] Results, however, have been somewhat difficult to interpret, for reasons which have been debated.[7] As a consequence, assessment of satisfaction through either direct questioning or use of the higher VAS change cut-off level, appears best placed as a secondary outcome.

To demonstrate the potential for VAS change cut-offs to provide additional useful clinical information, the findings of the therapeutic RCT included in this analysis are provided as an example. In the therapeutic RCT, the mean VAS changes for ondansetron 4 mg, metoclopramide 20 mg and placebo were -28 mm (95% CI: 33 to -22), -29 mm (95% CI: -35 to -22) and -22 mm (-30 to -15) respectively, p = 0.11 (ANOVA). [4] While not statistically significant, the clinical significance of these differences is unclear. Had a measured VAS change cut-off of -8 mm been applied to detect symptom improvement, treatment success rates for the ondansetron, metoclopramide and placebo groups would have been reported as 79%, 78% and 58% respectively. The between-group differences for ondansetron-placebo, and metoclopramide-placebo, are 21% (95% CI: 8 – 35) and 20% (95% CI: 7 – 34), respectively. The NNT in

favour of both active drugs over placebo is about 5 (95% CI: 3 – 13). We believe that provision of this additional information better allows the reader to weigh these differences against other factors, such as drug costs and side-effects, in order to decide if treatment might be worthwhile.

Limitations

This analysis combines data from three different studies, which varied in purpose. Inclusion and exclusion criteria were consistent, however, and data was collected in the same format.[4,12,13] Studies recruited convenience samples of patients, so representativeness is not guaranteed. While there are many more antiemetic studies, these were three of the only four ED-based papers which rated change in severity on both the VAS and the ordinal description of change scale.[4,12–14]

The type of antiemetic treatment, including placebo, and provision of other measures (e.g. drug type and dose, amounts of IV fluid) varied between studies.[4,12,13] As this pooled analysis examined the relationship between VAS change and described symptom improvement, these differences are not relevant.

Splitting a continuous measure to create a binary outcome can cause information loss and compromise sensitivity for detection of change.[16] In this setting, however, the mean VAS changes remain valuable, with the cut-offs serving to augment the currently reported information.

Conclusion

Both measured and percentage VAS changes accurately discriminate for symptom improvement in adult ED patients with nausea. Inclusion of VAS change cut-off levels would enhance the information currently provided by group mean VAS change.

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Box 1. Definitions and measurements for the outcomes reported.

Rating	Definition/Measurement
Visual analog scale (VAS)	Patient marks a 100 mm line, labelled 'no nausea' at extreme left and 'worst nausea imaginable' at extreme right. Single ratings reported as mm measured from the left end of the scale.
Measured VAS change	Change reported as the first rating subtracted from the second so that a negative number indicates reduction in severity. (Box 2)
Percentage VAS change	Change reported as the amount of measured change divided by the first rating. A negative number equates with reduction in severity. (Box 2)
Description of change scale	Patient circles an option: 'a lot less', 'a little less', 'the same', 'a little more', 'a lot more'
Symptom improvement versus not	Ordinal options dichotomized to a combination of 'a lot less' and 'a little less', versus a combination of 'the same', 'a little more' and 'a lot more'
Symptoms being 'a lot less' versus not	Ordinal options dichotomized to 'a lot less' versus the combination of 'a little less', 'the same', 'a little more' and 'a lot more'
Interpretation of ROC analysis: Area Under Curve	0.90 – 1 = excellent; 0.8 – 0.89 = good; 0.7 – 0.79 = fair; 0.6 – 0.69 = poor; 0.5 – 0.59 = fail.
Three-fold cross-validation method employed	Pooled analysis of the Therapeutic RCT and Measurement Study – diagnostic performance of the best VAS change cut-offs (measured and percentage) calculated for the Management Survey population.
	Pooled analysis of the Therapeutic RCT and Management Survey – diagnostic performance of the best VAS change cut-offs (measured and percentage) calculated for the Measurement Study population.
	Pooled analysis of the Management Survey and Measurement Study – diagnostic performance of the best VAS change cut-offs (measured and percentage) calculated for the Therapeutic RCT population.

Box 2. Example calculation of measured and percentage VAS change.

VAS: 100 mm line on which patients mark their response with a vertical line. The rating is measured in mm from the left end of the line.

_____|_____|_____

N**o nausea** (40 mm post-treatment) (80 mm baseline) **Worst nausea imaginable**

Measured VAS change is calculated here as: 40 – 80 = -40 mm.

Percentage VAS change is then calculated as: (-40 mm / 80 mm) x 100 = -50%

The use of the negative number is a conceptual aid, indicating symptom reduction.

Table 1. Comparison of baseline variables between participants from the three included studies.

	Data source			P value
	Measurement study (n = 236)	Therapeutic RCT (n = 249)	Management survey (n = 168)	
Age: median years (IQR)	46 (28 – 62)	42 (27 – 61)	43 (29 – 61)	0.85*
Male sex: n (%) [95% CI]	94 (40%) [34 – 46]	86 (35%) [29 – 41]	54 (32%) [25 – 40]	0.25**
Baseline VAS rating: mean mm (sd) [95% CI]	54 (26) [51 – 57]	55 (24) [53 – 58]	58 (26) [54 – 62]	0.26†

IQR = Interquartile Range, CI = confidence interval (binomial exact), VAS = Visual Analog Scale

* Kruskal-Wallis, ** Pearson chi square, † one-way ANOVA

Table 2. Symptom improvement: accuracy of detection by VAS change and diagnostic performance of cut-offs of ≥ -8mm and ≥ -20 percent.

Three-fold cross-validation and total sample.

Measured VAS change									
Three-fold cross-validation of performance		Findings of pooled R + M data (n = 485) tested on S population (n = 168)		Findings of pooled M + S data (n = 404) tested on R population (n = 249)		Findings of pooled R + S data (n = 417) tested on M population (n = 236)		Findings for pooled R + S + M data (n = 653)	
Accuracy: ROC AUC (95% CI)		0.90 (0.87 – 0.93)		0.86 (0.82 – 0.90)		0.83 (78 – 87)		0.86 (0.83 – 0.90)	
Diagnostic Performance		Symptoms improved		Symptoms improved		Symptoms improved		Symptoms improved	
		Yes	No	Yes	No	Yes	No	Yes	No
VAS change ≥ -8mm	Yes	103	28	164	18	146	13	413	59
	No	4	33	17	50	15	62	36	145
Sensitivity: n (%) [95% CI]		103/107 (96%) [91 – 99]		164/181 (91%) [85 – 94]		146/161 (91%) [85 – 95]		413/449 (92%) [89 – 94]	
Specificity: n (%) [95% CI]		33/61 (54%) [41 – 67]		50/68 (74%) [61 – 83]		62/75 (83%) [72 – 90]		145/204 (71%) [64 – 77]	
PPV: n (%) [95% CI]		103/131 (79%) [71 – 85]		164/182 (90%) [85 – 94]		146/159 (92%) [86 – 96]		413/472 (88%) [84.2 – 90.3]	
NPV: n (%) [95% CI]		33/37 (89%) [75 – 97]		50/67 (75%) [63 – 84]		62 /77 (81%) [70 – 89]		145/181 (80%) [74 – 85]	
Percentage VAS change									
Accuracy: ROC AUC (95% CI)		0.90 (0.86 – 0.93)		0.88 (0.84 – 0.92)		0.85 (80 – 89)		0.87 (0.84 – 0.90)	
Diagnostic Performance		Symptoms improved		Symptoms improved		Symptoms improved		Symptoms improved	
		Yes	No	Yes	No	Yes	No	Yes	No
VAS change ≥ -20%	Yes	103	27	161	14	147	11	411	52
	No	4	34	20	54	14	64	38	152
Sensitivity: n (%) [95% CI]		103/107 (96%) [91 – 99]		161/181 (89%) [83 – 93]		147/161 (91%) [86 – 95]		411/449 (92%) [89 – 94]	
Specificity: n (%) [95% CI]		34/61 (56%) [2 – 68]		54/68 (79%) [68 – 88]		64/75 (85%) [75 – 92]		152/204 (75%) [68 – 80]	
PPV: n (%) [95% CI]		103/130 (79%) [71 – 86]		161/175 (92%) [87 – 96]		147/158 (93%) [88 – 96]		411/463 (89%) [86 – 92]	
NPV: n (%) [95% CI]		34/38 (89%) [75 – 97]		54/74 (73%) [61 – 83]		64/78 (82%) [72 – 90]		152/190 (80%) [74 – 85]	

R = therapeutic RCT, M = measurement study, S = management survey, PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval

Table 3. Symptoms being 'a lot less': accuracy of detection by VAS change and diagnostic performance of cut-offs of ≥ -45mm and ≥ -67 percent.

Three-fold cross-validation and total sample.

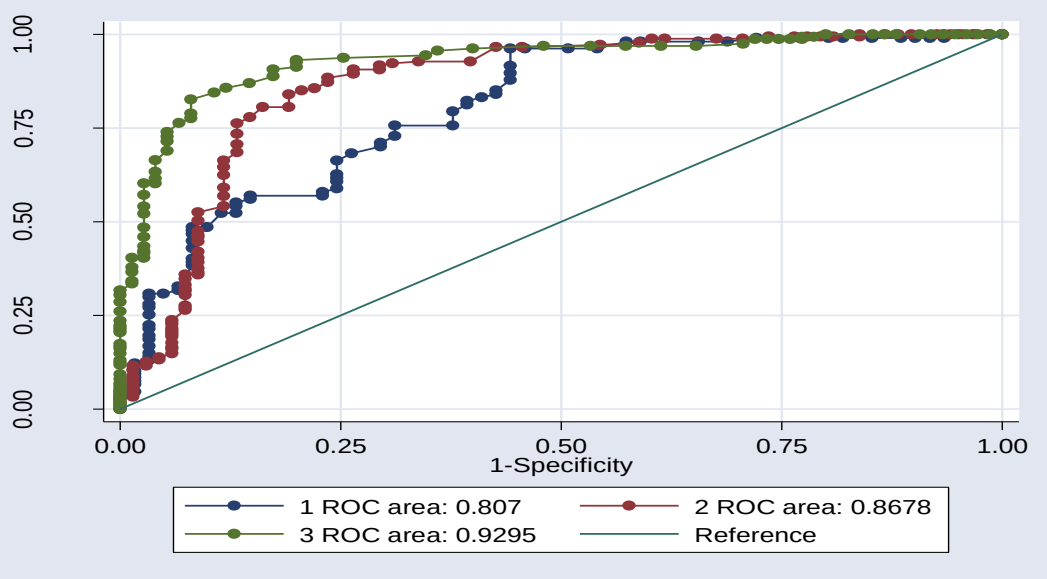
Measured VAS change									
Three-fold cross-validation of performance		Findings of pooled R + M data (n = 485) tested on S population (n = 168)		Findings of pooled M + S data (n = 404) tested on R population (n = 249)		Findings of pooled R + S data (n = 417) tested on M population (n = 236)		Findings for pooled R + S + M data (n = 653)	
Accuracy: ROC AUC (95% CI)		0.81 (0.77 – 0.85)		0.81 (0.77 – 0.86)		0.81 (77 – 85)		0.81 (0.77 – 0.84)	
Diagnostic Performance		Improved		Improved		Improved		Improved	
		Yes	No	Yes	No	Yes	No	Yes	No
VAS change ≥ -45 mm	Yes	34	22	41	21	35	7	110	50
	No	13	99	49	138	48	146	110	383
Sensitivity: n (%) [95% CI]		34/47 (72%) [57 – 84]		41/90 (46%) [35 – 56]		35/83 (42%) [31 – 54]		110/220 (50%) [43 – 57]	
Specificity: n (%) [95% CI]		99/111 (89%) [82 94]		138/159 (87%) [81 – 92]		146/153 (95%) [91 – 98]		383/433 (88%) [85 – 91]	
PPV: n (%) [95% CI]		34/56 (61%) [47 – 74]		41/62 (66%) [53 – 78]		35/42 (83%) [69 – 93]		110/160 (69%) [61 – 76]	
NPV: n (%) [95% CI]		99/112 (88%) [81 – 94]		138/187 (74%) [67 – 80]		146/194 (75%) [69 – 81]		383/493 (78%) [74 – 81]	
Percentage VAS change									
Accuracy: ROC AUC (95% CI)		0.86 (0.83 – 0.90)		0.85 (0.81 – 0.89)		0.85 (81 – 88)		0.85 (0.82 – 0.88)	
Diagnostic Performance		Improved		Improved		Improved		Improved	
		Yes	No	Yes	No	Yes	No	Yes	No
VAS change ≥ -67%	Yes	45	38	72	35	56	10	173	83
	No	2	83	18	124	27	143	47	350
Sensitivity: n (%) [95% CI]		45/47 (96%) [85 – 99]		72/90 (80%) [70 – 88]		56/83 (67%) [56 – 77]		173/220 (79%) [73 – 84]	
Specificity: n (%) [95% CI]		83/121 (69%) [60 – 77]		124/159 (78%) [71 – 84]		143/153 (93%) [88 – 97]		350/483 (72%) [68 – 76]	
PPV: n (%) [95% CI]		45/83 (54%) [43 – 65]		72/107 (67%) [58 – 76]		56/66 (85%) [74 – 92]		173/256 (68%) [61 – 73]	
NPV: n (%) [95% CI]		83/85 (98%) [92 – 100]		124/142 (87%) [81 – 92]		143/170 (84%) [78 – 89]		350/397 (88%) [85 – 91]	

R = therapeutic RCT, M = measurement study, S = management survey, PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval

Figure 1. Measured and percentage VAS change for detection of symptom improvement: comparison of ROC curves for the individual studies.

Note: 1 = Management survey, 2 = Therapeutic RCT, 3 = Measurement study

a) **Measured change**



b) **Percentage change**

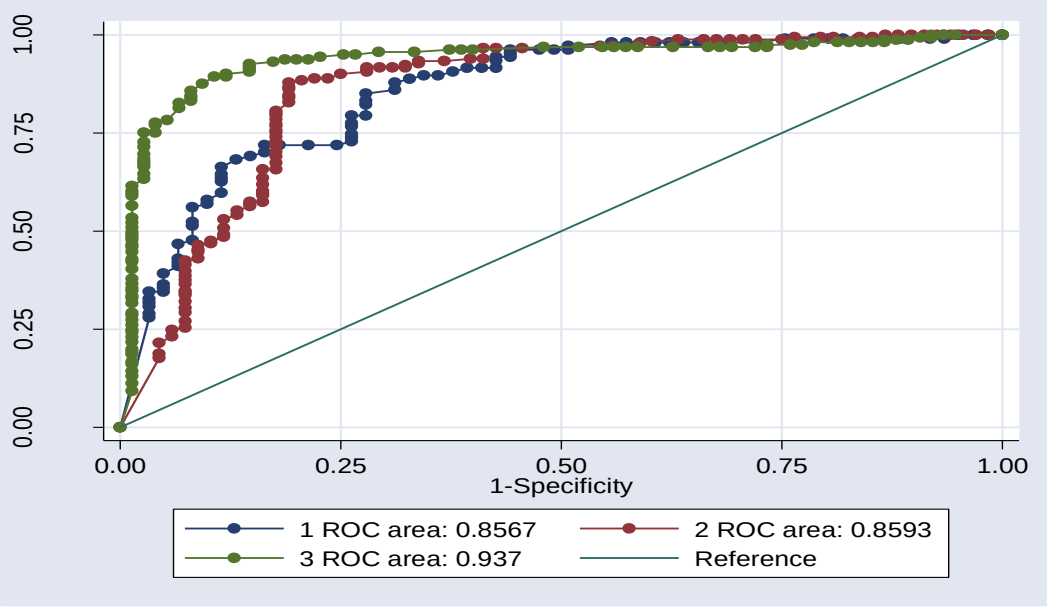
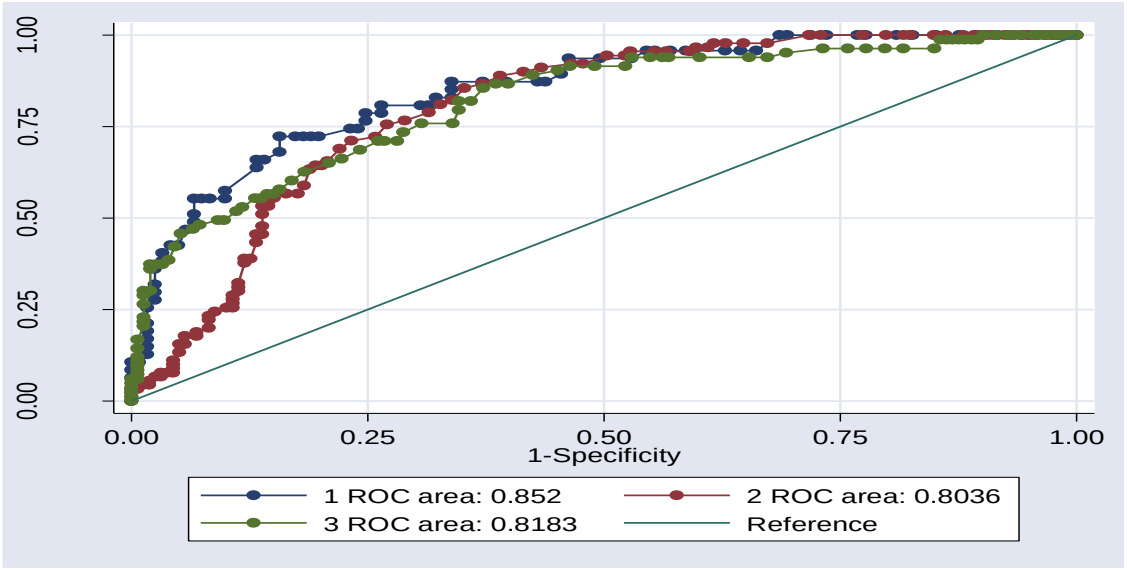


Figure 2. Measured and percentage VAS change for detection of symptoms being 'a lot less': comparison of ROC curves for the individual studies.

Note: 1 = Management survey, 2 = Therapeutic RCT, 3 = Measurement study

a) **Measured change**



b) **Percentage change**

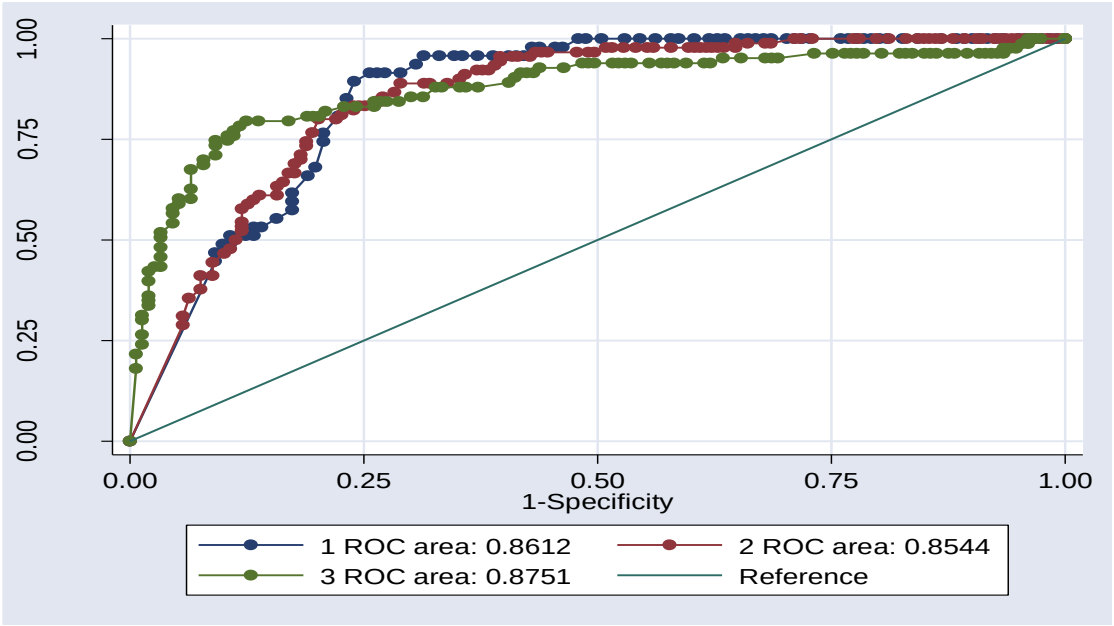
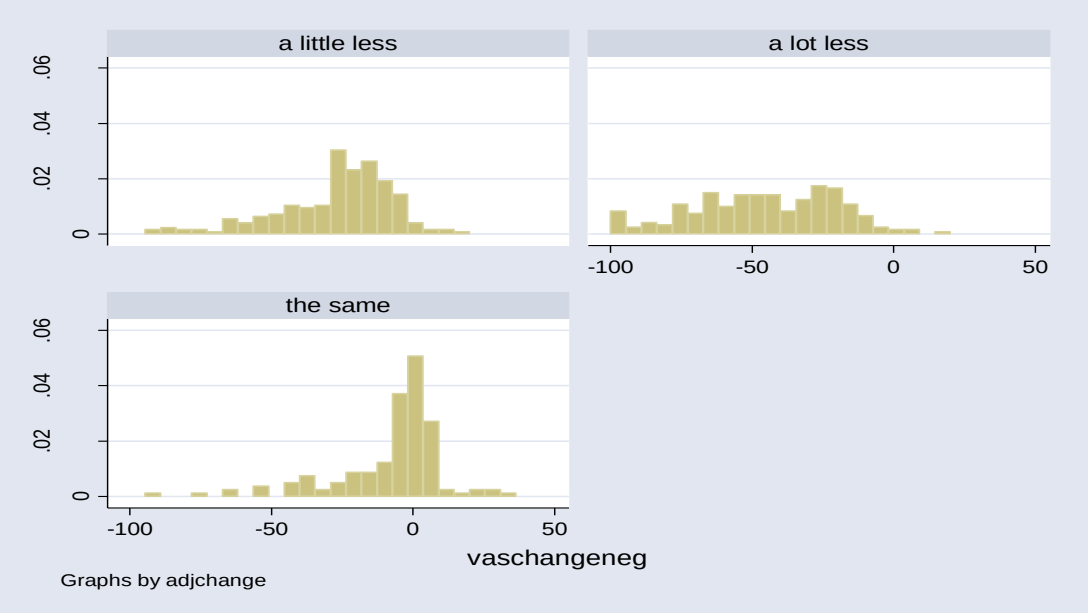
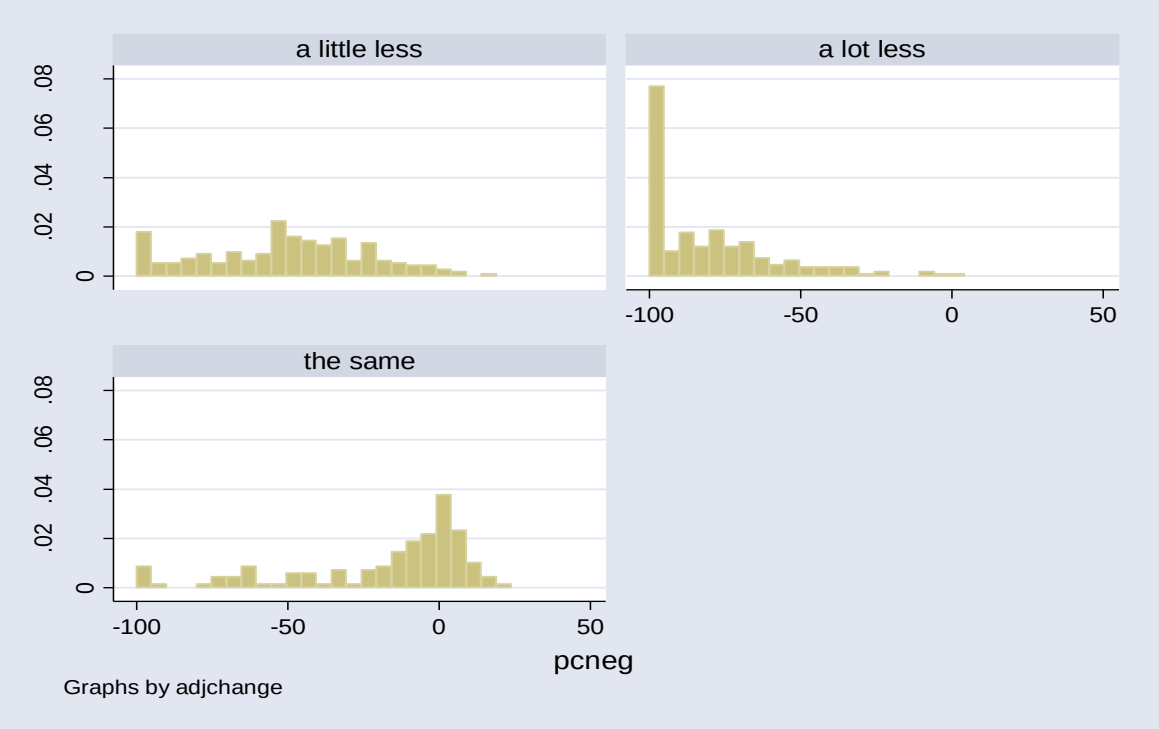


Figure 3. Distribution of VAS change when symptoms are 'a lot less', 'a little less' or 'the same' after 30 minutes.

a) **Measured change**



b) **Percentage change**



14.3 Brief discussion and implications for further ED-based research.

Examination of this larger sample, using ROC curve analyses, confirmed the ability of both measured and percentage VAS change to discriminate between improved and non-improved patients. The best measured VAS cut-off level was -8 mm, although measures between about -5 mm and -9 mm were similarly accurate. This was considered sufficient support for the use of the measured VAS change cut-off as an outcome measure in the final therapeutic RCT. Since the performance of percentage VAS change was equivalent, the use of both was unnecessary. The -8 mm cut-off could now be applied in a post-hoc analysis of the first RCT,[40] in order to guide the sample size calculation for the follow-up RCT.

VAS change proved to be less accurate for the detection of symptoms becoming 'a lot less'. This was not surprising giving the findings of the previous nausea measurement research. VAS change when symptoms become 'a little less' or 'a lot less' are known to differ significantly with initial severity.[69,78] As a consequence, VAS distributions for these amounts of change vary between populations depending on the initial severity mix. By contrast, the distribution of VAS change when symptoms remain 'the same' is known to be tightly concentrated around zero, and is not influenced by initial severity.[66,69,78] Hence, it seemed preferable that delivery of the desired treatment effect would be better assessed in therapeutic trials as a secondary outcome, using direct patient questioning.

CHAPTER 15. Randomized placebo-controlled trial of droperidol and ondansetron for treatment of adult emergency department patients with nausea: demonstration of a new outcome measure.

15.1 Brief rationale, aims and planning.

Having identified two suitable additional outcome measures for ED-based antiemetic trials, planning for the follow-up RCT was finalized. It was determined that a measured VAS change of ≥ -8 mm would be used as the primary outcome measure.[80] A post-hoc analysis of the first RCT [40] showed that VAS change of ≥ -8 mm was reported by 79% and 57% of patients in the ondansetron 4 mg IV and placebo groups respectively. This suggested that design as a superiority study was reasonable, and the sample size was based on these figures. Given the limited amount of evidence, and the known variation in the reported mean VAS changes for the same drug regimen in different studies, uncertainty about the sample size persisted.

Mean VAS change was to be presented and compared between groups in the traditional manner as a secondary outcome. A patient-centered question on experiencing the desired treatment effect was also included. It was expected that this format would allow the study results to be both easily understandable and clinically meaningful with regard to the primary treatment objective.

The best choice of drugs to trial against placebo could be debated. Previous research suggested that ondansetron 4 mg IV and metoclopramide 20 mg IV may be little different to placebo. As ondansetron had become the most commonly used antiemetic drug in the ED,[81] it was included again, but at a higher dose of 8 mg IV. Droperidol 1.25 mg IV was chosen as a second active drug, as it was the only antiemetic for which there had been any support using the traditional outcome measure. [35]

15.2 Citation and paper.

Meek R, Egerton-Warburton D, Mee MJ, Graudins A, Meyer A, Pouryahya P, Blecher G, Fahey J. Randomized placebo-controlled trial of droperidol and ondansetron for treatment of adult emergency department patients with nausea: demonstration of a new outcome measure. Acad Emerg Med. 2018, May. Submitted for publication.

PAPER FOLLOWS

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Randomized placebo-controlled trial of droperidol and ondansetron for adult emergency department patients with nausea: demonstration of a new outcome measure.

Journal:	*Academic Emergency Medicine*
Manuscript ID	Draft
Manuscript Type:	Original Contribution
Classifications:	Abdominal/Gastrointestinal, General EM Practice, Methodology < Research Concepts

Randomized placebo-controlled trial of droperidol and ondansetron for adult emergency department patients with nausea: demonstration of a new outcome measure.

Abstract

Objective: To compare effectiveness of intravenous (IV) droperidol 1.25 mg and ondansetron 8 mg IV with 0.9% saline placebo for adult emergency department (ED) patients with nausea. A novel primary outcome measure, expected to aid interpretation of reported results, was employed.

Methods: A randomised controlled trial was conducted at the three EDs of Monash Health, Melbourne, Australia. Design was to demonstrate superiority of the active drugs over placebo. The new primary outcome measure of symptom improvement was defined as a visual analog scale (VAS) rating change of ≥ -8 mm from baseline at 30-minutes post-treatment. Mean VAS changes per group, and percentages experiencing the desired treatment effect were also compared. The study was concluded after recruitment of 215 of the planned 378 patients, as interim analysis confirmed that continuation could not result in a finding of superiority.

Results: Of 215 patients, 73 (34%), 71 (33%) and 71 (33%) received droperidol, ondansetron and placebo. Symptom improvement occurred in 75% (95% CI: 64 - 85), 80% (95% CI: 69 - 89) and 76% (95% CI: 64 - 85), respectively. Mean VAS changes were -29 mm (95% CI: -36 to -23), -34 mm (95% CI: -41 to -28), and -24 mm (95% CI: -29 to -19), respectively. Desired

treatment effect was experienced by 77% (95% CI: 65 – 86), 73% (95% CI: 61 – 83) and 59% (95% CI: 47 – 71), respectively.

Conclusion: For adult ED patients with nausea, superiority was not demonstrated for droperidol or ondansetron over placebo. The new primary outcome measure comparing symptom improvement rates ensured that results were clinically meaningful and easily understandable. Marginally greater mean VAS reductions and rates of experiencing the desired treatment effect in the active drug groups are of debatable clinical value.

A randomized placebo-controlled trial of droperidol and ondansetron for treatment of adult emergency department patients with nausea: demonstration of a new outcome measure.

Introduction

Emergency department (ED) patients commonly suffer nausea and vomiting as part of their presenting symptom complex.[1] Effective treatment is desirable to alleviate patient distress and to reduce the potential for complications. Surveys report that ED patients with nausea expect to receive antiemetic drugs, and that ED doctors are willing to prescribe them.[2,3] ED-based trials, however, have failed to demonstrate superiority for commonly used antiemetic drugs over placebo.[4–7] Doubts have been expressed about these seemingly counter-intuitive findings,[8,9] and the difficulty of interpreting the main study results has been highlighted.[10,11]

From 2000 to the present time, ED-based antiemetic trials have used the visual analog scale (VAS) to rate symptom severity.[4–6,12–15] For the measurement and monitoring of nausea severity, the VAS has a number of advantages. Its reliability for discriminating between different amounts of described change has been validated,[16,17] it is sensitive for the detection of change and is easy for patients to use and understand.[18] The way in which severity is measured on the VAS, and the standard methods for analysis of VAS change are illustrated in Box 1. In antiemetic research, findings of superiority or equivalence have been based on the statistical significance of the difference in mean VAS change between treatment groups.[4–6,12,13] This has been the primary outcome measure used in all three ED-based placebo-controlled trials conducted to date.[4–6]

The primary objective of antiemetic treatment for ED patients with nausea is clinically significant symptom improvement during the ED episode of care. The primary outcome measure of any study must provide the best evidence with regard to the primary objective. The mean VAS change, however, does not provide specific information about the number of improved patients in a treatment group.[10] Recent research has demonstrated that a VAS change cut-off level reliably identifies improved patients; this enables symptom improvement rates to be compared between groups.[11] This would provide more direct evidence regarding the primary treatment objective than mean VAS change, but the utility of this approach has not yet been demonstrated in a prospective antiemetic trial. The theoretical basis for the method is illustrated in Box 1.

The aim of this study was to compare droperidol and ondansetron to placebo for the treatment of adult ED patients with nausea. The primary outcome was symptom improvement, which was defined using a VAS change cut-off level. The purpose of this new outcome measure was to more closely align the treatment outcome with the treatment objective. This was expected to better clarify the situation with regard to antiemetic drug effectiveness in the ED setting. Mean VAS change and patients' experiencing of the desired treatment effect were included as secondary outcomes.

Methods

Study design, setting and period

A triple blind, randomized, controlled trial was designed to demonstrate the superiority of two antiemetic drugs, droperidol and ondansetron, over placebo. The study was conducted at the

three EDs of Monash Health, Melbourne, Victoria, Australia. These are: Monash Medical Centre (tertiary referral hospital, ED annual census 79,000 patients), Dandenong Hospital (urban district hospital, ED annual census 72,000 patients), Casey Hospital (urban district hospital, ED annual census 67,000 patients). A convenience sample of eligible patients was recruited from 1 April 2017 to 10 November 2017. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000224325). Study conduct was approved by the Monash Health Human Research Ethics Committee (HREC).

Eligibility criteria

Inclusion: Patients aged 18 years or more, with nausea severity at recruitment of 4 or more (0 to 10 numerical rating scale), from any underlying cause.

Exclusion: Allergy to ondansetron or droperidol; use of an antiemetic drug in the previous 4 hours (Box 2); too unwell to participate for any reason (e.g. cardiovascular instability or altered mental state); contraindication to a normal saline infusion (e.g. fluid-restricted patients); Parkinson's disease or restless leg syndrome; current use of a dopamine antagonist medication (Box 2); cognitive impairment or language barrier compromising study understanding; purely motion related nausea; pregnant or breast feeding women; chemotherapy or radiotherapy induced nausea.

Outcome measures

Nausea severity was rated at baseline and 30-minutes post-treatment on a VAS, with change calculated as per previously published ED-based antiemetic trials. (Box 1)

A VAS change cut-off level was used to categorize patients as 'improved' or 'non-improved'. At the time of trial registration, based on the one relevant report available at the time,[11] the cut-off was planned to be -5 mm. This was altered to -8 mm due to the findings of a locally conducted pooled analysis of data from three nausea measurement studies which linked VAS and described change in a similar way.[3,11,17] This analysis found that the reliability for all cut-points between -5 mm and -9 mm was very similar, with -8 mm being the most accurate.

Study objectives

Primary: Between-group comparisons of the number (percentage) of patients with a measured VAS change of ≥ -8 mm.

Secondary: Between-group comparisons of: mean VAS change per group; number (percentage) of patients experiencing the desired treatment effect. Number (percentage) of patients requesting additional antiemetic drugs and adverse events are reported for each group. (Box 1)

Randomization, blinding and study drug preparation

Randomization and study drug preparation was performed in the independent Monash Clinical Trials Pharmacy. Study drugs appeared identical as four mL of clear fluid in a five mL syringe. Each syringe was labeled with a unique study identification number, the HREC study reference number and an expiry date. These were kept refrigerated and had a shelf-life of seven days. Prepared study drugs were delivered to each ED as required.

Study drugs

a) **Droperidol** (Droleptan®, Phebra Pty Ltd, Sydney, NSW, Australia). One half mL from the 2.5 mg/mL ampoule was diluted with 3.5 mL of 0.9% saline to make a total of 1.25 mg in 4 mL. b) **Ondansetron** (Ondansetron MYX, Mayne Pharma International Pty Ltd, Salisbury South, SA, Australia). Two of the 4 mg/mL ampoules remained undiluted to make a total of 8 mg in 4 mL.

c) **Placebo:** The syringe contained 4 mL of 0.9% sodium chloride.

Study drug choice: Droperidol 1.25 mg IV is the only antiemetic drug to have shown a statistically significant greater reduction in mean VAS rating in comparison with placebo.[4] Ondansetron is the most commonly used antiemetic in the ED setting;[2] the 8 mg IV dose was chosen as studies have reported 4 mg IV ondansetron to be equivalent with placebo.[5,6]

Recruitment and study procedure

Study education took place prior to, and throughout the study period. Attending ED clinical staff checked eligibility; patients could be recruited at any time of any day. Following informed consent, an IV infusion of 0.9% saline at a rate of 1000 mL over 4 hours was commenced. After recording the baseline VAS rating, the study drug was administered as a hand-delivered, two-minute IV infusion. At 30-minutes post-treatment, the second VAS rating was taken and the patient-centered efficacy question asked. The attending doctor completed the adverse event information. Regardless of recorded response, the patient was offered further antiemetic medication. If prescribed, ondansetron 8 mg IV was recommended, but final choice was at physician discretion. Recording of failure to recruit (e.g. exclusion criteria, patient declined) was encouraged.

157

158 **Data analysis**

159 Participant flow is reported using the Consort methodology; the analysis is intention to treat.
160 Baseline information of age, gender and initial severity are reported and compared between study
161 sites and treatment groups using Kruskal-Wallis, one-way ANOVA and chi square tests as
162 appropriate. Patients who were improved and those experiencing the desired effect are reported
163 as number (%), and compared using the chi square test. As distribution approximates normal,
164 VAS rating change is reported as mean mm with 95% confidence intervals (CI). Use of
165 additional medication and occurrence of adverse events are described.

166

167 Data were entered by one investigator (RM) into a secure database (Microsoft Excel 2007,
168 Microsoft Corporation, Mountain View, CA USA) at which time it was de-identified. A random
169 sample of 10% was checked for accuracy by another investigator (SC). Data were analyzed
170 using Stata Version 12.0 statistical software (Stata Corporation, College Station, Texas, USA).

171

172 **Sample Size**

173 This was informed by re-analysis of the raw data from one previous ED-based study, which
174 compared ondansetron (4 mg IV) with placebo.[6] VAS reduction of ≥ -8 mm was reported by
175 79% and 57% of patients respectively.[10] Replication of this result required a sample of 111 per
176 group to demonstrate superiority for ondansetron over placebo (alpha 0.05, beta 0.90). The
177 potential between-group difference of 22% (95% CI: 10 – 34) and number needed to treat (NNT)
178 of 5 (95% CI: 3 – 10), were considered clinically worthwhile. No corresponding information
179 was available for droperidol. To allow for a drop-out rate of up to 10%, the aim was to recruit

126 patients per group, for a total of 378. The secondary outcomes were not considered relevant for sample size calculation.

Interim analysis and sensitivity analysis

Due to ongoing concerns about the limited support for the calculated sample size, an interim analysis was performed after recruitment of 215 patients. Specialist statistical advice confirmed that there was no realistic prospect of demonstrating superiority for the active drugs over placebo by continuing recruitment to the planned sample size. A sensitivity analysis was conducted: additional potential treatment successes ('best imaginable' for the active drugs and 'lowest imaginable' for placebo) were calculated as follows: (remaining number per group to reach n = 111) x (upper 95% confidence limit for active drugs or lower 95% confidence limit for placebo). This number was added to the actual number of improved patients in each group at the time of the analysis. 'Best imaginable' between-group differences were calculated from these theoretical treatment success rates.

Results

Characteristics of the study subjects

A total of 215 patients were recruited, 145 (68%) at Dandenong Hospital, 50 (23%) at Monash Medical Centre and 20 (9%) at Casey Hospital. The median age of all participants was 44 years (range 18 – 91), 40% were male and the mean baseline VAS rating was 61 mm (95% CI: 58 – 65). There were no significant differences in baseline characteristics between sites. Patient flow is detailed in Figure 1. Of the total, 195 (91%) fell in to nine diagnostic categories, the most frequent being infective gastroenteritis (42, 20%). (Table 1)

Of the 215 patients, 73 (34%), 71 (33%) and 71 (33%) received droperidol, ondansetron and placebo, respectively. There were no significant differences in baseline characteristics between groups. (Table 2) The median time between study drug administration and the second VAS rating was 30 minutes (IQR: 30 – 35).

Main results

Primary outcome

Numbers with VAS change ≥ -8 mm for droperidol, ondansetron and placebo were 55/73 (75%, 95% CI: 64 - 85), 57/71 (80%, 95% CI: 69 - 89) and 54/71 (76%, 95% CI: 64 - 85), respectively ($p = 0.75$, Pearson chi square). The between-group differences and NNT are shown in Table 3.

Secondary outcomes

The mean VAS changes for the droperidol, ondansetron and placebo groups were -29 mm (95% CI: -36 to -23), -34 mm (95% CI: -41 to -28) and -24 mm (95% CI: -29 to -19), respectively. The between-group differences were: droperidol-placebo = 5 mm (95% CI: -3 to 13); ondansetron-droperidol = 5 mm (95% CI: -4 to 14); ondansetron-placebo = 10 mm (95% CI: 2 to 18). Individual patient VAS changes (mm) and experiencing of the desired treatment effect are illustrated in Figure 2. Treatment having the desired effect was reported for droperidol, ondansetron and placebo by 56/73 (77%, 95% CI: 65 – 86), 52/71 (73%, 95% CI: 61 – 83) and 42/71 (59%, 95% CI: 47 – 71), respectively. The between-group differences and NNT are shown in Table 4.

Additional medication and adverse events

Additional antiemetic medication was requested by 11/73 (15%, 95% CI: 8 – 25), 16/71 (23%, 95% CI: 13 – 34) and 21/71 (30%, 95% CI: 19 – 42), respectively. Of the 48 who requested extra medication, 43 (90%) had not experienced the desired treatment effect.

For the droperidol, ondansetron and placebo groups, an abnormal level of alertness was noted for 31/73 (42%, 95% CI: 31 – 55), 11/71 (15%, 95% CI: 8 - 26) and 14/71 (20%, 95% CI: 11 - 31), respectively. The full range of agitation-sedation ratings are shown in Figure 3. Headache was reported by 12/73 (16%), 13/71 (18%) and 20/71 (28%), respectively. Dizziness was reported by 11/73 (15%), 5/71 (7%) and 11/71 (15%), respectively.

Sensitivity analysis and quality control

Calculations for the sensitivity analysis are shown in Table 5. The greatest potentially conceivable difference in the symptom improvement rate was between ondansetron and placebo: 12% (95% CI: 1 - 22).

VAS change was re-measured from 22 randomly selected case report forms. Of these, the measured VAS change differed by 0-1 mm for 19 (87%), and by 2-3 mm for three (13%).

Non-enrolled patients

Data were collected on 159 non-enrolled patients who met inclusion criteria. Median age was 49 years (IQR: 32 – 67) and 124 (78%) were female. Of the 159, 106 (67%) had exclusion criteria. The most frequent were: 43 (41%) received an antiemetic drug prior to ED arrival, 21 (20%) had

cognitive impairment and 16 (15%) were pregnant. Of the 53 without exclusion criteria, 39 (74%) declined participation; the remaining 14 were not recruited for a variety of reasons including ED activity at the time and lack of an available study drug syringe.

Discussion

Main findings with regard to treatment effectiveness:

For a population of adult ED patients with nausea from any underlying cause, this study found post-treatment symptom improvement rates of 75%, 80% and 76% for the droperidol, ondansetron and placebo groups respectively. The between-group differences of 4% to 5% were not statistically significant; the NNT of 20 to 25 were not clinically worthwhile. This is not to say that the treatments are equally effective. This was not designed as an equivalence trial, which would be unusual for a placebo-controlled study. It should also be noted that in this setting, placebo does not equate with 'no treatment'. Patients are still being actively managed for the primary condition to which their nausea relates. For the secondary outcomes, the mean VAS changes were -29 mm, -34 mm and -24 mm for the droperidol, ondansetron and placebo groups respectively. The percentages of patients who experienced the desired treatment effect were 77%, 73% and 59% respectively. The clinical value of the 14% to 18% between-group differences and associated NNT of six to seven for this outcome is debatable.

Why a new outcome measure? What was wrong with the old one?

This is the first ED-based antiemetic trial to use a VAS change cut-off level as the primary outcome measure. The new measure was employed as recent literature suggested it would provide better evidence with regard to the primary treatment objective than the traditionally used

between-group comparisons of mean VAS change.[10,11] As the latter measure has been used in ED-based antiemetic trials for almost twenty years, some discussion of its limitations is warranted.

This requires understanding of three important properties of the VAS, which have been demonstrated in nausea measurement research.[16,17] Firstly, the distribution of VAS rating change approximates normal. Secondly, the amounts of VAS change reported when symptoms are described as being either 'the same', 'a little less', or 'a lot less' are significantly different from each other.[16,17] (Box 1) The mean VAS change when symptoms become 'a little less' is referred to as the 'minimum clinically significant difference' (MCSD).[16,17] Thirdly, the amounts of VAS change which equate with symptoms being 'a little less' or 'a lot less' significantly differ depending on whether initial symptoms are 'mild', 'moderate' or 'severe'.[17]

The difficulties of interpreting group mean VAS change are best illustrated using an example. Figure 4 shows four hypothetical treatment groups, A, B, C and D. The mean VAS change for groups A and B is identical at -20 mm. Despite this, they are surprisingly dissimilar with regard to the number of improved patients. The same is the case for groups C and D, which both have a group mean VAS change of -35 mm. This type of difference in the VAS distribution occurs when the severity mix of the populations are not the same. Perhaps more importantly, Figure 4 also shows that the difference in mean VAS change of -15 mm between groups A and C is likely to be statistically significant, even though all patients in both groups are improved to some degree. By contrast, the identical -15 mm difference between groups B and D will not be statistically significant, although clearly more patients in group B are unimproved.

To relate this to real data, the seven ED-based antiemetic studies published from 2000 to 2014 reported mean VAS changes of between -22 mm and -41 mm for sixteen of the nineteen different treatment groups.[4–6,12–15] As these changes exceed the MCSD, it can be inferred that most patients in all groups will have improved, but precise numbers are unknown and cannot be directly compared. Regardless of statistical significance, it is not possible to know what, if any, clinically significant differences exist between two groups with mean VAS changes in this range.[10]

Why does the new outcome measure work?

Nausea measurement research has also demonstrated that when symptoms remain 'the same', mean VAS changes are tightly concentrated around zero and are not influenced by initial severity.[11,16,17] The reported upper 95% confidence limits of the VAS change vary little between studies, being between about -5 mm and -9 mm.[11,16,17] This means that when VAS reductions exceed this amount, symptoms will almost certainly be improved.(Box 1) Recent research has confirmed that VAS change cut-offs in this range have a sensitivity and positive predictive value of over 90% for identification of patients with symptom improvement.[11] This is only a minor variation on the concept of the MCSD, as it equates noticeable change with symptoms no longer being 'the same' rather than having become 'a little less'.

Is improvement 'clinically significant' if symptoms are only no longer 'the same'?

Both the VAS change cut-off level and the MCSD assume that symptom improvement to any degree is clinically significant.[11,16,17] Since improvement may be viewed as beneficial, this

remains a reasonable primary outcome. However, a recent survey of ED patients with nausea reported that the desired effect of treatment was for symptoms to become 'a lot less'.[3] For this reason, experiencing the desired treatment effect was included as a secondary outcome in this study. It was found that non-significantly greater numbers in the active drug groups (77% and 73% for droperidol and ondansetron) did report this outcome in comparison with placebo (59%). This may seem at odds with the results for symptom improvement, but it must be remembered that these outcomes relate to different amounts of symptom change. It may be inferred that although similar numbers of patients were improved, relatively more in the active drug groups felt that symptoms were 'a lot less'. This is supported by two of the other secondary outcomes. The group mean VAS changes of -29 mm and -34 mm for droperidol and ondansetron were modestly greater than the -24 mm for placebo. The requests for additional medication by 15% and 23% in the droperidol and ondansetron groups were slightly lower than the 30% in the placebo group. The absolute differences of 14% to 18% and NNT of six to seven for experiencing the desired effect are both clinically meaningful and easy to understand. This is not to say that they are clinically worthwhile, but there is now an opportunity for these effect sizes to be balanced against other factors such as drug costs and side-effects when making individual treatment recommendations. For the drugs used in this study, the costs are low and the reasonably minor adverse effects did not require any treatment.

How do these study results compare with the previous literature?

Although the primary outcome measure used in this study was different, the finding remains generally consistent with the body of previous research on the topic.[4–7] Ever since the first ED-based, placebo-controlled antiemetic trial was published in 2006,[4] there has been a consistent

lack of support for the effectiveness of antiemetic drugs in the ED setting.[5–7,15] In the past, a number of reasons have been proposed in the literature as to why the multiple study findings might be erroneous.[8,9] The difficulty in accepting that antiemetic drugs may offer little for ED patients might stem from the decades of apparent support for their effectiveness in the post-operative and oncology settings. In those fields, studies have consistently demonstrated that the prophylactic administration of antiemetic drugs reduces the incidence of post-stimulus (anaesthetic or chemotherapy) nausea and vomiting.[19–23] Interestingly, however, when nausea does develop, difference in severity has not been demonstrated between treatment groups.[22,24] Perhaps antiemetic drugs are more effective for prevention than they are for cure.

What does this mean for ED patients with nausea?

The purpose of using the new primary outcome measure in this study was to present results which related directly to the primary treatment objective in an easily understandable and clinically meaningful way.[10] It was expected that the added clarity concerning relative treatment effectiveness would be beneficial for both treating doctors and patients. It is not useful, for example, to inform a patient that without antiemetic drug treatment their nausea severity is likely to improve by about -24 mm on the VAS, but that on average, droperidol might reduce it by -29 mm. The following seems far more helpful: 'Whether or not you have an anti-nausea drug, there is a 75 to 80% chance that your nausea will ease as your underlying condition is treated. An anti-nausea drug might give a little extra benefit to about one-in-seven of those who do improve. There are some people, however, whose nausea will not settle no matter what we do. The anti-nausea drugs do have some side-effects, but these are usually fairly mild.'

Nausea management surveys already suggest that for mild nausea, most ED doctors do not routinely prescribe antiemetic drugs [1] and most patients do not believe they are necessary.[2,3] Given this, the findings of this study seem unlikely to significantly impact on current ED practices. It also must be remembered that the ED-based antiemetic studies to date have only examined the response to a single administration of one drug at 30 or 60-minutes post-treatment. As a consequence, further ED-based antiemetic research remains important. The response to either higher drug doses, repeated dosages over a longer time period, or the concurrent delivery of antiemetic drugs from different groups may be quite different. Characterizing treatment responders versus non-responders could also be of value and the need for condition-specific research has never been entirely discounted.[25]

Limitations

The original sample size calculation for the study was based on 'anticipated' symptom improvement rates for ondansetron and placebo of 79% and 57%. As this was drawn from a post-hoc analysis of only one study,[6,10] doubts about the accuracy of the estimate persisted. For this reason, conduct of an interim analysis was deemed prudent, and in retrospect, not pre-planning this was an error. At that time, it was found that the 'actual' and 'anticipated' symptom improvement rates for the placebo group were markedly different (76% versus 57%). Also, the mean VAS change of -29 mm for droperidol was much lower than the -55 mm previously reported.[4] The degree of these differences is probably not surprising given the known variation in mean VAS changes for the same treatment regimens in different ED-based studies. For example, two different studies reported post-treatment mean VAS changes for ondansetron (4

mg IV) of -34 mm and -22 mm;[5,13] two other studies reported mean VAS changes for placebo of -39 mm and -16 mm.[4,5] This is despite patient populations appearing otherwise similar.

The conclusion from the interim analysis was that there was no realistic prospect of demonstrating superiority for the active drug groups over placebo by continuing recruitment as initially planned. Early cessation following interim analysis may lead to a study becoming 'under-powered' but that is clearly not the issue in this case. The size of the mismatch between 'actual' and 'anticipated' results meant the study was effectively 'under-powered' from the outset, in which case, continuation to the originally planned sample size was futile. Interestingly, one of the three previous ED-based placebo-controlled antiemetic trials was also terminated early when 'actual' and 'anticipated' mean VAS changes significantly differed.[5] Researchers can only make best estimates based on the information available, but for the reasons given, this has proved surprisingly difficult in ED-based antiemetic trials.[4,5]

Other potential limitations include that the convenience sample may not be representative of all ED patients with nausea. Although incomplete, monitoring of reasons for non-recruitment was attempted. Pre-hospital antiemetic administration was the most frequent reason for exclusion. This may have led to recruitment of fewer patients with severe nausea; the potential impact of this on results is unknown. The study instructions dictated that all patients receive 250 mL of IV fluid during the 30-minute study period, but exact amounts may have varied. Research on the use of a VAS change cut-off level for the detection of symptom improvement is somewhat limited. Validation in different populations is still required, but the theoretical support for its

reliability from the body of nausea measurement research is reassuring.[11,16,17] A quality assurance check suggested that study measurements were sufficiently accurate.

Conclusions

For adult ED patients with nausea, this study did not demonstrate superiority for droperidol 1.25 mg IV or ondansetron 8 mg IV in comparison with placebo. This was based on the similar rates of symptom improvement between groups, defined using a new primary outcome measure. This measure appeared to deliver results in a format which was clinically meaningful and easy to understand. The marginally greater mean VAS reductions and rates of experiencing the desired treatment effect in the active drug groups may aid treatment decision making in individual cases.

Acknowledgements

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Box 1. VAS measurements: standard and theoretical methods for determining significant change.

VAS: 100 mm line on which patients mark their response with a vertical line. The rating is measured in mm from the left end of the line. An example is shown:

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No **nausea** (40 mm post-treatment) (80 mm baseline) **Worst nausea imaginable**

Measured VAS change is calculated here as: 40 – 80 = -40 mm.

The use of the negative number is a conceptual aid, indicating symptom reduction.

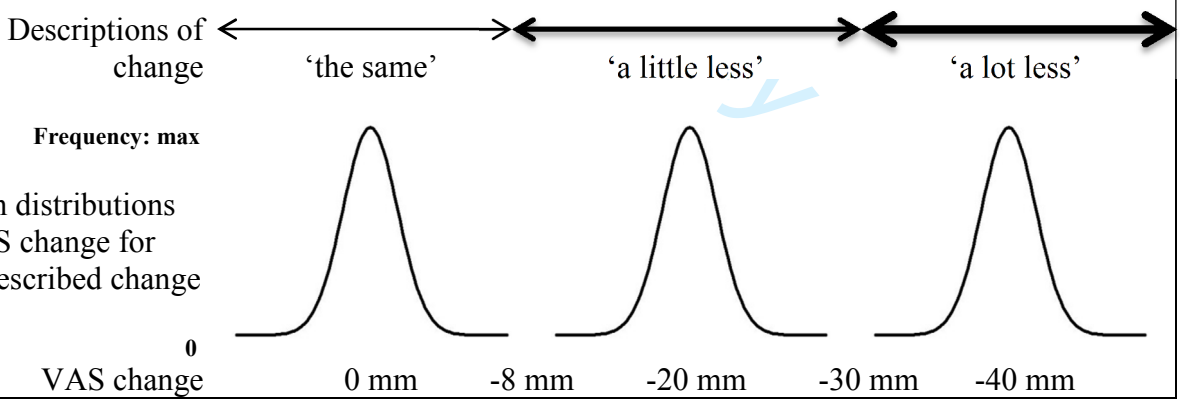
Standard analysis and reporting:

1) Post-treatment change is measured (usually at 30-minutes)

2) Mean VAS change for each treatment group is calculated from the individual patient data and reported with standard deviation or 95% confidence interval

3) Between-group comparisons of mean VAS change are performed using t-tests or one-way ANOVA.

Theoretical basis for reliability of a VAS change cut-off level of about -8 mm for detection of symptom improvement:



VAS = Visual analog scale; ANOVA = analysis of variance.

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552 **Box 2. Study measures and exclusion criteria.**
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Patient-centered efficacy. The patient responded to the following question: "The drug I received had the desired effect for me." Yes or No
Richmond Agitation-Sedation Scale (RASS): The assessing doctor rates as follows from observation, with verbal or physical stimulation as required: +4 (Combative); +3 (Very agitated); +2 (Agitated); +1 (Restless); 0 (Alert and calm); -1 (Drowsy); -2 (Light sedation); -3 (Moderate sedation); -4 (Deep sedation); -5 (Unrousable)
Severity of headache and dizziness, self-reported by the patient using the ordinal scale: None Mild Moderate Severe
Exclusion for prior (previous 4 hours) antiemetic use included: ondansetron, droperidol, metoclopramide, promethazine, chlorpromazine, prochlorperazine and any steroid medication.
Exclusion for regular use of dopamine antagonist medications included: amisulpride, chlorpromazine, clopenthixol or flupenthixol, domperidone, haloperidol, paliperidone, quetiapine, risperidone, thioridazine.

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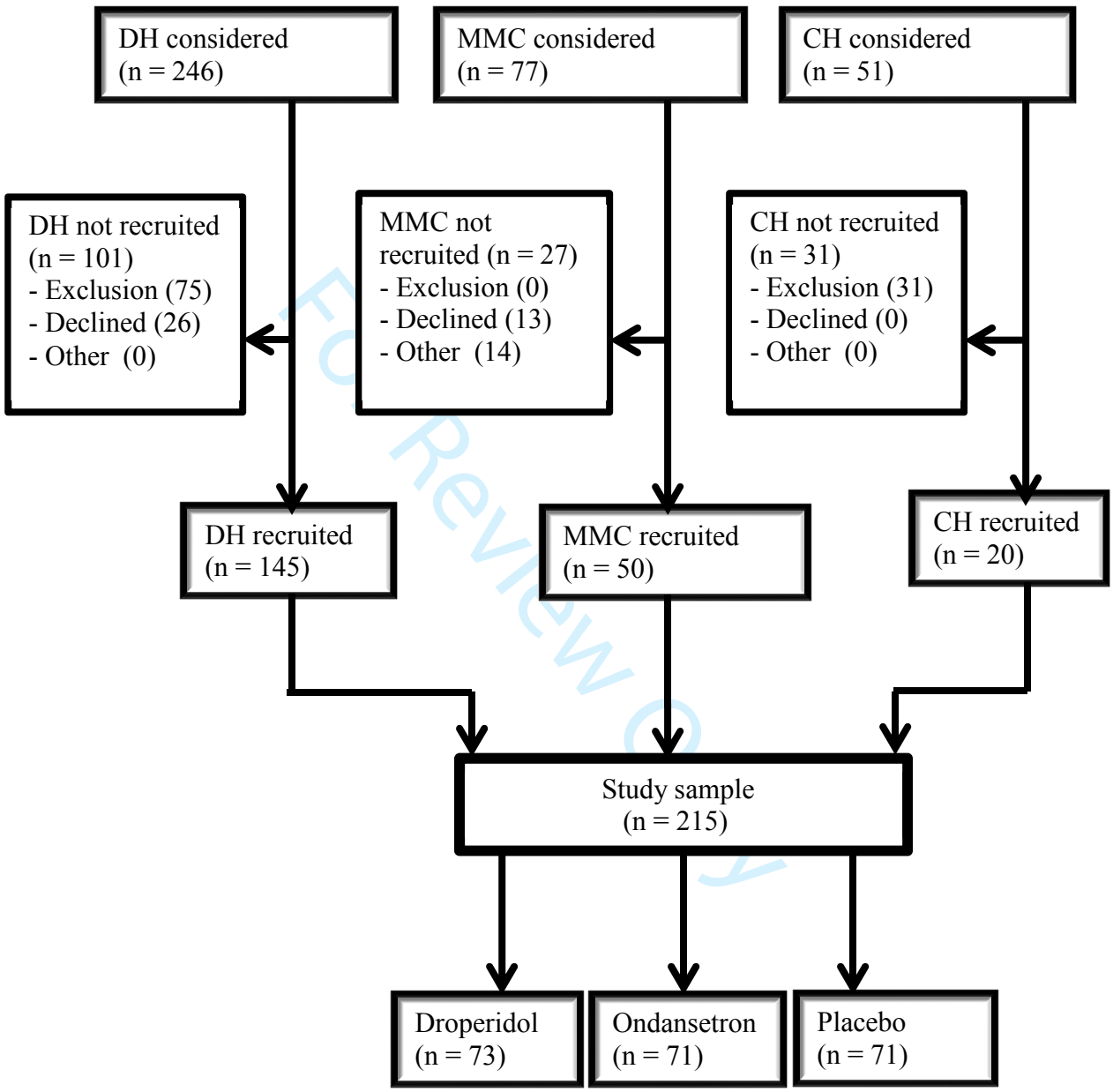
Figure 1. Patient flow diagram.

DH = Dandenong Hospital, MMC = Monash Medical Centre, CH = Casey Hospital



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591 **Table 1. Most frequent diagnostic groups (n > 6).**

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Diagnostic group	Frequency: n (%)
Gastroenteritis (presumed infective)	42 (20%)
Infective illness (excluding gastroenteritis)	40 (19%)
Abdominal pain (unspecified)	29 (13%)
Abdominal pain (condition specified)	28 (13%)
Opioid related	17 (8%)
Gastritis (unspecified type)	13 (6%)
Drug related (including alcohol)	12 (6%)
Renal colic	7 (3%)
Headache	7 (3%)
Other (individual frequencies of < 7)	20 (9%)

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609 **Table 2. Baseline variables: total population and comparison between**
610 **treatment groups.**

Variable	Total (n = 215)	Droperidol (n = 73)	Ondansetron (n = 71)	Placebo (n = 71)	P value
Age: median years (IQR)	44 (32 – 60)	42 (31 – 61)	47 (36 – 63)	44 (26 – 58)	0.23[a]
Male sex: n (%) [95% CI]	87 (40%) [34 – 47]	30 (41%) [30 – 53]	26 (37%) [25 – 49]	31 (44%) [32 – 56]	0.69[b]
Baseline VAS: mean mm (95% CI)	61 mm (58 – 65)	61 mm (56 – 66)	61 mm (56 – 65)	62 mm (58 – 66)	0.91[c]

611 a= Kruskal-Wallis test; b = Pearson chi square test; c = one-way ANOVA

612 IQR = interquartile range; CI = confidence interval

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628 **Table 3. Symptom improvement: difference and NNT for each treatment pair.**

Comparison	Between-group difference in symptom improvement: % [95% CI]	NNT†
Ondansetron versus Droperidol	5% [-9 to 19]	20
Ondansetron versus Placebo	4% [-10 to 18]	25
Droperidol versus Placebo	-1% [-15 to 13)	99*

629 * Favoring Placebo; NNT = Number needed to treat; CI = confidence interval

630 † 95% CI for NNT are not reliable for non-significant differences

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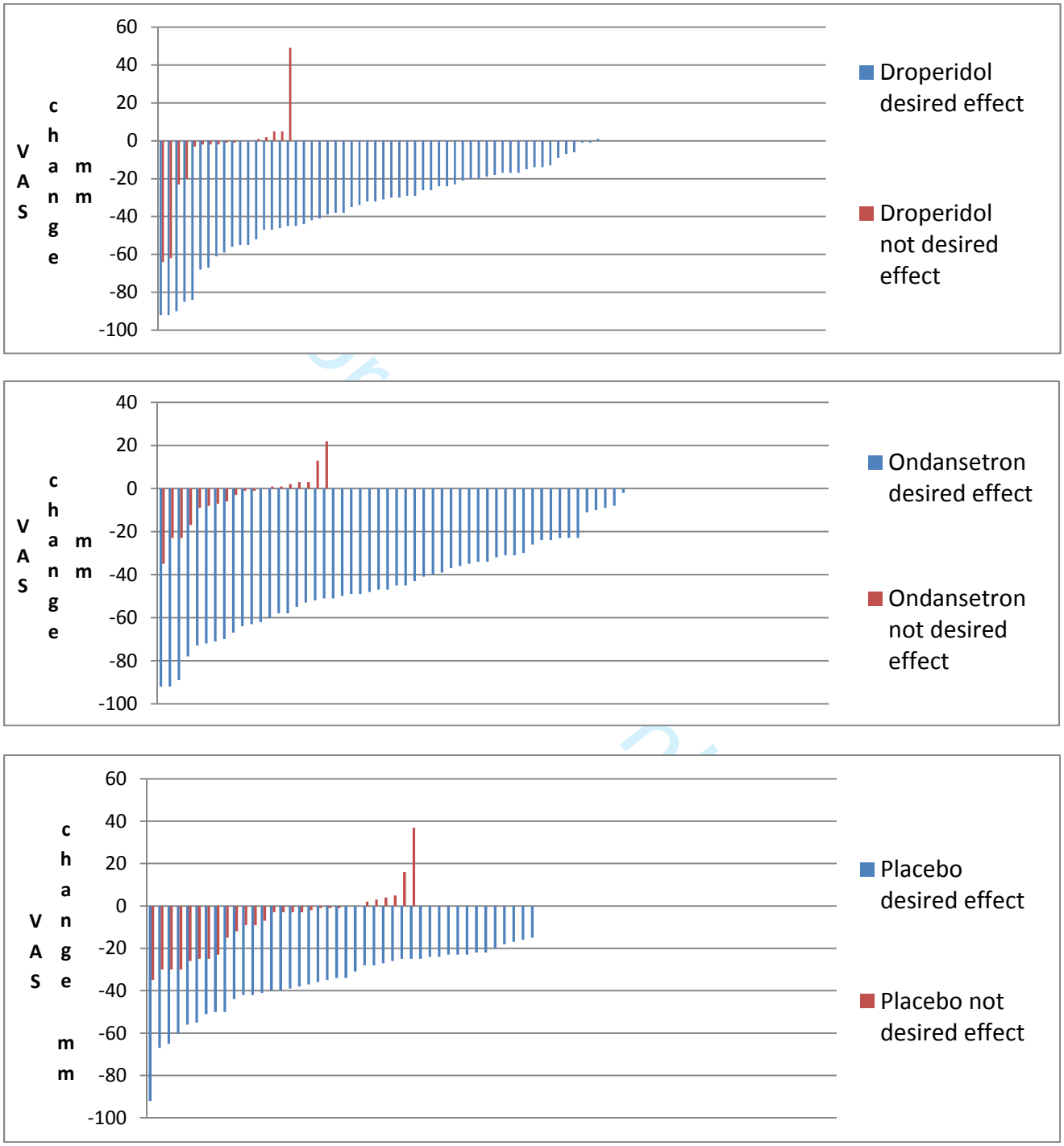
Figure 2. VAS change for individual patients in each group when desired effect present or not.



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657 **Table 4. Desired effect: difference and NNT for each treatment pair.**

Desired effect	Between-group difference: % (95% CI)	NNT† (95% CI)
Droperidol versus Ondansetron	4% (-10 to 18)	25
Droperidol versus Placebo	18% (3 to 33)	5 (3 to 33)
Ondansetron versus Placebo	14% (-1 to 29)	7

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659 NNT = Number Needed to Treat; CI = confidence interval;
660 † 95% CI for NNT are not reliable for non-significant differences
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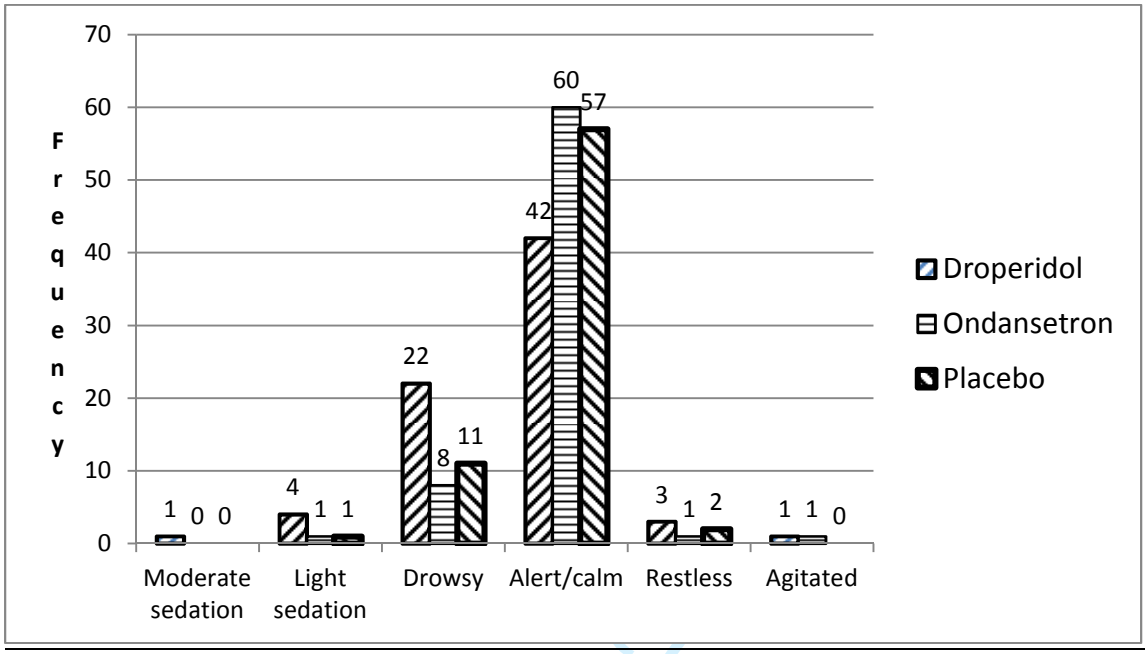
677 **Figure 3. Level of alertness: RASS ratings for each treatment group.**

678 RASS = Richmond Agitation and Sedation Scale.



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694 **Table 5. Sensitivity analysis: hypothetical best imaginable case for superiority of**
695 **active drugs over placebo.**

Analysis	Treatment	Treatment success - actual	Potential success in additional patients to n = 111	Treatment success - potential
Best imaginable case	Droperidol: n (%) [95% CI]	55/73 (75%) [64 – **85**]	38 patients x **0.85** = 32	87/111 (79%) [71 – 87]
	Ondansetron: n (%) [95% CI]	57/71 (80%) [69 – **89**]	40 patients x **0.89** = 36	93/111 (84%) [77 – 91]
Worst imaginable case	Placebo: n (%) [95% CI]	54/71 (76%) [**64** – 85]	40 patients x **0.64** = 26	80/111 (72%) [64 – 80]
Treatment pair			Best imaginable between-group difference: % (95% CI)	
Ondansetron versus Droperidol			5% (-5 to 15)	
Ondansetron versus Placebo			12% (1 to 22)	
Droperidol versus Placebo			7% (-4 to 18)	

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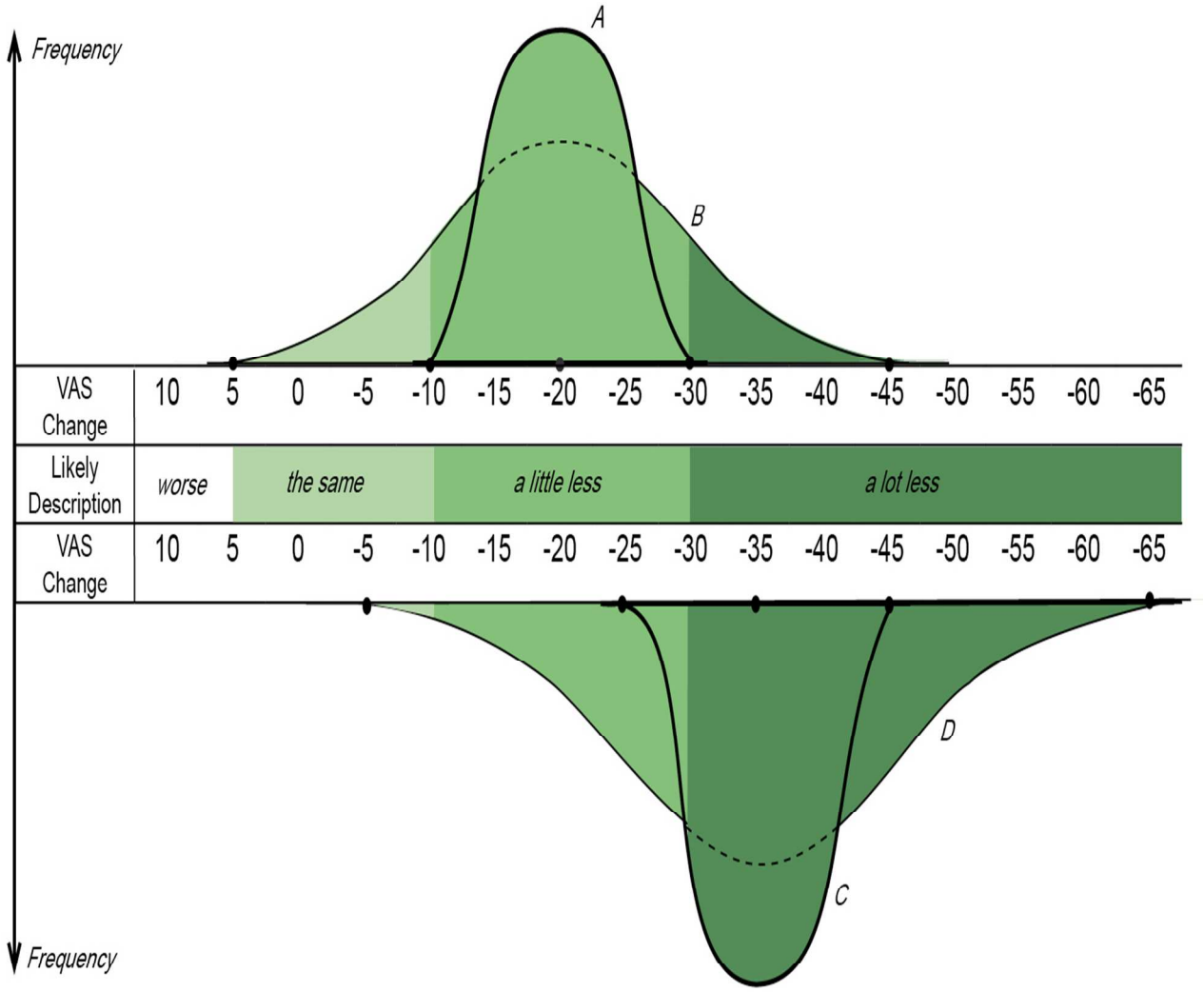
712 **Figure 4. Difficulties of determining clinical meaning from group mean VAS change and**
713 **between-group differences in VAS change.**

714 **Groups A and B have identical mean VAS changes of about -20 mm; groups C and D have**
715 **identical mean VAS changes of about -35 mm.**



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15.3 Brief discussion and implications for further ED-based research.

For reasons previously outlined, the new primary outcome measure equated symptom improvement with a VAS change of -8 mm or more. It could be inferred from the group mean VAS changes of -24 mm to -34 mm that most people in each group would be improved, but exact numbers could not be known. It was now possible to demonstrate that the symptom improvement rates for all groups were between 75% and 80%, and that between-group differences were neither statistically significant nor clinically worthwhile. This is both easy to understand and clinically meaningful with regard to the primary treatment objective.

The mean VAS changes were generally consistent with those of previous studies. The differences were not statistically significant between groups. Although this might be attributed to type 2 error from under-powering, the study was not designed to seek a statistically significant result for what was now a secondary outcome measure. From the other secondary outcome, it could be seen that marginally more patients in the droperidol and ondansetron groups experienced the desired treatment effect (77% and 73%), in comparison with placebo (59%). Although total symptom improvement rates were the same in all groups, it appears that relatively more in the active drug groups felt that symptoms were 'a lot less'. This is consistent with the mean VAS changes having been slightly higher in the droperidol and ondansetron drug groups, but the clinical value of these differences is debatable.

These greater insights into relative treatment effectiveness support that further ED-based antiemetic research is warranted. Future studies might evaluate the use of higher drug dosages, repeated doses over a longer period, or the concurrent administration of antiemetic agents from different drug groups. Attempting to characterize treatment responders versus non-responders might also be of use.

CHAPTER 16. Final summary and conclusions.

16.1 Introduction.

Nausea and vomiting are common symptoms which occur in many different clinical settings. The distress experienced by patients,[4,7,9] the potential for direct medical complications,[14,18,20,24] and the economic burden imposed by these symptoms,[8,25,29] all make effective treatment desirable.

When comparing potential antiemetic treatments in RCTs, the primary outcome measure should provide the best evidence with regard to the primary objective. For ED patients with nausea, the primary treatment objective is clinically significant symptom improvement. The traditional primary outcome measure, a between-group comparison of mean VAS change, provided only indirect and imprecise information with regard to the likely between-group differences in symptom improvement rates.

The primary objective of this series of related research projects was to identify and develop improved outcome measures for ED-based antiemetic trials. The purpose was to ensure that presented ED-based antiemetic study results relate directly to the primary treatment objective, and can be presented in an easily understandable and clinically meaningful way.

16.2 Key results.

The key study results and the implications of these have been summarized in each of the preceding chapters, alongside the full version of each published paper. These are summarized together in Table 16-1.

16.3 Brief summary of findings from the related research projects.

Again, the aim of this series of research projects was to identify, test and demonstrate the reliability of alternate outcome measures which would improve the reporting of findings from ED-based antiemetic RCTs. This aim was met. It should be remembered that the aim of this research was not to definitively answer the question as to whether or not antiemetic drugs are effective for the treatment of nausea in adult ED patients. For this question to be answered, further ED-based research on antiemetic drug efficacy is still required. The underlying issue which led to the undertaking of this research was that the primary outcome measure being used in ED-based antiemetic trials did not appear to provide the best evidence with regard to the primary treatment objective.

Table 16-1. Brief summary of key aspects of the design, results and implications of each study in the series of research.

Study	Main aim	Key results	Implications
Survey of Australasian emergency physicians.	To identify the most commonly used antiemetic drugs in Australian EDs.	Metoclopramide used first line by 87%. Ondansetron used second line by 51%.	Metoclopramide and ondansetron chosen for first antiemetic RCT.
Therapeutic RCT as a framework to explore outcome measures.	Comparison of metoclopramide 20 mg IV and ondansetron 4 mg IV with placebo.	Mean VAS changes of -27 mm, -28 mm and -23 mm respectively.	Treatments equivalent using this 'traditional' primary outcome measure.
Nausea measurement and monitoring study. (Concurrent with RCT.)	Exploration of relationship between VAS and ordinal description of change scale.	VAS change cut-off of -5 mm had sensitivity and positive predictive value of over 90% for detection of symptom improvement.	Identified outcome based on reliability of VAS change for identification of improved patients.
Outcome measure perspective article.	To highlight the issue of outcome measures used in ED-based antiemetic RCTs.	Limitations of mean VAS change and the potential for using a VAS change cut-off as an outcome measure were broadly discussed.	Raised awareness of the issues; raised possibility of also using percentage VAS change to identify symptom improvement.
Survey of adult ED patients with nausea.	To describe patient attitudes towards and expectations of antiemetic drug treatment.	For satisfaction with treatment, 87% wanted symptoms to be at least 'a lot less'; only 13% satisfied with 'a little less'.	The beneficial treatment effect (improvement) and the desired effect (symptoms 'a lot less') are not the same.
Nausea measurement validation study (pooled analysis of individual patient data from multiple similar studies)	ROC curve analyses to test accuracy of VAS change for detection of symptom improvement and symptoms becoming 'a lot less'.	Detection of symptom improvement good to excellent: ROC AUC 0.87. Best cut-off level -8 mm. Performance only fair to good for symptoms becoming 'a lot less': ROC AUC 0.79.	VAS change accurately detects symptom improvement. Experiencing desired effect best assessed through direct questioning.
Therapeutic RCT using the new primary outcome measure.	Comparison of droperidol 1.25 mg and ondansetron 8 mg with placebo. VAS change cut-off defining symptom improvement as primary outcome measure. Mean VAS change and experiencing the desired treatment effect secondary.	Improvement rates 75%, 80% and 76% respectively. Between-group differences of 4-5%, NNT 20-25. Desired effect rates 77%, 73% and 59%. Between-group differences of 14 – 18%, NNT of 6 – 7. Mean VAS changes -29 mm, -34 mm and -24 mm respectively.	Main results directly relate to the primary treatment objective. No difference in primary outcome. Secondary outcome results may aid informed treatment decision-making. Further research in the field seems warranted.

For the first ED-based antiemetic RCT, conducted in 2000, Ernst (2000) chose a between-group comparison of mean VAS change as the primary outcome measure.[76] There was no ED nausea measurement literature to support this choice, but it was the first study of its type. Perhaps due to the lack of any obviously superior alternative, the same primary outcome measure was used in all following ED-based antiemetic studies conducted up to 2014.[35–40] The difficulties, however, of interpreting group mean VAS changes and the likely clinical significance of between-group differences has been illustrated in some detail in Chapter 8 of this thesis.

Once again, the primary objective of antiemetic treatment in the ED is clinically significant symptom improvement. A primary outcome measure should provide the best evidence with regard to the primary treatment objective. To fulfil this criterion, it seemed most important to ensure that study patients who experienced clinically significant symptom improvement could be reliably identified. If this was possible, direct comparisons of symptom improvement rates could be made between treatment groups. From this, the relative effectiveness of different antiemetic drug regimens, with regard to the primary treatment objective, would be more readily apparent.

For reasons outlined in Chapter 8 of this thesis, continued use of the VAS to measure and monitor change in severity had a number of advantages. Given the known relationship between the ordinal description of change scale and the VAS, it seemed possible that amounts of VAS change might reliably identify patients with symptom improvement. The first measurement study in this series of research projects (Chapter 11) suggested that a VAS change cut-off level could accurately discriminate between improved and non-improved patients. This was subsequently confirmed by performing ROC curve analyses on a larger population (Chapter 14). The best VAS change cut-off level was shown to be -8 mm. This finding is not surprising given that this approximates the upper 95% confidence limit of the VAS range when patients describe symptoms as being ‘the same’. It follows that patients with VAS changes in excess of -8 mm would almost certainly be improved (‘a little less’ or ‘a lot less’).

This does assume that symptom improvement of any amount is clinically significant. As improvement is beneficial, this remains reasonable as a primary outcome. However, the patient survey conducted as part of this series of research, did find that the desired treatment effect was for symptoms to be ‘a lot less’. Unfortunately, for reasons previously presented (Chapter 14), the VAS was not so reliable for identifying patients who had improved to this degree. As such, experiencing

of the desired treatment effect was felt best assessed through direct questioning as a secondary outcome measure.

The purpose of conducting the second RCT, which completed this series of research projects, was to determine if use of the newly defined outcome measures did improve reporting of the study results. The aim was that their relationship to the primary treatment objective was clear, that they were clinically meaningful and easy to understand. The primary outcome measure was a between-group comparison of symptom improvement rates, this being defined as a VAS change of -8 mm or more. Secondary outcomes were a comparison of the numbers experiencing the desired treatment effect, and the group mean VAS changes with between-group comparisons. Although the latter measures, previously used for the primary outcome, do not provide the best evidence with regard to the primary treatment objective, they still contribute useful information on relative treatment effectiveness. The results of the second RCT [82] are briefly discussed here, in order to demonstrate how the overall aim of the related research projects has been met.

Application of the VAS change cut-off level of -8 mm identified that symptom improvement occurred in 75%, 80% and 76% of the patients in the droperidol, ondansetron and placebo groups respectively. The between-group differences of 4 to 5% and the NNT of 20 to 25 were neither statistically significant nor clinically worthwhile. From the results of previous ED-based studies, it had only been possible to infer that the majority of patients in all treatment groups would have been improved to some degree. For the first time, it could more specifically be said that 75 to 80% of patients in each group had experienced clinically significant symptom improvement. This adequately fulfils the criterion that the primary outcome measure should provide the best evidence with regard to the primary treatment objective. In addition, the symptom improvement rates, between-group differences and NNT are all clinically meaningful and easy to understand. As a side-issue, the study was terminated early, largely because the symptom improvement rate for the placebo group of 76% was markedly different to the 57% which had been anticipated from the post-hoc analysis of the first RCT. In retrospect, such a difference may not be so surprising, given the known between-study variations in mean VAS change for the same drug regimens (Figure 6-1), but it remains difficult to explain.

For the secondary outcomes, the desired treatment effect was experienced by 77%, 73% and 59% of patients in the droperidol, ondansetron and placebo groups respectively. This may seem at odds with the results for symptom improvement, but it must be remembered that these outcomes relate

to different amounts of symptom change. For most patients, the desired treatment effect is for symptoms to become 'a lot less'. As a consequence, these results imply that although similar numbers of patients were improved, relatively more in the active drug groups felt that symptoms were 'a lot less'. This is supported by the group mean VAS changes of -29 mm and -34 mm for droperidol and ondansetron being slightly greater than the -24 mm for placebo. In previous studies, regardless of statistical significance, the clinical meaning of these differences in mean VAS change had been unclear. Now it can be seen that they were just sufficiently higher in the active drug groups for more patients to have experienced the desired treatment effect. As opposed to between-group differences in mean VAS change, the absolute differences of 14% to 18% and the NNT of 6 to 7 for experiencing of the desired treatment effect are both clinically meaningful and easy to understand. This is not to say that they are clinically worthwhile, but there is now an opportunity for these effect sizes to be balanced against other factors such as drug costs and side-effects when making individual treatment recommendations.

16.4 Limitations.

The limitations of each individual study which comprise this series of research projects are detailed within those papers. It is worth mentioning specifically that the studies only involved adult ED patients who received IV antiemetic medications. The ED management of children with vomiting more frequently involves oral medication and the measurement tools used to assess severity and change are necessarily different. Although detailed in Chapters 11 and 14, it should also be remembered that not all patients with a VAS change of -8 mm or more would report symptom improvement. It is because the false positives and negatives are well-balanced that the number beyond the cut-off accurately reflects the number of patients who do have symptom improvement.

16.5 Conclusions and recommendations.

In conclusion, a VAS change cut-off of -8 mm reliably identifies patients with symptom improvement. Use of this allows the number of improved patients to be directly compared between treatment groups in ED-based antiemetic trials. This outcome measure provides the best evidence with regard to the primary treatment objective, which is clinically significant symptom improvement. Between-group comparisons of the symptom improvement rates are clinically meaningful and easy to understand. The group mean VAS changes and between-group comparisons of these continue to provide useful general information on relative treatment effectiveness. The additional secondary outcome of experiencing the desired treatment effect adds clinical meaning to the differences in mean VAS change.

Given these results, it is recommended that future ED-based antiemetic trials continue to measure and monitor change in nausea severity using the VAS. The VAS change cut-off can then be used to identify improved patients as the primary outcome measure; reporting of group mean VAS change and between-group differences should continue as a secondary outcome. A direct question pertaining to experiencing of the desired treatment effect also appears to be a useful addition.

Further measurement research to validate the reliability of the VAS change cut-off for the detection of symptom improvement in different populations should be undertaken. For the outcome of symptom improvement, the amount of between-group difference and NNT which should be considered clinically worthwhile warrants discussion. This may vary with the clinical situation, but some broad agreement would aid future study planning. There might still be better ways to assess experiencing the desired treatment effect.

CHAPTER 17. Bibliography.

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Appendix. Related papers: (1) Drug treatment of adults with nausea and vomiting in primary care. (2) Drugs for the treatment of nausea and vomiting in adults in the ED setting (Cochrane Systematic Review).

A.1 Introduction.

These two papers, to which I contributed significantly, were published during the course of this thesis. They do not relate directly to the aims and purpose of the research projects which comprise this thesis, but add to the general body of knowledge concerning ED nausea management and ED-based antiemetic research.

As such, full text copies have been included here as an Appendix. In particular, the Systematic Review may be used as a resource if further detail is required regarding the appraisal of the ED-based antiemetic studies in Chapter 6 of this thesis.

A.2 Citations and papers (1) and (2).

(1) Furyk JS; Meek R; McKenzie S. Drug treatment of adults with nausea and vomiting in primary care. BMJ. 2014; 349:g4714.

(2) Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD010106. DOI: 10.1002/14651858.CD010106.pub

PAPERS FOLLOW

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PRACTICE

THERAPEUTICS

Drug treatment of adults with nausea and vomiting in primary care

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Albert Ferro, professor of cardiovascular clinical pharmacology, King's College London. To suggest a topic, please email us at practice@bmj.com.

A usually healthy 25 year old man presents to you as his general practitioner at 9 am. He has had fluctuating nausea with four vomits and one loose stool overnight, associated with colicky central abdominal pain. No blood was present in the vomit or stool, and he reports that his girlfriend was recently diagnosed as having "viral gastro." He is afebrile, intermittently uncomfortable, but otherwise well, with mild epigastric tenderness but no guarding or rebound. Clinically, you believe viral gastroenteritis is the most likely cause of his symptoms, and you consider his request for treatment that will help to stop his vomiting so that he can get to his evening shift at a factory.

What drugs are available and how do they work?

Nausea and vomiting are a common reason for patients to seek treatment in primary care, which we take here to include general practice and the emergency department. Identification and management of underlying problems are important, if these are apparent on clinical grounds. This article will focus on common causes in primary care such as gastroenteritis (usually viral), adverse drug reactions, pregnancy, vestibular disorders, and motion sickness. Other causes of nausea and vomiting such as postoperative, chemotherapy and radiotherapy associated, and specific conditions such as migraines are briefly discussed but are beyond the scope of this article.

Although still incompletely understood, nausea and vomiting are thought to follow activation of a medullary "vomiting centre," by either afferent input from the gastrointestinal tract due to presence of local irritants or stimulation of the central chemoreceptor trigger zone by circulating emetogenic substances; however, other pathways exist. Dopamine and serotonin seem to be key transmitters both centrally and in the gastrointestinal tract.

Surveys of emergency physicians in Australia and the United States identified the most commonly prescribed agents as metoclopramide, prochlorperazine, promethazine, droperidol, and ondansetron.[1 2] Anecdotally, cyclizine and domperidone are also commonly prescribed in the United Kingdom.

Metoclopramide and domperidone are benzamides that are thought to act through a combination of antidopaminergic and gastrointestinal tract pro-kinetic effects.[3] Domperidone penetrates the blood-brain barrier poorly, so although it still has effects on the chemoreceptor trigger zone, it has minimal centrally mediated side effects, in contrast to metoclopramide. Droperidol (a butyrophenone compound) and the phenothiazines (prochlorperazine and promethazine) have actions mediated primarily through central antidopaminergic mechanisms. Ondansetron and tropisetron are serotonin (5-HT) receptor antagonists both centrally and peripherally, although their action is thought to be predominantly mediated in the chemoreceptor trigger zone. Cyclizine is a histamine H_1 receptor antagonist with a central antiemetic effect. Scopolamine is an anticholinergic agent that acts to inhibit vestibular input to the central nervous system.

Current approved indications for the older antiemetics in Australia and the UK are broad and non-specific. For example, metoclopramide's indications include relief of nausea and vomiting associated with infectious disease, malignant disease, uraemia, migraine, labour, cancer treatment (chemotherapy or radiation), and postoperative vomiting and to assist in small bowel intubation. Selective antagonists are preferred for nausea

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and vomiting associated with specific mechanisms such as motion sickness, which is mediated via histaminic receptors. The newer serotonin antagonists, such as ondansetron, are approved only for the treatment of nausea and vomiting either postoperatively or with cancer treatment,[4 5] although this restriction is not adhered to in emergency department practice.[1]

How well do antiemetic agents work?

Table 1⇓ summarises the usual agents recommended for specific indications, with the level of evidence. Most antiemetic drug research has been in cancer treatment and postoperative nausea and vomiting. Systematic reviews have shown efficacy of serotonin antagonists in chemotherapy settings,[6] whereas drugs have been shown to be beneficial in postoperative nausea and vomiting, but with no drug group being clearly superior to any other.[7]

For paediatric gastroenteritis, ondansetron has been shown to be somewhat more effective than placebo in reducing vomiting and intravenous fluid requirements in the emergency department, as well as hospital admissions, although at the expense of a slight increase in diarrhoea.[8] For nausea in pregnancy, a recent narrative review article found no evidence of superiority of any agent over another.[9] Metoclopramide, prochlorperazine, promethazine, and ondansetron all seem to be somewhat effective and have no apparent teratogenicity. For motion sickness, the presumed pathogenesis remains incompletely understood; a recent systematic review of several small controlled trials concluded that scopolamine was more effective than placebo and equivalent to antihistamines for the prevention or amelioration of nausea and vomiting in this specific setting.[10]

Despite the frequency of adults presenting with nausea and vomiting in primary care, surprisingly little research has been done in this setting. We were unable to locate any general practice based studies and found only seven from emergency department practice.[11-17] Study designs for research in cancer treatment and postoperative nausea and vomiting involve concurrent administration of an antiemetic drug and an emetogenic substance, with measurement of the severity of the ensuing nausea and vomiting. In emergency department based studies, designs involve antiemetic administration followed by measurement of change in severity of the already present symptoms. Although nausea and vomiting are largely mediated through the same pathways regardless of the underlying cause,[3] results of research from different clinical settings may not be generalisable. The complexity of migraine and the difficulties of conducting randomised controlled trials in pregnancy have similarly left uncertainty about the effectiveness of antiemetic drugs in these more specific settings.[18 19]

For people with nausea and vomiting who might be managed in primary care, evaluation of findings in the emergency department based studies is somewhat difficult owing to relatively small sample sizes, clinical heterogeneity, inconsistent drug regimens, and emergency department based studies' use of the intravenous route, which is not routinely used in general practice. All patients in these studies received varying amounts of intravenous fluid, but four studies lacked a placebo arm.[12 14 15 17] Table 2⇓ summarises the primary outcome of reduction in severity of nausea at 30 minutes. The effect sizes vary between studies, probably owing to minor differences in methods; however, within studies, results between all drug and placebo arms (where used) are similar, other than in the one small study by Braude et al in 2006, in which the now out of favour droperidol seemed to be superior to the similarly effective metoclopramide, prochlorperazine, and placebo.[13] As all reductions in severity, whether with drug or placebo, exceeded the accepted level of clinical significance,[20] these studies suggest that patients' nausea and vomiting does improve, provided they receive some intravenous fluid and, where possible, treatment for their underlying condition, and that the addition of an antiemetic drug may add little. Two non-randomised, uncontrolled pre-hospital trials have suggested that oral transmucosal ondansetron is useful for nausea in the pre-hospital setting.[21 22] However, whether these emergency department and pre-hospital results can be extrapolated to the general practice setting, where drugs usually need to be given orally or intramuscularly and intravenous fluid administration is rarely possible, remains unclear. Despite reportedly frequent use in the UK, we are not aware of any studies evaluating cyclizine as an antiemetic in the primary care setting.

How safe are these agents?

Adverse effects of antiemetic drugs are usually mild, but some adverse effects warrant consideration.

Metoclopramide and the phenothiazines—Adverse effects are relatively common, although milder symptoms are possibly under-recognised. The most common adverse events are centrally mediated extrapyramidal side effects,[23] which range from mild restlessness, agitation, and akathisia to (less commonly) overt dystonia and dyskinesia, with more distressing opisthotonus and oculogyric crises being rare (a few per thousand). Extrapyramidal effects are more common in young children and adults up to about the age of 20 years, as well as in women and older people.[5 24]

Domperidone—This has recently been investigated by the European Medicines Agency,[25] owing to concerns about a small increased risk of cardiac adverse drug reactions. Although still available for the relief of nausea and vomiting, its use has been restricted for other indications.

Droperidol—Use is associated with sedation, agitation, and restlessness, but it has fallen out of favour despite evidence of efficacy, owing to concerns about prolonged QT interval and potential cardiac complications, the importance of which remains controversial.[26]

Antihistamines—These are associated with drowsiness in clinical use.

Scopolamine—Anticholinergic side effects such as dizziness, blurred vision, and dry mouth are usually mild at therapeutic doses. It can be associated with drowsiness and occasionally causes confusion and agitation.

Ondansetron—Serious side effects are uncommon but include a risk of QT interval prolongation (including torsade de pointes) and extrapyramidal reactions. Headache is frequently reported but generally not severe.

What are the precautions?

Metoclopramide and the phenothiazines:

- Avoid in children, young adults, and patients with a previous history of extrapyramidal side effects, all of whom are at higher risk of these.
- Use with caution in older people because of the possibility of renal dysfunction leading to increased risk of dystonic reactions.
- Avoid prolonged use owing to the risk of parkinsonism and tardive dyskinesia.

- Avoid in people with Parkinson's disease or depression, as symptoms may worsen.

When administering these agents intravenously, drugs for the management of possible dystonic reactions should be available, including diphenhydramine, benztropine, and benzodiazepines.

Antihistamines and phenothiazines:

- Can have anticholinergic effects and may precipitate some conditions such as constipation in patients prone to this or urinary retention in those with prostatomegaly.
- Can have a sedative effect, so warn about risks for driving or operating machinery.

Scopolamine:

- Can have a sedative effect, so warn about risks for driving or operating machinery.
- Can aggravate urinary difficulty or precipitate urinary retention in patients with bladder outflow obstruction.

Antiemetics in pregnancy:

- Metoclopramide's safety for use in pregnancy has been well established over several decades.[5]
- Ondansetron is being increasingly used, with few side effects reported and no reports of teratogenicity to date.[27]

Antiemetics in breastfeeding women:

- Little information on antiemetic use in lactation is available.
- Most antiemetics are known to be excreted in breast milk, and use in breastfeeding mothers is not generally recommended.

How cost effective are these agents?

No formal cost effectiveness evaluations have been done, these being limited by lack of high quality efficacy data. The two most commonly prescribed agents are metoclopramide and ondansetron. Metoclopramide is relatively inexpensive. Each 10 mg ampoule for parenteral use costs about $1.85 (£1.02; €1.28; $US1.74) in Australia and £0.30 in the UK. For oral use, a 25 tablet prescription costs about $13.50 in Australia and a 28 tablet prescription about £0.87 in the UK. In the primary care setting, where an initial parenteral dose might be followed by a maximum of three tablets on the first day and four on the second, the total cost of acute usage over two days is about $6 in Australia and £0.60 in the UK. In contrast, the most commonly used serotonin antagonist, ondansetron, is more expensive. Each 4 mg ampoule for parenteral use costs about $15 in Australia and £11.39 in the UK. The 4 mg and 8 mg oral preparations cost about $4 and $8 per dose respectively in Australia and about £2.10 and £4.70 in the UK. So an acute regimen over two days might cost about $70 in Australia and £25 in the UK.[28 29]

How are they taken and monitored?

Drug selection and dosage

For nausea and vomiting in the primary care setting, no convincing evidence of efficacy exists for any drug. If drug treatment is considered necessary, evaluate possible underlying causes (table 1⇓), costs, and precautions (see previous section) and discuss the risks versus benefits with the patient (see box). Prescribe these for the shortest period needed for symptom relief or control. Dose reductions may vary with presence and degree of renal impairment.

Route

Home use of oral antiemetics is suitable for milder or less frequent symptoms, with more than one initial parenteral dose rarely being feasible in general practice. The transmucosal route of administration, oral or rectal, may have a role in the future, but requires further evaluation in this setting. More severe or intractable vomiting often requires referral to hospital for consideration of intravenous administration of drug and fluid in the emergency department, along with assessment, monitoring, and management of the clinical consequences of the vomiting. The need for further investigation of possible underlying conditions is assessed on an individual basis.[5]

Monitoring

Monitoring requires clinical evaluation only. Checking patients' satisfaction with their progress, including effectiveness and possible side effects, usually suffices.

Outcome of hypothetical case

On examination, no evidence of any complications or dehydration, which might require hospital referral, is seen and no contraindications to any drugs exist. As the patient is keen to try an antiemetic, you administer 10 mg of intramuscular metoclopramide and advise him to continue taking oral fluids regularly. You advise him against attending work until his symptoms have resolved and issue him with a certificate to this effect.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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Tips for patients with nausea and vomiting who are well enough to be managed in primary care

Nausea and vomiting are common symptoms that can occur with many different underlying problems. In most cases, the nausea and vomiting component tends to resolve within the first 12-48 hours, regardless of treatment

It is not certain how much extra benefit you will get from using anti-vomiting drugs, beyond making sure you try to take enough fluids, haveing sufficient rest, and using simple painkillers as required

If you would like to try anti-vomiting drugs, they are reasonably safe; however, they can have unpleasant side effects. No single drug is clearly better than any other

About one in six people can get side effects from drugs such as metoclopramide and prochlorperazine. These are usually mild and will resolve so long as you stop taking the drug. If you develop worrying restlessness and agitation, muscle stiffness and limb jerking, tongue thrusting, or facial grimacing, you should see your doctor or go to a hospital emergency department

Use of regular metoclopramide for more than two weeks must be discussed with your doctor

You will need to see a doctor again if you are worried that you aren't keeping enough fluid down; if you develop new or worsening symptoms, such as blood in your vomit (or diarrhoea); or if abdominal pain becomes severe

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Tables

Table 1| Commonly prescribed antiemetics for specific indications

Indication	Receptors involved	Preferred drugs	Supporting evidence
Gastroenteritis (adult)	Dopamine/serotonin	Varies by region; acceptable agents include metoclopramide, prochlorperazine, ondansetron, cyclizine	Limited evidence: few small randomised trials (see table 2)
Gastroenteritis (paediatric)	Dopamine/serotonin	Ondansetron	Systematic review of randomised controlled trials[8]
Nausea and vomiting in pregnancy and hyperemesis gravidarum	Unknown	Metoclopramide, promethazine, ondansetron	Systematic review of randomised controlled trials (no evidence for superiority of any single agent)[9]
Motion sickness	Incompletely understood; include histamine and acetylcholine	Scopolamine, antihistamines	Systematic review supports superiority of scopolamine over placebo and equivalence with antihistamines[10]
Vestibular disorders	Histamine and acetylcholine	Antihistamines	Expert opinion[30]

Table 2| Reductions in severity of undifferentiated nausea and vomiting in adult emergency department patients

Randomised controlled trial	Intravenous drug/dose (sample size)	30 minute reduction: mean mm on VAS or units on 11 point NRS
Braude 2006[13]	Droperidol* 1.25 mg (n=22)	55 (SD 18) mm
	Metoclopramide 10 mg (n=25)	40 (24) mm
	Prochlorperazine 10 mg (n=24)	41 (24) mm
	Saline placebo 10 mL bolus (n=26)	39 (21) mm
Egerton-Warburton 2014[16]	Ondansetron 4 mg (n=87)	27 (95% CI 22 to 33) mm
	Metoclopramide 20 mg (n=88)	28 (22 to 34) mm
	Saline placebo 10 mL bolus (n=83)	23 (16 to 30) mm
Barrett 2011[11]	Ondansetron 4 mg (n=42)	40 (IQR 23-63) mm
	Metoclopramide 10 mg (n=43)	32 (20-47) mm
	Promethazine 12.5 mg (n=45)	35 (22-59) mm
	Placebo 2 mL bolus (n=41)	37 (23-56) mm
Cham 2004[15]	Metoclopramide 10 mg (n=24)	4 (95% CI 3 to 5) units
	Metoclopramide 0.4 mg/kg (max 32 mg) (n=24)	5 (4 to 6) units
Braude 2008 [12]	Ondansetron 4 mg (n=60)	34 (SD 29) mm
	Promethazine 25 mg (n=60)	36 (28) mm
Chae 2011[14]	Tropisetron 5 mg (n=50)	25 (25) mm
	Metoclopramide 10 mg (n=50)	26 (20) mm
Ernst 2000[17]	Prochlorperazine 10 mg (n=42)	45 mm (IQR not reported)
	Promethazine 25 mg (n=42)	27 mm (IQR not reported)

IQR=interquartile range; NRS=numerical rating scale; VAS=visual analogue scale.
*Difference from placebo statistically significant.

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Drugs for the treatment of nausea and vomiting in adults in the emergency department setting (Review)

Furyk JS, Meek RA, Egerton-Warburton D

Furyk JS, Meek RA, Egerton-Warburton D.
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[Intervention Review]

Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

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ABSTRACT

Background

Nausea and vomiting is a common and distressing presenting complaint in emergency departments (ED). The aetiology of nausea and vomiting in EDs is diverse and drugs are commonly prescribed. There is currently no consensus as to the optimum drug treatment of nausea and vomiting in the adult ED setting.

Objectives

To provide evidence of the efficacy and safety of antiemetic medications in the management of nausea and vomiting in the adult ED setting.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 8), MEDLINE (OvidSP) (January 1966 to August 2014), EMBASE (OvidSP) (January 1980 to August 2014) and ISI Web of Science (January 1955 to August 2014). We also searched relevant clinical trial registries and conference proceedings.

Selection criteria

We included randomized controlled trials (RCTs) of any drug in the treatment of nausea and vomiting in the treatment of adults in the ED. Study eligibility was not restricted by language or publication status.

Data collection and analysis

Two review authors independently performed study selection, data extraction and assessment of risk of bias in included studies. We contacted authors of studies to obtain missing information if required.

Main results

We included eight trials, involving 952 participants, of which 64% were women. Included trials were generally of adequate quality, with six trials at low risk of bias, and two trials at high risk of bias. Three trials with 518 participants compared five different drugs with placebo; all reported the primary outcome as mean change in visual analogue scale (VAS) (0 to 100) for nausea severity from baseline to

30 minutes. Trials did not routinely report other primary outcomes of the change in nausea VAS at 60 minutes or number of vomiting episodes. Differences in mean VAS change from baseline to 30 minutes between placebo and the drugs evaluated were: metoclopramide (three trials, 301 participants; mean difference (MD) -5.27, 95% confidence interval (CI) -11.33 to 0.80), ondansetron (two trials, 250 participants; MD -4.32, 95% CI -11.20 to 2.56), prochlorperazine (one trial, 50 participants; MD -1.80, 95% CI -14.40 to 10.80), promethazine (one trial, 82 participants; MD -8.47, 95% CI -19.79 to 2.85) and droperidol (one trial, 48 participants; MD -15.8, 95% CI -26.98 to -4.62). The only statistically significant change in baseline VAS to 30 minutes was for droperidol, in a single trial of 48 participants. No other drug was statistically significantly superior to placebo. Other included trials evaluated a drug compared to "active controls" (alternative antiemetic). There was no convincing evidence of superiority of any particular drug compared to active control. All trials included in this review reported adverse events, but they were variably reported precluding meaningful pooling of results. Adverse events were generally mild, there were no reported serious adverse events. Overall, the quality of the evidence was low, mainly because there were not enough data.

Authors' conclusions

In an ED population, there is no definite evidence to support the superiority of any one drug over any other drug, or the superiority of any drug over placebo. Participants receiving placebo often reported clinically significant improvement in nausea, implying general supportive treatment such as intravenous fluids may be sufficient for the majority of people. If a drug is considered necessary, choice of drug may be dictated by other considerations such as a person's preference, adverse-effect profile and cost. The review was limited by the paucity of clinical trials in this setting. Future research should include the use of placebo and consider focusing on specific diagnostic groups and controlling for factors such as intravenous fluid administered.

PLAIN LANGUAGE SUMMARY

Medicines in the treatment of emergency department nausea and vomiting

Review question

We reviewed the effects of medicines in the treatment of nausea and vomiting in adults in the emergency department.

Background

Nausea (feeling sick) and vomiting (being sick) is a common symptom in people in emergency departments, and can result from a number of different causes. In addition to being distressing, it can lead to other problems such as dehydration (where the body is losing more fluid than it is taking in). Medicines to treat nausea have been useful in other settings, such as after operations, although it is not known what is the best medicine for people in emergency departments.

Study characteristics

The evidence is current to August 2014. We included eight clinical trials of 952 participants. The trials assessed many different medicines at different doses, but only three trials included a placebo group (dummy medication). Six of these trials were of high quality, with low risk of error (i.e. bias, where the true effect is exaggerated). For this review, we included the effects of the medicines on nausea and vomiting up to one hour after the medicine was given.

Key results and quality of the evidence

The main results of interest were the effect on nausea between zero and 60 minutes after the medicine was given, number of vomits and side effects to medicines. Of these, only nausea at 30 minutes and side effects were reported by all trials. From all trials, only one medicine was reported to be better than placebo and other medicines. That was droperidol, which was included in one small trial of 97 participants. No other single medicine was definitely better than any other medicine, and none of the other trials that included a placebo group showed that the active medicines definitely worked better than the placebo. Side effects were mild.

Our results suggest that in people in the emergency department, nausea will generally improve, whether they are treated with specific medicines or placebo. Therefore, supportive treatment, such as intravenous fluids (where fluid is given directly into a blood vessel) may be sufficient for many people. Overall, the quality of the evidence was low, mainly because there was not enough data.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Metoclopramide for nausea and vomiting in the emergency department

Patient or population: people with nausea and vomiting
Settings: emergency department
Intervention: metoclopramide
Comparisons: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Metoclopramide				
Change in nausea severity at 30 minutes Visual analogue scale Scale from: 0 to 100 Follow-up: 30 minutes	The mean nausea severity decrease - metoclopramide vs. placebo ranged across control groups from **23 to 38 mm**	The mean nausea severity decrease - metoclopramide vs. placebo in the intervention groups was **5.27 lower** (11.33 lower to 0.8 higher)	-	301 (3 studies)	⊕⊕◯◯ low[1]	A larger decrease in nausea severity score indicates better control of symptoms. A difference of > 15 mm is thought to be the 'minimum clinically significant difference'
Number of vomiting episodes	See comment	See comment	Not estimable	301 (3 studies)	See comment	This outcome was not reported in any of the included studies
Adverse reactions	See comment	See comment	Not estimable	301 (3 studies)	See comment	No pooling of results was possible, due to variations in reporting. No studies reported any serious adverse reactions or significant difference in adverse reactions

Proportion of participants requiring rescue medication Physician's discretion Follow-up: 60 minutes	**Study population**		**OR 0.3** (0.17 to 0.53)	299 (3 studies)	⊕⊕◯◯ low[2]	An OR < 1 means less need for the medication with metoclopramide
	381 per 1000	**156 per 1000** (95 to 246)				
	Moderate					
	363 per 1000	**146 per 1000** (88 to 232)				
Participant satisfaction with intervention Self report	**Study population**		**OR 1.07** (0.6 to 1.91)	216 (2 studies)	⊕⊕◯◯ low[1]	An OR < 1 implies better satisfaction with metoclopramide
	657 per 1000	**672 per 1000** (535 to 785)				
	Moderate					
	721 per 1000	**734 per 1000** (608 to 832)				

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

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

[1] Downgraded for imprecision (wide confidence interval and not achieving optimal information size).
[2] Downgraded as this outcome was poorly described and variable in the included trials and imprecision.

BACKGROUND

Description of the condition

Nausea and vomiting is a common and distressing presenting complaint in emergency departments (ED) with more than eight million presentations annually in the US (LaValley 2003). Nausea describes the unpleasant sensation of the imminent need to vomit, whereas vomiting refers to the forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature (Quigley 2001). Therefore, whereas nausea is a subjective experience, vomiting represents a physical event.

Nausea and vomiting can be extremely distressing and complications can range from trivial to serious, for example, dehydration, electrolyte disturbance, aspiration, Mallory-Weiss syndrome (tears of gastric and oesophageal mucosa) and oesophageal rupture (Bork 2011; Zun 2010). The most common cause of nausea and vomiting in the ED is acute gastroenteritis (inflammation of the gastrointestinal tract); however, the aetiology of nausea and vomiting in the ED setting is diverse and may include physiological and pathological responses of the gastrointestinal tract, central nervous system disorders, endocrine or metabolic problems and toxins or medications, among others (Zun 2010). Nausea and vomiting in the ED may co-exist with other medical conditions (e.g. myocardial infarction or small bowel obstruction) or result from other treatments prescribed in the ED (e.g. opiate analgesia)

Description of the intervention

ED management of a patient often involves identification of the cause of nausea and vomiting as well as recognition and correction of consequences and complications (AGA 2001; Quigley 2001). Antiemetics are commonly prescribed for undifferentiated nausea and vomiting in the ED setting, although there is little consensus as to the optimum management. Therapy is often directed at the presumed pathophysiological cause or extrapolated from evidence in other settings.

How the intervention might work

The pathophysiology of nausea and vomiting is a complex process. The physical aspect of vomiting is co-ordinated by the vomiting centre of the brain, functionally located in the lateral reticular formation of the medulla. Efferent pathways from the vomiting centre are mainly through the vagus, phrenic and spinal nerves (Zun 2010). The vomiting centre receives afferent input from various sources including the chemoreceptor trigger zone (CTZ) located in the area postrema in the floor of the fourth ventricle, the vagus and sympathetic nerves, as well as impulses directly from the gastrointestinal tract and other sources (Bork 2011; Carpenter 1990). The CTZ is also activated by mediators in the circulation, which may include hormones, peptides, medications or toxins (Zun 2010).

Reflecting the complex nature of the process of nausea and vomiting, antiemetics consist of a diverse group of chemicals with varying mechanisms and sites of action. Targets of action include the CTZ through dopamine receptors, serotonin receptors in the area postrema and nucleus tractus solitarius, and cholinergic and histamine receptors. Other agents have their action peripherally on the gastrointestinal tract, and for others the mechanism of action is incompletely understood.

Why it is important to do this review

High-level evidence supports the use of antiemetics in the management of nausea and vomiting in many settings and populations; however, there is little guidance or consensus in recommendations for the management of nausea and vomiting in the adult ED setting. Recommendations are inconsistent and rarely evidence based. Preferred pharmacological agents differ significantly between countries and regions (LaValley 2003; Mee 2011). Postoperative nausea and vomiting (Carlisle 2006), chemotherapy (Billio 2010; Jordan 2007), and radiotherapy (Kris 2006; Maranzano 2005) induced nausea and vomiting, in particular, have been extensively researched with systematic reviews and guidelines published. Cochrane systematic reviews have also been published on antiemetic use in people receiving palliative care (Dorman 2010; Perkins 2009), paediatric and adolescent gastroenteritis (Fedorowicz 2011), nausea and vomiting associated with early pregnancy (Mathews 2010), and the use of acupuncture pressure points (Ezzo 2006; Lee 2009). However, extrapolation of the evidence from these settings to the ED population is not straightforward because of differences in aetiologies, patient populations and other factors. This review is important to help establish the current evidence for management of nausea and vomiting in this clinically diverse setting, and to help determine future research priorities.

OBJECTIVES

To provide evidence of the efficacy and safety of antiemetic medications in the management of nausea and vomiting in the adult ED setting.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) of any drug in the treatment of nausea and vomiting in the ED setting. We did not restrict the study eligibility by language or publication status. We excluded prospective cohort studies and quasi-randomized studies.

Types of participants

We included adult ED participants aged 16 years and older with nausea and vomiting. We only included trials if the study participants were identified as an 'adult', or if over 80% of the participants were aged over 16 years. We contacted study authors if age data were not available, and we did not include studies in this review if ages of the participants were not clear. We clearly identified the setting as ED.

Types of interventions

Interventions included any pharmacological agent prescribed for the treatment of nausea and vomiting. We considered any dose, formulation or route of administration. Appropriate comparators included placebo, no treatment or "active control" (alternative antiemetic).

Types of outcome measures

Severity of nausea, as assessed by use of any scale or score, and number of vomiting episodes.

Primary outcomes

1. Severity of nausea. Nausea was assessed as measured on any scale or score used by study authors, and transformed if required to a score between 0 and 100. It was recorded as complete resolution of nausea (e.g. including score 0 on a visual analogue scale (VAS)) and change from baseline value, with a minimum clinically significant difference (MCSD) from baseline defined as 15 mm on the VAS (Hendey 2005). We included time points between zero and 60 minutes as relevant to the practice of emergency medicine.
2. Number of vomiting episodes, both self reported and clinician-reported outcomes.
3. Any adverse reactions.

Secondary outcomes

1. Proportion of participants requiring rescue medication.
2. Proportion of participants who required hospital admission.
3. Mean or median ED length of stay.
4. Participant satisfaction with intervention.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 8), MEDLINE (OvidSP) (January 1966 to August 2014), EMBASE (OvidSP) (January 1980 to August 2014) and ISI Web of Science (January 1955 to August 2014). The search used a combination of text words and MeSH, with no language restriction. We developed a specific strategy for each database. The search strategy for MEDLINE is outlined in Appendix 1, which contains the Cochrane highly sensitive search strategy (Higgins 2011). Search strategies for EMBASE (Appendix 2) and CENTRAL (Appendix 3) are also included.

Searching other resources

We handsearched the reference lists of identified papers to identify further relevant trials. We examined clinical trial registries for unpublished trials on the International Clinical Trials Registry Platform (www.who.int/ictrp/en/), USA Clinical Trials registry (clinicaltrials.gov/), and Controlled Trials metaRegister of Controlled Trials (www.controlled-trials.com/mRCT and www.controlled-trials.com/mrct/archived), and contacted study authors. We handsearched key journals (*Annals of Emergency Medicine*, *Academic Emergency Medicine*, *Emergency Medicine*, *Journal of Emergency Medicine and Emergency Medicine Australasia*) from January 2009 to August 2014.

We also handsearched the published abstracts from relevant conference proceedings for additional unpublished trials. The conferences searched included:

1. Society for Academic Emergency Medicine (SAEM) Annual Meeting - Academic Emergency Medicine (1996 to August 2014);
2. American College of Emergency Physicians (ACEP) Scientific Assembly/Research Forum (1996 to August 2014);
3. Canadian Association of Emergency Medicine (CAEM) Annual Conference - *Canadian Journal of Emergency Medicine*;
4. Australasian College of Emergency Medicine (ACEM) - Annual Scientific Meeting - Emergency Medicine Australasia (2004 to August 2014);
5. College of Emergency Medicine (UK) Scientific conference (2006 to August 2014) - *Emergency Medicine Journal* - supplements;
6. European Society for Emergency Medicine (EuSEM) Mediterranean Emergency Medicine Congress - *European Journal of Emergency Medicine*.

We contacted other experts in the field to provide details of any ongoing clinical trials or unpublished materials.

Data collection and analysis

Selection of studies

We merged the search results with reference management software and removed duplicates. Two review authors (JF and RM) independently assessed titles and abstracts from studies identified by the search. We obtained full copies of all relevant or potentially relevant studies identified by either review author. We planned to obtain translations, if necessary, and contacted study authors for clarification, if necessary.

Two review authors (JF and RM) independently applied inclusion and exclusion criteria, and confirmed eligibility using a checklist in the data collection form (Appendix 5), which we developed for this review. We resolved disagreements by consensus or by consulting the third review author (DEW). We listed the characteristics of key excluded studies in the Characteristics of excluded studies table.

Data extraction and management

Two review authors (JF and RM) independently extracted data using a specifically designed, piloted data collection form. We resolved discrepancies by consensus and by consulting the third review author (DEW). One review author (JF) entered data into Review Manager 5 (RevMan 2014).

Assessment of risk of bias in included studies

Two review authors (JF and RM) independently assessed methodological quality of the eligible trials. We resolved disagreements by discussion and, if we could not reach a consensus, a third review author (DEW) arbitrated.

We performed risk of bias assessment using the 'Risk of bias' tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed each trial according to the quality domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and any other potential threats to validity (Appendix 5).

We considered a trial as having a low risk of bias if we assessed all domains as adequate. We considered a trial as having a high risk of bias if we assessed two or more domains as inadequate or unclear, or if we considered any one of the domains of allocation concealment, blinding participants or personnel, or blinding outcome assessors inadequate or unclear. We performed sensitivity analysis to determine whether excluding studies at high risk of bias affected the results of the meta-analysis.

We reported the 'Risk of bias' table as part of the Characteristics of included studies table and presented a 'Risk of bias' summary figure, which detailed all of the judgements made for all included studies in the review.

Measures of treatment effect

We reported the primary outcomes of included studies as either a dichotomous or continuous variable, for example vomiting yes or no; or nausea VAS score. We reported dichotomous outcomes as number and proportions and present continuous outcomes as mean change.

Unit of analysis issues

We used only individual level data.

Dealing with missing data

We contacted study authors by e-mail with requests to provide missing data. We intended to use imputation methods for missing data using 'worst-case', 'best-case' and 'average-case' scenarios for the primary outcome of change in nausea severity, and perform sensitivity analyses to assess how sensitive results were to assumptions made.

Assessment of heterogeneity

We assessed for statistical heterogeneity by visual inspection of the confidence intervals (CI) of forest plot results, P value < 0.05 for Chi^2 test and I^2 statistic with a value > 50% indicating significant heterogeneity (Higgins 2011). In addition, we assessed for clinical heterogeneity with consideration of the characteristics of included studies regarding participants, interventions and outcome measures. We presented the primary analysis using the random-effects model to account for clinical heterogeneity.

Assessment of reporting biases

We planned to test for funnel plot asymmetry using weighted linear regression of effect estimates on their standard error (Egger 1997), if we included more than 10 trials. However, we included only eight studies in this review.

Data synthesis

We based outcome data on intention-to-treat analysis results. We combined data from dichotomous and continuous outcomes and performed meta-analysis using Review Manager 5 when data from two or more RCTs were sufficient (RevMan 2014). For trials with multiple intervention groups, we combined groups to create single pair-wise comparisons as outlined in Chapter 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For dichotomous outcomes, we summed both the sample sizes and the numbers of people with events across groups, and for continuous outcomes, we combined means and standard deviations (SD) using the methods described in Section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used odds ratio (OR) to measure the treatment effect of dichotomous outcomes and the mean difference (MD) for continuous data using the inverse variance method. We used random-

effects model for analyses due to clinical heterogeneity of interventions and outcomes. When it was not appropriate to combine results, we presented them in narrative form.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis on nausea and vomiting associated with pregnancy, opiate administration and chemotherapy. This analysis was not possible as no data were available.

Sensitivity analysis

We performed sensitivity analyses using both the fixed-effect and random-effects models, and the effect on the overall primary results by excluding studies at high risk of bias (as defined above).

'Summary of findings' tables

We used the principles of the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system (Guyatt 2008) to assess the quality of the body of evidence associated with the specific outcomes change in nausea severity number of vomiting episodes, adverse reactions, proportion of participants requiring rescue medication and participant satisfaction with intervention, in our review and constructed Summary of findings for the main comparison using GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

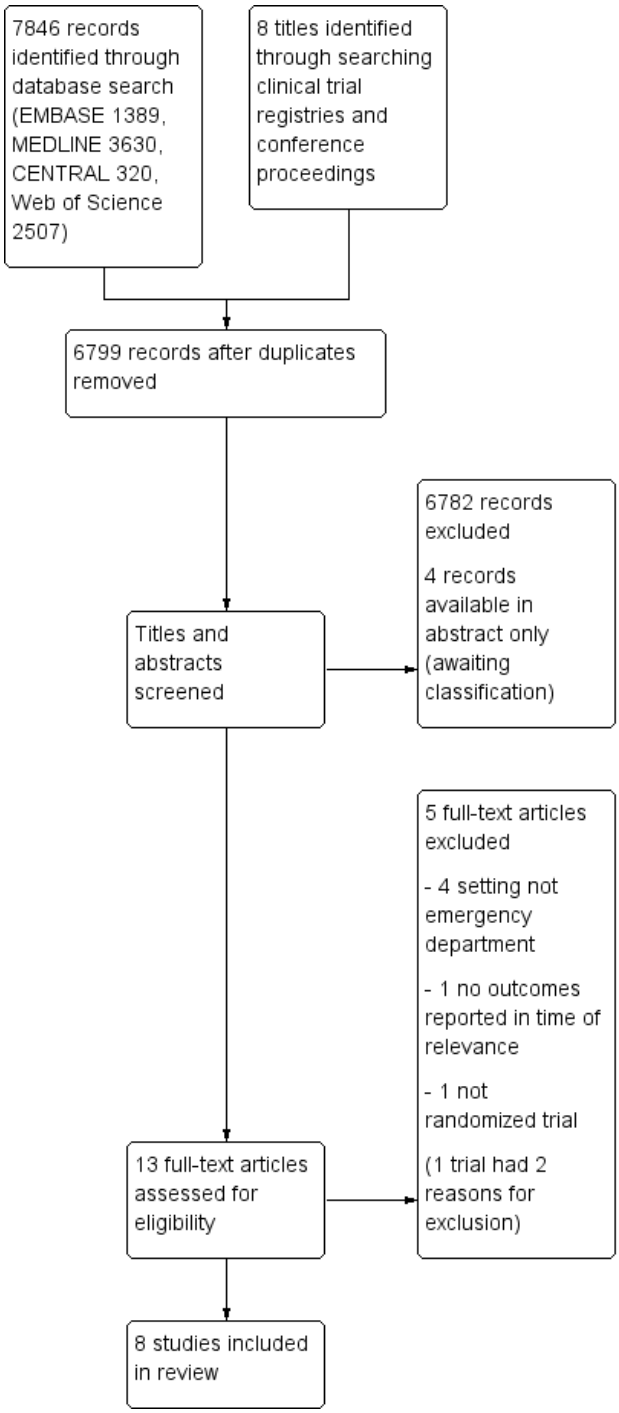
RESULTS

Description of studies

Results of the search

The electronic search identified 6799 studies with duplicates removed, consisting of 1389 from EMBASE, 3630 from MEDLINE, 320 from CENTRAL and 2507 from Web of Science. After screening titles and abstracts, we identified 13 studies for examination of the full text. We identified eight relevant studies from searching conference proceedings and clinical trial registries. Four of the studies appeared to report unique studies of relevance to our review, whereas four of the studies reported data subsequently published in journals and identified by the electronic database search. We contacted authors of the four other studies, but received no data from investigators, meaning information was only available in abstract form. Two of the authors of this Cochrane review were co-authors of the Egerton-Warburton 2014 study. Therefore, the search yielded 17 studies for consideration for inclusion. After evaluation of the full-text articles, we included eight studies in the review (see Characteristics of included studies table), we excluded five studies (see Characteristics of excluded studies table), and we identified four studies that were available in abstract form, and had insufficient information to assess (see Characteristics of studies awaiting classification table). For a PRISMA flow diagram of search strategy, see Figure 1.

Figure 1. Study flow diagram.



Included studies

We included eight trials in this review (Barrett 2011; Braude 2006; Braude 2008; Chae 2011; Cham 2004; Egerton-Warburton 2014; Ernst 2000; Patka 2011). Further details are available in the Characteristics of included studies table.

Design

The eight included trials were all parallel group, randomized trials. One trial was described as single blind (Cham 2004), the remainder were described as double blind. The included trials had two to four treatment arms, with only three trials including a placebo arm (Barrett 2011; Braude 2006; Egerton-Warburton 2014), the other trials using an active control. One trial was described as a non-inferiority trial (Braude 2008). The total sample size was 952 participants, consisting of 338 men and 614 women.

Participants and setting

The included trials were conducted in EDs in the US and Australia, mostly identified as university affiliated or teaching hospitals. All only included adults aged over 18 years. Most trials included nausea and vomiting from a variety of aetiologies, three trials excluded participants if their initial nausea VAS score was less than 40 mm (Barrett 2011; Braude 2006; Braude 2008). One trial specified the requirement for "uncomplicated gastritis and gastroenteritis" for eligibility (Ernst 2000). Women outnumbered men in all trials.

Intervention

The trials evaluated six different antiemetics. All trials included only intravenous antiemetics. Two trials had four arms (Barrett 2011; Braude 2006), and one trial had three arms (Egerton-Warburton 2014). Only three trials included a placebo arm (Barrett 2011; Braude 2006; Egerton-Warburton 2014). Five trials evaluated metoclopramide in doses of 10 mg, 20 mg and 0.4 mg/kg up to 32 mg. One trial compared two different doses of metoclopramide (Cham 2004). Five trials evaluated 5-hydroxytryptamine-3 (5-HT3) blockers (Barrett 2011; Braude 2008; Chae 2011; Egerton-Warburton 2014; Patka 2011), four using ondansetron 4 mg (Barrett 2011; Braude 2008; Egerton-Warburton 2014; Patka 2011), and one using tropisetron 0.5 mg (Chae 2011). Three trials included prochlorperazine 10 mg (Braude 2006; Ernst 2000; Patka 2011); three trials evaluated promethazine, one trial at 12.5 mg (Barrett 2011), and two trials at 25 mg (Braude 2008; Ernst 2000). All trials involved administration of a single stat dose as a bolus or over two to five minutes. Most trials included administration of varying amounts of intravenous fluid during the study period.

Outcomes

All included studies reported the primary outcome of severity of nausea reported on any scale or score. Seven of the studies reported nausea on a 100-mm VAS (Barrett 2011; Braude 2006; Braude 2008; Chae 2011; Egerton-Warburton 2014; Ernst 2000; Patka 2011), and one study used a 0 to 10 numerical rating scale (NRS) (Cham 2004). All studies included the time point of 30 minutes; three trials also reported data at 60 minutes (Chae 2011; Ernst 2000; Patka 2011); two trials reported outcomes beyond 60 minutes that we did not consider relevant to this review (Chae 2011; Patka 2011).

Three trials reported the number of vomiting episodes (Chae 2011; Egerton-Warburton 2014; Patka 2011). All trials reported adverse events, but the trials classified and reported them differently. All trials reported the outcome of requirement for rescue medication, but this was variably defined, or not defined in trials. Three trials reported the proportion of participants requiring hospital admission (Braude 2008; Ernst 2000; Patka 2011). No trials reported on ED length of stay, while three reported participant satisfaction (Braude 2006; Braude 2008; Egerton-Warburton 2014).

Excluded studies

We excluded five studies; see Characteristics of excluded studies table for details. The study by Roy 1991 compared oral doses of metoclopramide and domperidone, three times a day over one week. The setting appeared to be in general practice and outcomes were measured beyond the time frame of relevance to this review. Another excluded trial, which evaluated one or two doses of intramuscular domperidone 10 mg versus placebo, measured outcomes beyond the relevant time frame and was not clearly identified as ED (Agorastos 1981). We excluded one report as it was not an RCT, but an uncontrolled prospective design with no appropriate comparator group (Ordog 1984). We excluded one large multicentre trial evaluating two different doses of ondansetron (8 mg and 16 mg) versus placebo for opiate-associated nausea and vomiting (Sussman 1999). The setting was not clearly an ED, although it was stated that "many" participants were managed in EDs, and the primary outcome was resolution of symptoms at 24 hours, which was not relevant to this review. Finally, we excluded one single-centre study from Israel because the setting was not an ED, but rather an outpatient setting, participants requiring intravenous treatment were excluded and time points of the outcome assessments were not of relevance to this review (Cohen 1999).

Awaiting classification

There are four trials awaiting classification (Friedland 2008; Haensel 2007; Thacker 2003; Thacker 2004; see Characteristics

of studies awaiting classification table). These trials were available in abstract form only, with insufficient detail to allow inclusion in the review. We were unable to obtain further information from authors of these trials.

Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

We assessed the risk of bias of each trial; see Characteristics of included studies table, Assessment of risk of bias in included studies and 'Risk of bias' summary (Figure 2; Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

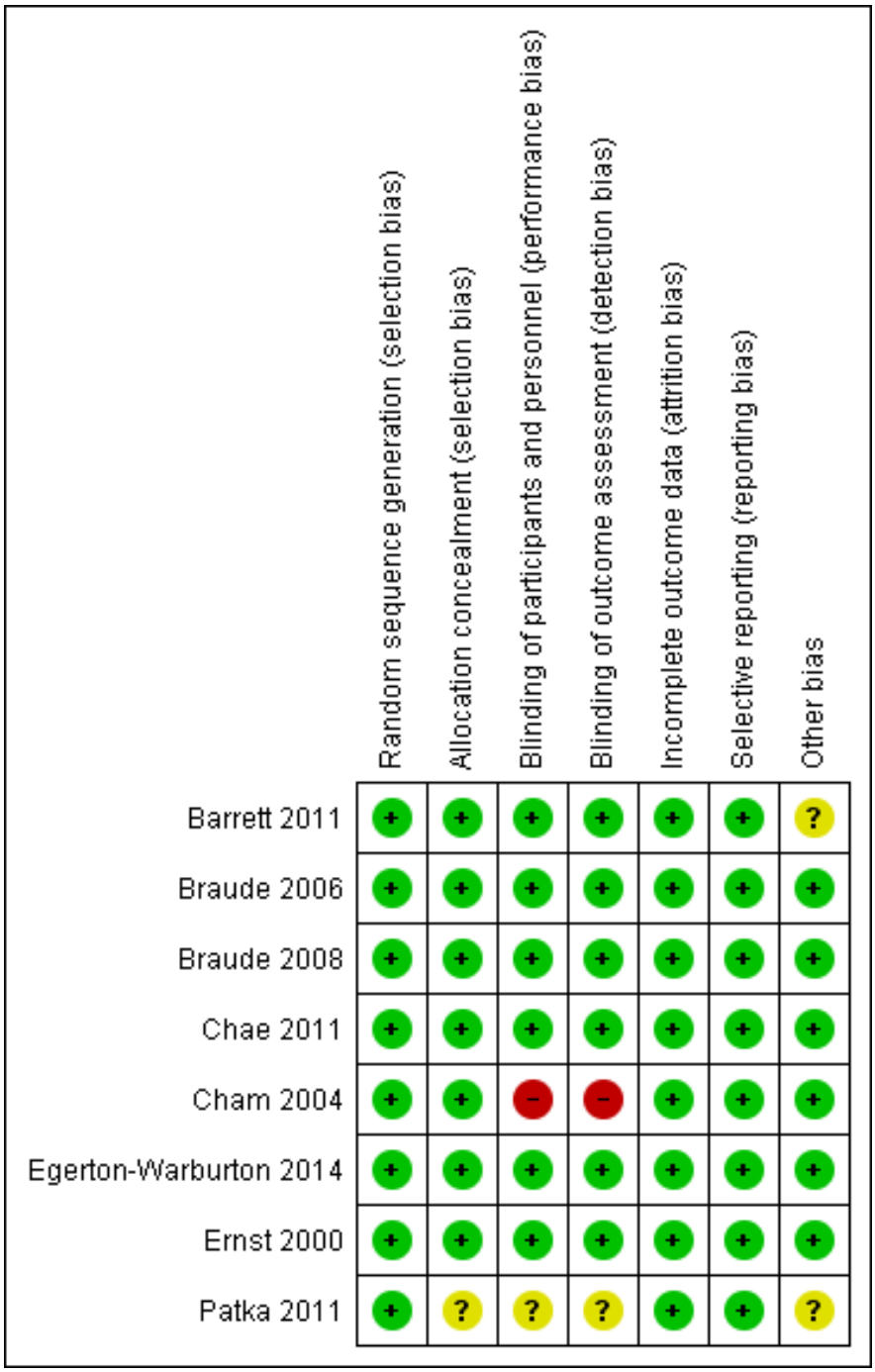
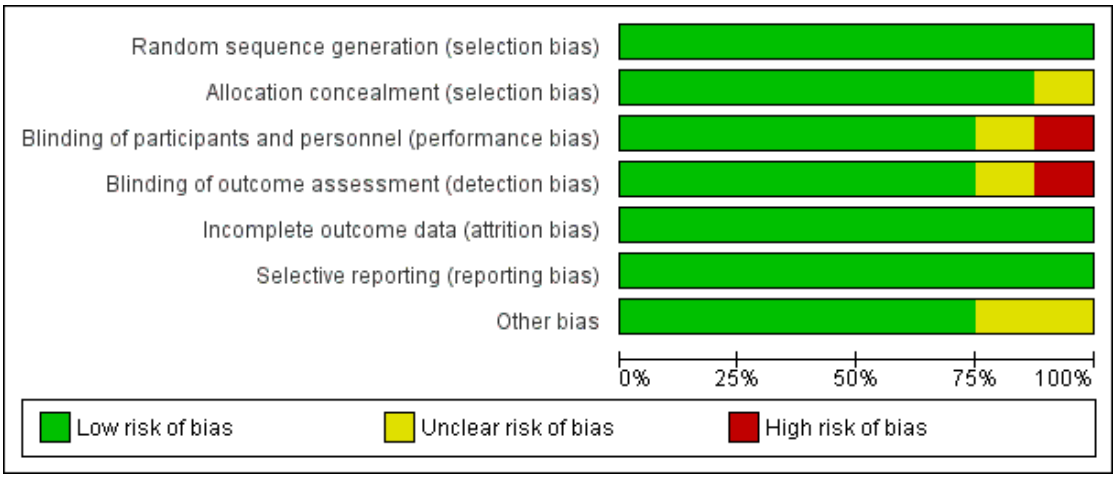


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All included trials reported acceptable methods of random sequence generation. The report by Braude 2008 reported only that drugs were "randomized in blocks of 10" and the method of sequence generation was not explicitly stated. This was clarified with the authors as being generated by computer program and recorded as low risk of bias for the review. Allocation concealment was adequate in seven out of eight studies. One study did not elucidate any mechanism of allocation concealment in the report, and was, therefore, considered unclear risk of bias (Patka 2011).

Blinding

Blinding of participants and personnel was adequate in six trials (Barrett 2011; Braude 2006; Braude 2008; Chae 2011; Egerton-Warburton 2014; Ernst 2000), unclear in one trial (Patka 2011), and judged as high risk of bias in one trial (Cham 2004). Outcomes were self reported in all included trials. The trial judged to be high risk of bias was reported as single blind, with no further details provided, but made no attempt to blind clinical staff (Cham 2004). One other trial described preparation of the study drug by independent nurses from the usual ward stock, keeping the drug allocation concealed from the participant and treating doctor (Chae 2011). While we considered that this procedure could potentially compromise blinding, we thought this would have been unlikely to have occurred sufficiently to affect the outcome, and we, therefore, judged the trial to be low risk of bias for this domain. We assessed one trial as unclear risk of bias as the authors did not report any mechanism for blinding (Patka 2011).

With regards to detection bias, outcomes were all self reported, consequently the same trial was rated as high risk of bias (Cham 2004), and the same trial was reported as unclear risk of bias (Patka 2011) due to similar reasons as described above.

Incomplete outcome data

All trials were at low risk of attrition bias. Although two trials had some unexplained missing data (Chae 2011; Patka 2011), these appeared balanced between intervention groups, outside the time points considered most relevant to this review, and unlikely to have a significant impact on the intervention effect estimates.

Selective reporting

There was no evidence of selective reporting in any of the trials. Outcomes listed in methods sections were reflected in results reported. One trial listed two primary outcomes on a clinical trial registry, and reported the non-significant outcome as a secondary outcome in the published report (Chae 2011). However, as all results were reported, we considered this to be low risk of bias.

Other potential sources of bias

We assessed two trials as 'unclear' with regards to other potential sources of bias. The Patka 2011 trial was generally poorly reported, with inconsistencies throughout the report, and no reason given for non-recruitment of substantial numbers of potentially eligible participants. The trial by Barrett 2011 reported an unplanned interim analysis and post hoc power calculation. The trial was then stopped at just over one-third of their planned recruitment target, because the likelihood of achieving a statistically significant result was remote, hence introducing the possibility of a type 2 error, which was acknowledged in the report. We judged that this may have introduced some bias.

Effects of interventions

See: **Summary of findings for the main comparison** Metoclopramide for nausea and vomiting in the emergency department

See Summary of findings for the main comparison for the comparison of metoclopramide, the drug most commonly evaluated, versus placebo.

This section included results from all eight trials. The three trials that included a placebo arm evaluated five different drugs: metoclopramide, ondansetron, prochlorperazine, promethazine and droperidol (Barrett 2011; Braude 2006; Egerton-Warburton 2014). The five non-placebo trials evaluated the same five drugs (Braude 2008; Chae 2011; Cham 2004; Ernst 2000; Patka 2011), with one trial including the 5-HT3 blocker tropisetron (Chae 2011).

To address the aims of this review, we combined the trials to allow comparisons of drugs versus placebo and each drug versus active control. Despite a degree of heterogeneity, this did allow for some pooling of results. We also presented the results of each drug studied versus each other drug. Some of these comparisons involved small numbers from one or two trials only, so caution is advised in interpretation of these findings.

Comparison of drug versus placebo

Three trials, with 518 participants, compared five different drugs with placebo (Barrett 2011; Braude 2006; Egerton-Warburton 2014).

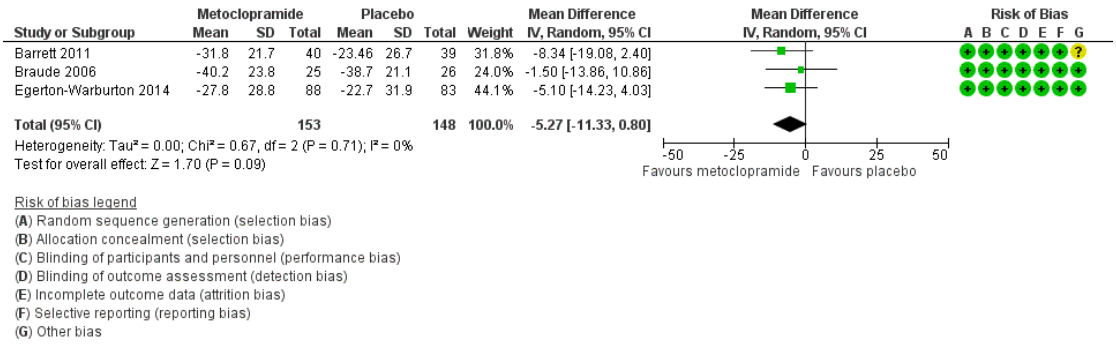
Primary outcomes

Severity of nausea

All three trials reported the primary outcome of mean VAS rating change for nausea severity from baseline to 30 minutes (Barrett 2011; Braude 2006; Egerton-Warburton 2014).

All three trials evaluated metoclopramide and involved 301 participants. From pooled results, the MD in VAS rating change at 30 minutes between metoclopramide and placebo was -5.27 (95% CI -11.33 to 0.80) (Figure 4).

Figure 4. Forest plot of comparison: 1 Metoclopramide versus placebo, outcome: 1.1 Change in nausea severity at 30 minutes.



Two trials evaluated ondansetron and involved 250 participants (Barrett 2011; Egerton-Warburton 2014). From pooled results, the MD in nausea VAS rating change at 30 minutes between ondansetron and placebo was -4.32 (95% CI -11.20 to 2.56) (Analysis 2.1).

One trial each evaluated prochlorperazine (50 participants; Braude 2006), promethazine (82 participants; Barrett 2011), and droperidol (48 participants; Braude 2006). The MD in VAS rating change at 30 minutes between prochlorperazine and placebo was -1.80

(95% CI -14.40 to 10.80) (Table 1). Between promethazine and placebo the MD was -8.47 (95% CI -19.79 to 2.85) (Table 2), and between droperidol and placebo the MD was -15.80 (95% CI -26.98 to -4.62) (Table 3).

Only the result for droperidol favoured drug over placebo (Braude 2006; Table 3).

Number of vomiting episodes

One trial reported the reduction in number of vomiting episodes, which were similar for ondansetron (median 0, interquartile range (IQR) 0 to 1), metoclopramide (median 0, IQR 0 to 2) and placebo (median 0, IQR 0 to 1) (Egerton-Warburton 2014). The other two trials did not report the number of vomiting episodes (Barrett 2011; Braude 2006).

Adverse reactions

All three trials reported adverse reactions (Barrett 2011; Braude 2006; Egerton-Warburton 2014); however, differences in reporting precluded pooling of results. None of the trials reported any serious adverse events.

Barrett 2011, evaluating ondansetron, metoclopramide and promethazine versus placebo, separately reported the proportion of participants with akathisia, headache and sedation at baseline and 30 minutes (characterized as none, mild, moderate and severe). These symptoms were commonly reported at baseline making interpretation of 30-minute data problematic. At 30 minutes, akathisia was more common with each drug compared with placebo (4/38 (11%) with ondansetron, 11/41 (27%) with metoclopramide, 2/43 (5%) with promethazine, 1/38 with placebo). Headache was reported by 11/39 (28%) participants with ondansetron, 8/41 (20%) with metoclopramide and 12/43 (28%) with promethazine, compared with 6/38 (16%) with placebo. Sedation was reported by 16/39 (41%) participants with ondansetron, 21/40 (53%) with metoclopramide and 25/43 (58%) with promethazine, compared with 13/38 (34%) with placebo.

Braude 2006 reported mean and SD change in anxiety and sedation on a VAS from baseline to 30 minutes. For anxiety, the mean change for droperidol was -25.9 (SD 30.2), metoclopramide -25.4 (SD 24.3), prochlorperazine -21.9 (SD 38.8) and placebo -31.7 (SD 31.6); these differences were not significant (P value = 0.79). For sedation, the mean change for droperidol was 13.5 (SD 32.2), metoclopramide 0.4 (SD 30.1), prochlorperazine 5.1 (SD 26.5) and placebo -4.8 (SD 25.0); these differences were not significant (P value = 0.75).

Egerton-Warburton 2014 reported adverse events in 9/258 (3.5%) participants: six in participants who received metoclopramide (two akathisia, two restlessness, one sweatiness and one muscle twitching), two in participants who received ondansetron (one dizziness and one stinging at injection site) and one in a participant who received placebo (shaking and restlessness).

The only significant result was a higher rate of akathisia for the "any drug" group compared with placebo (Barrett 2011).

Secondary outcomes

Proportion of participants requiring rescue medication

All three trials reported the proportion the participants requiring rescue medication, with 510 participants (Barrett 2011; Braude 2006; Egerton-Warburton 2014).

All three trials evaluated metoclopramide and included 299 participants (Barrett 2011; Braude 2006; Egerton-Warburton 2014). The pooled outcome versus placebo favoured metoclopramide (OR 0.3, 95% CI 0.17 to 0.53) (Analysis 1.2).

Two trials evaluated ondansetron and included 247 participants (Barrett 2011; Egerton-Warburton 2014). There was no difference in pooled outcome versus placebo for this outcome (OR 0.82, 95% CI 0.49 to 1.37) (Analysis 2.2).

One trial each evaluated prochlorperazine (50 participants; Braude 2006), promethazine (82 participants; Barrett 2011), and droperidol (48 participants; Braude 2006). There was no difference in outcome between any drug versus placebo (prochlorperazine: OR 1.83, 95% CI 0.45 to 7.51; Table 1; promethazine: OR 0.57, 95% CI 0.24 to 1.34; Table 2 droperidol: OR 0.26, 95% CI 0.03 to 2.54; Table 3).

The only result favouring a drug over placebo was for metoclopramide (Analysis 1.2).

Proportion of participants who required hospital admission

None of the three trials including a placebo arm reported the proportion of participants who required hospital admission (Barrett 2011; Braude 2006; Egerton-Warburton 2014).

Mean or median emergency department length of stay

None of the three trials including a placebo arm reported the mean or median ED length of stay (Barrett 2011; Braude 2006; Egerton-Warburton 2014).

Participant satisfaction with intervention

Two trials reported participant satisfaction with intervention (Braude 2006; Egerton-Warburton 2014). Both trials evaluated metoclopramide, involving 216 participants. From pooled results, there was no difference in participant satisfaction between metoclopramide and placebo (OR 1.07, 95% CI 0.60 to 1.91) (Analysis 1.3).

One trial each evaluated ondansetron (164 participants; Egerton-Warburton 2014), droperidol (48 participants; Braude 2006) and prochlorperazine (50 participants; Braude 2006). There was no difference in satisfaction for ondansetron, droperidol or prochlorperazine versus placebo (ondansetron: OR 0.80, 95% CI 0.43 to 1.49; Table 4 droperidol: OR 1.82, 95% CI 0.30 to 11.02; Table 3 prochlorperazine: OR 0.91, 95% CI 0.20 to 4.13; Table 1).

Comparison of metoclopramide versus active control

Five trials with 528 participants evaluated metoclopramide against an active control (Barrett 2011; Braude 2006; Chae 2011; Cham 2004; Egerton-Warburton 2014).

Primary outcomes

Severity of nausea

One trial, involving 58 participants, compared metoclopramide 0.4 mg/kg (up to 32 mg) with a standard 10-mg dose (Cham 2004). The outcome was reported as change in severity on a NRS of nausea 0 to 10. The median reduction in nausea was 5 (95% CI 4 to 6) in the 0.4-mg/kg group compared with 4 (95% CI 3 to 5) in the 10-mg group. This difference was not statistically significant (P value = 0.63).

The other four trials, involving 470 participants, included comparisons of metoclopramide with other active control, all reporting change in nausea severity on the VAS (mm) at 30 minutes (Barrett 2011; Braude 2006; Chae 2011; Egerton-Warburton 2014). From pooled results, the MD in VAS rating at 30 minutes between metoclopramide and any active control was -0.00 (95% CI -4.50 to 4.49) (Analysis 3.1).

Three trials, involving 356 participants, compared metoclopramide with a 5-HT3 antagonist (Barrett 2011; Chae 2011; Egerton-Warburton 2014). From pooled results, the MD in VAS rating at 30 minutes between metoclopramide and 5-HT3 antagonist was -1.74 (95% CI -6.88 to 3.40) (Analysis 4.1). Two of these trials, involving 256 participants, compared metoclopramide with ondansetron (Barrett 2011; Egerton-Warburton 2014), while the other trial, involving 100 participants, compared metoclopramide with tropisetron (Chae 2011). Separately for this outcome, the MDs were -2.00 (95% CI -8.30 to 4.29) (Analysis 5.1) for metoclopramide versus ondansetron and -1.20 (95% CI -10.11 to 7.71) (Table 5) for metoclopramide versus tropisetron. One trial, involving 83 participants, compared metoclopramide with promethazine (Barrett 2011). The change in VAS rating at 30 minutes between metoclopramide and promethazine was 0.10 (95% CI -10.06 to 10.26) (Table 6). One trial compared metoclopramide with prochlorperazine (49 participants) and droperidol (47 participants) (Braude 2006). The change in VAS rating at 30 minutes (MD) between metoclopramide and prochlorperazine was 0.30 (95% CI -13.12 to 13.72) (Table 7), and between metoclopramide and droperidol was 14.30 (95% CI 2.21 to 26.39) (Table 8).

The only statistically significant result between metoclopramide and any active control was that favouring droperidol over metoclopramide (Table 8) (Braude 2006).

Number of vomiting episodes

Four of the trials did not report the number of vomiting episodes within the time frame of interest to this review (Barrett 2011; Braude 2006; Chae 2011; Cham 2004). The related findings of Egerton-Warburton 2014 have been previously described (see 'Comparison of drug versus placebo: Primary outcomes: Number of vomiting episodes').

Adverse reactions

All five trials reported adverse events; however, differences in reporting precluded pooling of results. None of the trials reported any serious adverse events. The most commonly reported adverse events were akathisia and headache.

Cham 2004, evaluating a weight-based dose of metoclopramide with standard dose, reported similar adverse event rates (weight-based dose: 2/24 (8%); standard dose: 0/34 (0%); P value = 0.33).

Adverse events in three of the five trials have previously been described (see 'Comparison of drug versus placebo: Primary outcomes: Adverse reactions'), and there were no differences between metoclopramide and active control (Barrett 2011; Braude 2006; Egerton-Warburton 2014).

Chae 2011 comparing metoclopramide with tropisetron reported higher rates of akathisia (scored from 0 to 17) in the metoclopramide group at both 30 and 60 minutes (at 30 minutes: MD 1.1, 95% CI 0.1 to 22; at 60 minutes: 1.2, 95% CI 1.01 to 2.5). Baseline akathisia scores were also higher in the metoclopramide group (MD 0.3, 95% CI -0.22 to 0.8). Headache was reported by 5/50 (10%) participants in the metoclopramide group and 11/50 (22%) participants in the tropisetron group (difference 12%, 95% CI -4.2% to 28.2%, P value = 0.17). Dizziness was reported by 3/50 (6%) participants in the metoclopramide group and 5/50 (10%) participants in the tropisetron group (difference 4.0%, 95% CI -8.6% to 16.6%, P value = 0.71).

The only significant result was of more frequent akathisia for metoclopramide in comparison with tropisetron (Chae 2011).

Secondary outcomes

Proportion of participants requiring rescue medication

All five trials reported proportion of participants requiring rescue medication (Barrett 2011; Braude 2006; Chae 2011; Cham 2004; Egerton-Warburton 2014).

Cham 2004, comparing the different doses of metoclopramide, reported no difference in proportions requiring rescue medication (OR 0.83, 95% CI 0.18 to 3.86).

Four trials compared metoclopramide with any other active control on the outcome of rescue medication requirement in 469 participants (Barrett 2011; Braude 2006; Chae 2011; Egerton-Warburton 2014). The pooled results showed no difference in requirement for rescue medication between metoclopramide and any active control (OR 0.61, 95% CI 0.21 to 1.73) (Analysis 3.2). Three trials, involving 353 participants, compared metoclopramide with 5-HT3 blockers (Barrett 2011; Chae 2011;

Egerton-Warburton 2014). The pooled results showed no difference in the requirement for rescue medication (OR 0.71, 95% CI 0.20 to 2.50) (Analysis 4.2). However, pooled results from the two trials comparing metoclopramide and ondansetron, involving 253 participants, found that fewer participants receiving metoclopramide required rescue medication (OR 0.39, 95% CI 0.22 to 0.68) (Analysis 5.2) (Barrett 2011; Egerton-Warburton 2014). One study comparing metoclopramide with tropisetron, involving 100 participants, found that more participants receiving metoclopramide required rescue medication (OR 3.16, 95% CI 1.03 to 9.69) (Table 5) (Chae 2011).

One trial compared metoclopramide with promethazine with fewer participants requiring rescue medication for metoclopramide (9/43 (22%) with metoclopramide versus 19/45 (44%) with promethazine; OR 0.36, 95% CI 0.14 to 0.93) (Table 6) (Barrett 2011). One trial compared metoclopramide with prochlorperazine or droperidol (Braude 2006). It found no difference in requirement for rescue medication (1/25 (4%) with metoclopramide versus 6/24 (25%) prochlorperazine; OR 0.13, 95% CI 0.01 to 1.13) (Table 7); 1/25 (4%) with metoclopramide versus 1/22 (4.5%) with droperidol; OR 0.88, 95% CI 0.05 to 14.87) (Table 8).

Proportion of participants who required hospital admission

None of the five trials evaluating metoclopramide reported proportion of participants who required hospital admission (Barrett 2011; Braude 2006; Chae 2011; Cham 2004; Egerton-Warburton 2014).

Mean or median emergency department length of stay

None of the five trials evaluating metoclopramide reported mean or median ED length of stay (Barrett 2011; Braude 2006; Chae 2011; Cham 2004; Egerton-Warburton 2014).

Participant satisfaction with intervention

Two trials, involving 242 participants, reported participant satisfaction (Braude 2006; Egerton-Warburton 2014). From pooled results, there was no difference in participant satisfaction between metoclopramide and active control (OR 1.24, 95% CI 0.71 to 2.17) (Analysis 3.3).

Braude 2006 reported satisfaction as 21/25 (84%) with metoclopramide and 20/24 (83%) with prochlorperazine (OR 1.05, 95% CI 0.23 to 4.78) (Table 7) and 20/22 (95%) with droperidol (OR 0.53, 95% CI 0.09 to 3.19) (Table 8).

Egerton-Warburton 2014 reported satisfaction as 53/86 (61%) with metoclopramide and 46/85 (54.1%) with ondansetron (OR 1.36, 95% CI 0.74 to 2.50) (Table 9).

Comparison of 5-HT3 blockers versus active control

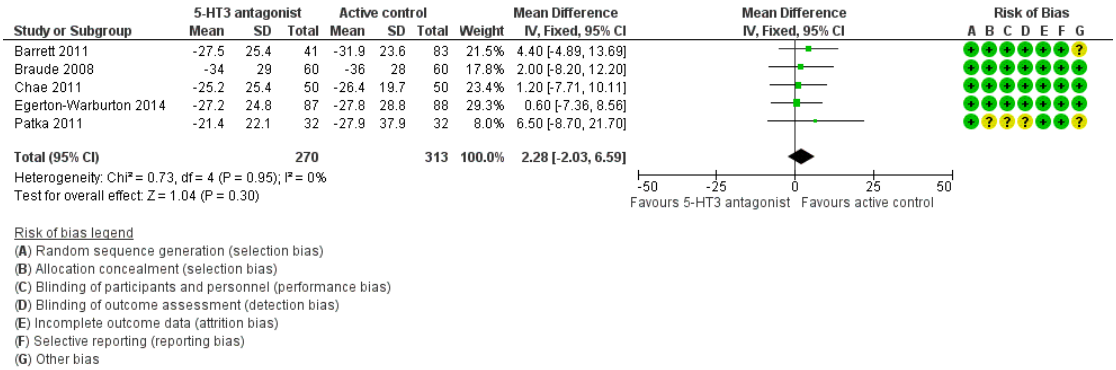
Five studies, involving 583 participants, compared 5-HT3 blockers against an active control (Barrett 2011; Braude 2008; Chae 2011; Egerton-Warburton 2014; Patka 2011). Four trials evaluated ondansetron (Barrett 2011; Braude 2008; Egerton-Warburton 2014; Patka 2011), and one trial evaluated tropisetron (Chae 2011).

Primary outcomes

Severity of nausea

All five trials reported the primary outcome of mean VAS rating change for nausea severity from baseline to 30 minutes (Barrett 2011; Braude 2008; Chae 2011; Egerton-Warburton 2014; Patka 2011). From pooled results, the difference in mean VAS rating change (MD) at 30 minutes between 5-HT3 blockers and any active control was 2.88 (95% CI -2.03 to 6.59) (Figure 5). The results were not affected by exclusion of the study with high risk of bias (Patka 2011), or by including studies only evaluating ondansetron (Analysis 7.1).

Figure 5. Forest plot of comparison: 3 5HT-3 Antagonists versus active control, outcome: 6.1 Change in nausea severity at 30 minutes.



Three trials, involving 356 participants, compared 5-HT3 blockers with metoclopramide (Barrett 2011; Chae 2011; Egerton-Warburton 2014). From pooled results, the difference in mean VAS rating change (MD) at 30 minutes between metoclopramide and 5-HT3 antagonist was -1.74 (95% CI -6.88 to 3.40) (Analysis 4.1). Separately, two trials, involving 256 participants, compared ondansetron with metoclopramide (Barrett 2011; Egerton-Warburton 2014), while the other trial, involving 100 participants, compared tropisetron with metoclopramide (Chae 2011). From pooled results, the difference in mean VAS rating change (MD) at 30 minutes between metoclopramide and ondansetron was -2.00 (95% CI -8.30 to 4.29) (Analysis 5.1), while for tropisetron it was -1.20 (95% CI -10.11 to 7.71) (Table 5).

Two trials, involving 204 participants, compared ondansetron with promethazine (Barrett 2011; Braude 2008). From pooled results, the difference in mean VAS rating change (MD) at 30 minutes was 3.16 (95% CI -4.29 to 10.60) (Analysis 8.1).

One trial, involving 64 participants, compared ondansetron with prochlorperazine (Patka 2011). The difference in mean VAS rating change (MD) at 30 minutes between ondansetron and prochlorperazine was 6.50 (95% CI -8.70 to 21.70) (Table 10). We deemed this trial at high risk of bias (Risk of bias in included studies).

Number of vomiting episodes

Three of the five trials evaluating 5-HT3 antagonists did not report the number of vomiting episodes within the time frame of interest to this review (Barrett 2011; Braude 2008; Chae 2011). The related findings from Egerton-Warburton 2014 have been previously described (see 'Comparison of drug versus placebo: Primary outcomes: Number of vomiting episodes'). Patka 2011 reported the proportion of participants vomiting from 0 to 30 minutes and 31 to 60 minutes. This was low for both ondansetron and prochlorperazine (0 to 30 minutes: 2/32 (6%) with ondansetron and 0/32 (0%) with prochlorperazine; 31 to 60 minutes: 0/32 (0%) with ondansetron and 1/32 (3%) with prochlorperazine).

Adverse reactions

All five trials reported adverse events (Barrett 2011; Braude 2008; Chae 2011; Egerton-Warburton 2014; Patka 2011); however, variability in reporting precluded meaningful pooling of results.

Adverse events from the trials of Barrett 2011; Chae 2011; Egerton-Warburton 2014 were described in preceding sections (see 'Comparison of drug versus placebo: Primary outcomes: Adverse reactions'). Braude 2008 reported mean change in anxiety and sedation on a VAS from baseline to 30 minutes. For anxiety, the mean changes for ondansetron and promethazine were -13 (SD 27) with ondansetron and -14 (SD 26) with promethazine (MD -1, 95% CI -10 to 10). For sedation, the mean changes were less for ondansetron compared with promethazine (5 (SD 25) with ondansetron versus 19 (SD 30) with promethazine; MD 14, 95% CI 5 to 24). Patka 2011 reported no difference in akathisia rates between ondansetron and prochlorperazine (1/32 (3%) with ondansetron versus 3/32 (9%) with prochlorperazine). Sedation scores were also reported to be similar between groups (no details given), while headache scores were reported to be "significantly lower" (P value < 0.05) for prochlorperazine at all time points, but no data were provided.

The result favouring ondansetron over active control was a lower rate of sedation (Braude 2008). The result favouring an active control over ondansetron was a lower headache score for prochlorperazine (Patka 2011).

Secondary outcomes

Proportion of participants requiring rescue medication

Five trials, involving 582 participants, reported the proportion of participants requiring rescue medication (Barrett 2011; Braude 2008; Chae 2011; Egerton-Warburton 2014; Patka 2011). From pooled results, there was no difference in requirement for rescue medication between 5-HT3 blockers and any active control (OR 1.47, 95% CI 0.72 to 3.01) (Analysis 6.2).

From the four trials, involving 482 participants, which evaluated ondansetron against any active control, the pooled analysis found a higher requirement for rescue medication for ondansetron than for active control (OR 2.00, 95% CI 1.29 to 3.09) (Analysis 7.2) (Barrett 2011; Braude 2008; Egerton-Warburton 2014; Patka 2011). This result did not change with exclusion of the study at high risk of bias (Patka 2011).

Three of the trials, involving 353 participants, compared 5-HT3 blockers with metoclopramide (Barrett 2011; Chae 2011; Egerton-Warburton 2014). From pooled results, there was no difference in requirement for rescue medication between metoclopramide and 5-HT3 blockers (OR 0.71, 95% CI 0.20 to 2.50) (Analysis 4.2). Two of these trials, involving 254 participants, compared ondansetron with metoclopramide (Barrett 2011; Egerton-Warburton 2014). Pooled results showed that more participants in the ondansetron group required rescue medication (OR 0.39, 95% CI 0.22 to 0.68) (Analysis 5.2).

Two trials, involving 207 participants, compared ondansetron with promethazine (Barrett 2011; Braude 2008). Pooled results showed no difference in requirement for rescue medication (OR 1.29, 95% CI 0.70 to 2.37) (Analysis 8.2).

One trial, involving 64 participants, which compared ondansetron with prochlorperazine, reported no difference in requirement for rescue medication (OR 5.74, 95% CI 0.63 to 52.23) (Table 10) (Patka 2011).

Pooled results favoured any active control over ondansetron for requirement for rescue medication (Analysis 7.2). For individual drugs, the only significant result was that favouring metoclopramide over ondansetron (Analysis 5.2).

Proportion of participants who required hospital admission

Two trials, involving 184 participants, compared need for admission between 5-HT3 blockers and active control (Braude 2008; Patka 2011). Pooled results showed no difference between 5-HT3 blockers and active control (OR 1.84, 95% CI 0.35 to 9.60) (Analysis 6.3). The result did not change with the exclusion of the trial at high risk of bias (Patka 2011). Separately, Braude 2008 reported the admission rates to be 13/60 (22%) with ondansetron versus 14/60 (23%) with promethazine (OR 0.91, 95% CI 0.39 to 2.14) (Table 11), while Patka 2011 reported admission rates to be 8/32 (25%) with ondansetron versus 2/32 (6%) with prochlorperazine (OR 5.00, 95% CI 0.97 to 25.77) (Table 10).

Mean or median emergency department length of stay

None of the trials reported the mean or median ED length of stay (Barrett 2011; Braude 2008; Chae 2011; Egerton-Warburton 2014; Patka 2011).

Participant satisfaction with intervention

Two trials, involving 263 participants, reported participant satisfaction with intervention (Braude 2008; Egerton-Warburton 2014). Pooled results showed no difference in satisfaction between ondansetron and any active control (OR 1.23, 95% CI 0.36 to 4.22) (Analysis 7.3). Separately, Braude 2008 reported satisfaction to be 40/44 (91%) with ondansetron versus 38/48 (79%) with promethazine (OR 2.63, 95% CI 0.76 to 9.11) (Table 11), while Egerton-Warburton 2014 reported satisfaction to be 53/86 (61.6%) with metoclopramide versus 46/85 (54.1%) with ondansetron (OR 1.36, 95% CI 0.74 to 2.50) (Table 9).

Comparison of prochlorperazine versus active control

Three trials, involving 219 participants, evaluated prochlorperazine against an active control (Braude 2006; Ernst 2000; Patka 2011).

Primary outcomes

Severity of nausea

Two trials, involving 135 participants, reported the primary outcome of mean VAS rating change for nausea severity from baseline to 30 minutes (Braude 2006; Patka 2011). From pooled results, the difference in mean VAS rating change (MD) at 30 minutes between prochlorperazine and active control was 0.93 (95% CI -11.57 to 13.42) (Analysis 9.1).

One trial, involving 84 participants, reported median VAS rating change at 30 and 60 minutes (Ernst 2000). These were 45 with prochlorperazine and 27 with promethazine at 30 minutes, and 60.5 with prochlorperazine and 47 with promethazine at 60 minutes. No variances were reported, but the difference was reported to be statistically significant in favour of prochlorperazine (P value = 0.004 at 30 minutes, and P value < 0.001 at 60 minutes).

One trial compared prochlorperazine with droperidol (46 participants), and metoclopramide (49 participants) (Braude 2006). Results favoured droperidol over prochlorperazine, with a difference in mean VAS rating change (MD) at 30 minutes of 14.00 (95% CI 1.67 to 26.33) (Table 12), but there was no difference between metoclopramide and prochlorperazine (MD 0.30, 95% CI -13.12 to 13.72) (Table 7).

One trial, involving 64 participants, compared prochlorperazine with ondansetron (Patka 2011). The difference in mean VAS rating change (MD) at 30 minutes was 6.50 (95% CI -8.70 to 21.70) (Table 10).

One result favoured prochlorperazine over promethazine (Ernst 2000). One result favoured droperidol over prochlorperazine (Table 12) (Braude 2006).

Number of vomiting episodes

None of the trials evaluating prochlorperazine reported the number of vomiting episodes. The related findings from Patka 2011 have been previously described (see 'Comparison of 5-HT3 blockers versus active control: Primary outcomes: Number of vomiting episodes').

Adverse reactions

All three trials reported adverse events (Braude 2006; Ernst 2000; Patka 2011); however, variations in reporting precluded pooling of data. There were no serious adverse events in any of the trials.
Adverse events from Braude 2006 and Patka 2011 have been described in previous sections (see 'Comparison of 5-HT3 blockers versus active control: Primary outcomes: Adverse reactions').
Ernst 2000 reported identical akathisia rates at 6/42 (14%) with prochlorperazine and promethazine, and drowsiness at 38% with prochlorperazine and 71% with promethazine (difference 33%, 95% CI 13% to 53%; P value = 0.02).
The significant result was of a lower rate of drowsiness for prochlorperazine compared with promethazine (Ernst 2000).

Secondary outcomes

Proportion of participants requiring rescue medication

All three trials, involving 219 participants, reported proportion of participants requiring rescue medication (Braude 2006; Ernst 2000; Patka 2011). From pooled results, there was no difference between prochlorperazine and active control (OR 0.77, 95% CI 0.07 to 8.74) (Analysis 9.2). Exclusion of results from the trial at high risk of bias did not change the result (Patka 2011).
Braude 2006 reported requirement for rescue medication in 1/25 (4%) with metoclopramide compared with 6/24 (25%) with prochlorperazine (OR 0.13, 95% CI 0.01, 1.13) (Table 7), and 1/22 (4%) with droperidol (OR 1.91, 95% CI 0.16 to 22.66) (Table 12). Patka 2011 reported requirement for rescue medication in 5/32 (16%) with ondansetron and 1/32 (3%) with prochlorperazine (OR 5.74, 95% CI 0.63 to 52.23) (Table 10). Ernst 2000 reported requirement for rescue medication in 3/42 (7%) with prochlorperazine and 12/42 (29%) with promethazine (OR 0.19, 95% CI 0.05 to 0.74) (Table 13).
The only significant result was that fewer participants required rescue medication with prochlorperazine compared with promethazine (Table 13) (Ernst 2000).

Proportion of participants who required hospital admission

Two trials, involving 148 participants, reported proportion of participants who required hospital admission (Ernst 2000; Patka 2011). From pooled results, the difference favoured prochlorperazine versus active control (OR 0.22, 95% CI 0.05 to 0.95) (Analysis 9.3). Exclusion of the trial at high risk of bias did change the result (Patka 2011), since Ernst 2000 reported the difference in proportions requiring admission as OR 0.33 (95% CI 0.01 to 8.22) (Table 13).

Mean or median emergency department length of stay

None of the trials evaluating prochlorperazine reported mean or median ED length of stay (Braude 2006; Ernst 2000; Patka 2011).

Participant satisfaction with intervention

Only one trial reported participant satisfaction (Braude 2006). There was no difference between the groups (20/24 (83%) with prochlorperazine versus 41/47 (87%) with active control; OR 0.73, 95% CI 0.19 to 2.89) (Table 14), or separately between prochlorperazine and droperidol (20/24 (83%) with prochlorperazine versus 20/22 (95%) with droperidol; OR 0.50, 95% CI 0.08 to 3.05) (Table 12), or prochlorperazine and metoclopramide (20/24 (83%) with prochlorperazine versus 21/25 (84%) with metoclopramide; OR 1.05, 95% CI 0.23 to 4.78) (Table 7).

Comparison of promethazine versus active control

Three trials, involving 328 participants, evaluated promethazine versus active control (Barrett 2011; Braude 2008; Ernst 2000).

Primary outcomes

Severity of nausea

Two trials, involving 244 participants, reported the primary outcome of mean VAS rating change for nausea severity from baseline to 30 minutes (Barrett 2011; Braude 2008). From pooled results, the difference in mean VAS rating change (MD) at 30 minutes between promethazine and active control was -2.17 (95% CI -8.99 to 4.66) (Analysis 10.1).
One trial, involving 84 participants, reported median VAS rating change at 30 and 60 minutes (Ernst 2000). These were 45 mm with prochlorperazine and 27 mm with promethazine at 30 minutes, and 60.5 mm with prochlorperazine and 47 mm with promethazine at 60 minutes. No variances were reported, but the difference was reported as being statistically significant in favour of prochlorperazine (P value = 0.004 at 30 minutes, and P value < 0.001 at 60 minutes).

Two trials, involving 204 participants, compared promethazine with ondansetron (Barrett 2011; Braude 2008). From pooled results, difference in mean VAS rating change (MD) to 30 minutes between ondansetron and promethazine was 3.16 (95% CI -4.29 to 10.60) (Analysis 8.1).

One trial, involving 83 participants, compared promethazine with metoclopramide (Barrett 2011). The difference in mean VAS rating change (MD) at 30 minutes was 0.10 (95% CI -10.06 to 10.26) (Table 6).

The only significant result was that favouring prochlorperazine over promethazine (Ernst 2000).

Number of vomiting episodes

None of the trials reported number of vomiting episodes.

Adverse reactions

All three trials reported adverse events, but variable reporting precluded pooling of results (Barrett 2011; Braude 2008; Ernst 2000). These have been described in detail in previous sections (see 'Comparison of drug versus placebo: Primary outcomes: Adverse reactions' and 'Comparison of prochlorperazine versus active control: Primary outcomes: Adverse reactions'). In brief, Ernst 2000 reported more drowsiness for promethazine versus prochlorperazine (71% with promethazine versus 38% with prochlorperazine; difference 33%, 95% CI 13% to 53%; P value = 0.02), while rates of akathisia were similar at 14% in both groups. Braude 2008 reported more sedation for promethazine versus ondansetron (difference in mean VAS rating at 30 minutes 14, 95% CI 5 to 24). Barrett 2011 reported no difference in sedation at 30 minutes between promethazine and any active control (OR 1.58, 95% CI 0.74 to 3.34).

Secondary outcomes

Proportion of participants requiring rescue medication

Three trials, involving 334 participants, reported proportion of participants requiring rescue medication (Barrett 2011; Braude 2008; Ernst 2000). From pooled results, there was no difference in need for rescue medication between promethazine and active control (OR 1.55, 95% CI 0.58 to 4.14) (Analysis 10.2).

Two trials, involving 207 participants, found no difference between ondansetron and promethazine (OR 1.29, 95% CI 0.70 to 2.37) (Analysis 8.2) (Barrett 2011; Braude 2008).

One trial, involving 88 participants, reported less need for rescue medication with metoclopramide versus promethazine (19/43 (22%) with metoclopramide versus 9/45 (44%) with promethazine (OR 0.36, 95% CI 0.14 to 0.93) (Table 6) (Barrett 2011).

One trial, involving 84 participants, reported less need for rescue medication with prochlorperazine versus promethazine (3/42 (7%) with prochlorperazine versus 12/42 (29%) with promethazine; OR 0.19, 95% CI 0.05 to 0.74) (Table 13) (Ernst 2000).

There was a greater requirement for rescue medication for promethazine in comparison with both metoclopramide (Table 6) (Barrett 2011) and prochlorperazine (Table 13) (Ernst 2000).

Proportion of participants who required hospital admission

Two trials, involving 204 participants, reported proportion of participants who required hospital admission (Braude 2008; Ernst 2000). From pooled results, there was no difference in admission requirement between promethazine and active control (OR 1.18, 95% CI 0.51 to 2.70) (Analysis 10.3). One trial, involving 120 participants, reported no difference in admission requirement between ondansetron and promethazine (13/60 (22%) with ondansetron versus 14/60 (23%) with promethazine; OR 0.91, 95% CI 0.39 to 2.14) (Table 11) (Braude 2008). One trial, involving 84 participants, reported no difference in admission requirement between prochlorperazine and promethazine (0/42 (0%) with prochlorperazine versus 1/42 (2.4%) with promethazine; OR 0.33, 95% CI 0.01 to 8.22) (Table 13) (Ernst 2000).

Mean or median emergency department length of stay

None of the three trials reported mean or median ED length of stay.

Participant satisfaction with intervention

One trial, involving 92 participants, reported participant satisfaction with intervention (Braude 2008). There was no difference between ondansetron and promethazine (40/44 (91%) with ondansetron versus 38/48 (79%) with promethazine; OR 2.63, 95% CI 0.76 to 9.11) (Table 11).

Comparison of droperidol versus active control

One trial, involving 71 participants, evaluated droperidol against active control (Braude 2006).

Primary outcomes

Severity of nausea

Braude 2006 reported the primary outcome of mean VAS rating change for nausea severity from baseline to 30 minutes. From pooled results, the difference in mean VAS rating change (MD) at 30 minutes between droperidol and active control was -14.10 (95% CI -24.26 to -3.94) (Table 15). Separately, the differences in mean VAS rating changes at 30 minutes also favoured droperidol in comparison with metoclopramide (MD 14.30, 95% CI 2.21

to 26.39) (Table 8), and with prochlorperazine (MD 14.00, 95% CI 1.67 to 26.33) (Table 12).

Number of vomiting episodes

The trial did not evaluated number of vomiting episodes.

Adverse reactions

Adverse events for this trial have been previously described (see 'Comparison of drug versus placebo: Primary outcomes: Adverse reactions') (Braude 2006). There were no serious adverse events reported. In brief, the mean changes for anxiety ratings were droperidol -25.9 (SD 30.2), metoclopramide -25.4 (SD 24.3) and prochlorperazine -21.9 (SD 38.8); and for sedation were droperidol 13.5 (SD 32.2), metoclopramide 0.4 (SD 30.1) and prochlorperazine 5.1 (SD 26.5).

Secondary outcomes

Proportion of participants requiring rescue medication

Braude 2006 reported requirement for rescue medication, which was similar for droperidol and active control (1/22 (4.5%) with droperidol versus 7/49 (14%) with active control; OR 0.29, 95% CI 0.03 to 2.48) (Table 15). Separately, 1/22 (4.5%) with droperidol was compared with the 1/25 (4%) with metoclopramide (OR 0.88, 95% CI 0.05 to 14.87) (Table 8) and 6/24 (25%) with prochlorperazine (OR 1.91, 95% CI 0.16 to 22.66) (Table 12).

Proportion of participants who required hospital admission

The trial did not report proportion of participants who required hospital admission.

Mean or median emergency department length of stay

The trial did not report mean or median ED length of stay.

Participant satisfaction with intervention

The trial reported participant satisfaction with intervention (Braude 2006). From pooled results, this was similar between droperidol and active control (20/21 (95%) with droperidol versus 41/48 (85%) with active control; OR 3.41, 95% CI 0.39 to 29.68) (Table 15). Separately, the 20/21 (95%) with droperidol was compared with 21/25 (84%) with metoclopramide (OR 0.53, 95% CI 0.09 to 3.19) (Table 8) and 20/24 (83%) with prochlorperazine (OR 0.50, 95% CI 0.08 to 3.05) (Table 12).

DISCUSSION

Summary of main results

Nausea and vomiting are frequently present in people in the ED with many different conditions. Early antiemetic drug use is common, regardless of the underlying cause, due to the distressing nature of the symptoms, and the potential for secondary complications. However, despite the frequency of the clinical problem, the limited number of studies eligible for inclusion in this systematic review was surprising. This limited the potential for pooling of results and consideration of potential confounding factors, such as primary diagnostic groups or amount of intravenous fluid administered was not possible.

Accepting these limitations, this Cochrane review found no convincing evidence that any one drug had a more clinically significant effect than any other drug, or that any one of a number of drugs was superior to placebo. The three trials with a placebo arm, both individually and with pooling of results where possible, found that there was no significant difference in the VAS reductions between placebo and metoclopramide, ondansetron, prochlorperazine or promethazine (Barrett 2011; Braude 2006; Egerton-Warburton 2014). For individual drugs versus any other drug (active control), where results could be pooled from three trials, together with the other four studies that compared different antiemetic drugs (Braude 2008; Chae 2011; Ernst 2000; Patka 2011), differences in VAS reductions between groups were not significant.

Only two trials made conclusions of superiority for a particular drug (Braude 2006; Ernst 2000). Braude 2006 reported that the VAS reduction for droperidol was significantly greater than that for each of metoclopramide, prochlorperazine and placebo, and Ernst 2000 concluded that the VAS reduction for prochlorperazine was significantly greater than that for promethazine, but since the reductions in all groups exceeded the MCSD, the clinical significance of this superiority is uncertain. Similarly, two of the trials that included a placebo arm reported a statistically non-significant trend towards superiority for ondansetron, metoclopramide and promethazine in comparison with placebo (Barrett 2011; Egerton-Warburton 2014), but in both these trials the lower limit of the 95% CI of the VAS reduction for placebo still exceeded the MCSD, so again, the clinical significance of these statistical trends is also doubtful. Although it may seem intuitive that statistically greater reductions would equate with greater clinical benefits, there is no literature to date that supports this notion.

Reduction in number of post-treatment vomiting episodes is used in other settings (Carlisle 2006), as a primary outcome measure, and so we included it in this review. It proved not be a useful measure, as the majority of participants included in the ED-based trials had nausea only, and in the three trials that reported number of vomits (Chae 2011; Egerton-Warburton 2014; Patka 2011), frequency was so low that demonstration of a significant reduction within a 30-minute period was impossible.

The final primary outcome measure of adverse events showed

variable results, but overall these were fairly mild and did not require specific therapies. There were no serious adverse events in any of the included trials. Promethazine was associated with more sedation or drowsiness in two trials (Braude 2008; Ernst 2000), ondansetron with headaches (Patka 2011), and metoclopramide and prochlorperazine with some akathisia (Chae 2011; Egerton-Warburton 2014; Patka 2011), although these effects were relatively unusual and mild. One large systematic review on drugs for preventing postoperative nausea and vomiting reported on adverse effects from 380 trials finding droperidol increased the risk of drowsiness, while decreasing the risk of headache, and ondansetron increased the risk of headache but found no evidence for a difference in risk in other adverse effects (Carlisle 2006).

Of the secondary outcome measures under consideration, only dispensing of additional rescue medication was included in all trials. The small number of trials, along with variable and inconsistent results, meant that this was of limited utility. This may stem from a lack of definition as to what constituted a need for rescue medication, as in all studies this was at the discretion of the treating ED doctor. Of note, treatment with promethazine was associated with higher requirement for rescue medication, and interestingly participants treated with ondansetron were more likely to require rescue medication compared to either active control or metoclopramide. Few trials reported participant satisfaction or hospital admission rates, with hospital admission rates not being included in any of the trials with placebo control. Participant satisfaction was similar with all drugs included in the review. None of the trials reported ED lengths of stay. It is noteworthy that we did not demonstrate the superiority of 5HT3 antagonists compared to other classes for any of the outcomes assessed, and perhaps contrary to the common anecdotal perception of effectiveness.

Overall completeness and applicability of evidence

Overall, there was a paucity of clinical trials assessing the effectiveness of antiemetic medications for nausea and vomiting in the ED setting. In total, fewer than 1000 participants have been evaluated in this setting. This is somewhat surprising, given the frequency of the symptom in EDs, and although treatment of the condition with antiemetics in clinical practice is very common, there is little consensus on the most appropriate treatment. Interpretation of the available evidence is hampered by clinical heterogeneity, specifically the variety of different drugs evaluated in studies to date, difference in baseline severity and inclusion criteria, and the wide variety of underlying illnesses leading to the symptom of nausea in the ED setting. Most of the trials included in this Cochrane review did have fairly broad inclusion criteria, so while general conclusions could be drawn, the applicability of the findings to all people with nausea in the ED, or to particular subsets of them, remains uncertain. Given the relative paucity of trials in the ED setting, in certain circumstances it may be appropriate to extrapolate evidence from systematic reviews in other settings (e.g. nausea and vomiting in early pregnancy) (Mathews 2010). The drugs evaluated in the eight included trials mirrored common practice, with metoclopramide being included in five trials, 5-HT3 antagonists in four, promethazine in three, prochlorperazine in two and droperidol in one, but there are other agents and the use of drugs in combination was not studied.

The use of change in the VAS, on which the conclusions of this review are primarily based, could also be debated. The VAS, for measurement and monitoring of change in nausea severity, has been validated. High correlation between adjectival descriptors of severity and VAS measurement ranges has been demonstrated, and the MCSD has been defined as the mean VAS change when people report symptom severity as being "a little less". Research on the MCSD is somewhat limited, however, but it appears that the MCSD is greater for people whose baseline nausea is severe, than for people with moderate or mild severity. Hence, reported figures have ranged between 12 and 30 mm, seemingly dependent on the severity mix of the particular population. In this review, we noted that while differences in VAS reductions between groups were similar, the VAS reductions reported for the same drugs in different studies varied quite widely. It was generally the case that when baseline VAS ratings were higher, the reported post-treatment reductions, including for placebo where included, were greater. This finding seems consistent with reports of variability in the MCSD for different severity subgroups, and highlights the difficulty of pre-defining a single MCSD for multiple populations. We did nominate a mid-range MCSD of 15 mm for use in this review, which is obviously problematic, but since VAS reductions for all treatments in all studies comfortably exceeded this figure, it seems reasonable to conclude that the reported levels of participant improvement were clinically significant.

Quality of the evidence

The methodology of the trials included in the review appeared to be adequate overall, and are reported further in the Assessment of risk of bias in included studies section. We judged two trials to have a high risk of bias because they were inadequately blinded or did not report adequately on certain domains that we were unable to clarify with authors (Cham 2004; Patka 2011). We judged the remaining included trials to be low risk of bias overall, although some minor methodological issues remained.

Potential biases in the review process

Potential biases were minimized by performing a comprehensive search for potentially eligible studies. We were unable to obtain trial reports, or sufficient data on four unpublished studies identified through searching clinical trial registries, which may introduce

some possibility of bias (Friedland 2008; Haensel 2007; Thacker 2003; Thacker 2004).

Clinical heterogeneity between trials made pooling of data for meta-analysis difficult for some outcomes. The clinical heterogeneity consisted of included trials evaluating different agents, different doses, and using different active control groups and only three trials including a placebo control arm (Barrett 2011; Braude 2006; Egerton-Warburton 2014). Results and analysis of random-effects model analysis were presented for outcomes comparing both individual drugs and combined with active controls. Comprehensive data comparing various doses of drugs included in the review were lacking, and we thought this unlikely to affect the results substantially. We believe the comparisons presented here to be valid and informative.

Two authors of this review were also authors of one of the included studies (Egerton-Warburton 2014). We minimized bias as data extraction and assessment of quality was conducted by an author not involved with the study (JF). There were no disagreements with this trial in assessment of quality or data extraction, and as such did not require arbitration with an independent person.

Agreements and disagreements with other studies or reviews

We are not aware of any previous systematic reviews on the treatment of nausea and vomiting in the ED setting.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review suggest that in an emergency department (ED) population, nausea severity tends to decrease by a similar and apparently clinically significant amount over a period of 30 minutes, regardless of whether an antiemetic drug or saline placebo is given. Presumably this initial improvement is due to whatever specific therapies are provided for the person's underlying condition, probably including the provision of intravenous fluids.

This review found no definite evidence to support the superiority of any one drug for the treatment of ongoing nausea, so choice of drug should be dictated by other considerations such as a person's preference, adverse-effect profile and cost.

Implications for research

Evidence supports that any future ED-based antiemetic studies should include a placebo control arm. Despite some likely variability in the minimum clinically significant difference (MCSD) for different populations, change in severity on the visual analogue scale (VAS) appears to be the most useful outcome measure in this setting, but the clinical importance of reductions greater than the MCSD warrants exploration. The change in number of vomiting episodes does not appear useful, and researchers should look to define need for rescue medication more tightly and what is contributing to a person's decision on satisfaction.

Research to date has almost exclusively compared the effect on self reported nausea severity of a single dose of one drug over a time period of 30 minutes, with the clinical significance of the severity reduction at this time point also being based on somewhat limited literature. Further investigation of the MCSD for both global ED populations and in different initial severity subgroups would be useful. The effect of initial concurrent administration of different drugs on early reduction of symptoms, as often occurs in the oncology setting, could also be explored and compared to placebo. The longer-term effect, still within the ED, of repeat doses of either the same or different drugs for persistent nausea might also be useful.

Further research would also be useful in focusing on specific individual diagnostic groups within the ED population (e.g. presumed, uncomplicated gastroenteritis), which may demonstrate more consistent results from antiemetic drug administration, than the more heterogeneous undifferentiated ED population with nausea and vomiting. A further consideration in future trials would be to control the amount of intravenous fluid administered accurately, or to evaluate the antiemetic effects of intravenous fluid alone.

Other participant-related outcomes, still confined to the ED episode of care, such as change in severity by time of disposition, ED length of stay and need for hospital admission should be considered in future studies.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Barrett 2011

Methods	Study design: randomized, double-blind, placebo-controlled trial Study duration: not stated Follow-up: 30 min
Participants	Country: USA Setting: single urban, university affiliated ED Annual census: 54,000 Inclusion criteria: aged ≥ 18 years, nausea and vomiting of any cause Exclusion criteria: received antiemetic drug in prior 24 hours, nausea VAS severity < 40 mm, hypotension, allergy Number: total allocated 171; treatment group 1: 42; treatment group 2: 43; treatment group 3: 45; control group: 41 Number: total analysed (primary outcome) 163; treatment group 1: 41; treatment group 2: 40; treatment group 3: 43; treatment group 4: 39 Median age (IQR) (years): treatment group 1: 34 (27-47); treatment group 2: 37 (24-52); treatment group 3: 28 (23-46); control group: 32 (22-44) Sex (M/W): treatment group 1: 15/27; treatment group 2: 13/30; treatment group 3: 14/31; control group: 14/27
Interventions	Treatment group 1: ondansetron 4 mg IV Treatment group 2: metoclopramide 10 mg IV Treatment group 3: promethazine 12.5 mg IV Control group: placebo All groups received IV fluid over the 30-min study period (median overall 500 mL)
Outcomes	Primary outcome: change in nausea severity score at 30 min Secondary outcomes: proportion of participants requiring rescue medication, adverse reactions (including akathisia, headache, pain at injection site and sedation)
Notes	All treatment groups received a median of 500 mL of isotonic IV fluid, control group received a median of 450 mL Additional data provided by author - means and SD for treatment groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Well described, randomization statistical software in blocks of 24
Allocation concealment (selection bias)	Low risk	Well described, prepared by study pharmacist and syringes sent by pneumatic tube

Barrett 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	All drugs presented as 2 mL of clear fluid in syringe labelled "antiemetic study medication". Poor agreement in kappa with doctors guessing study drug
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding seemed adequate. Primary outcome self reported VAS by participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis "modified intention to treat" as 3 people did not get their study drug, and a further person did not get 30 min nausea score. Minimal likely effect on results
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	An unplanned interim analysis and post hoc power calculation and an amended sample size may have introduced some bias

Braude 2006

Methods	Study design: randomized, double-blind, controlled trial Study duration: December 1998 to December 1999 Follow-up: 30 min
Participants	Country: USA Setting: single urban teaching hospital ED Annual census: 55,000 Inclusion criteria: aged 18-65 years, primary or secondary complaint of nausea or vomiting, or both Exclusion criteria: received antiemetic drug in prior 24 hours, nausea VAS severity < 40 mm, hypotension, known CCF or pregnancy, given > 1000-mL IV fluid prior to enrolment Number: total 97; treatment 1 (22); treatment group 2 (25); treatment group 3 (24); control group (26) Mean age ± SD (years): treatment group 1: 36.6 ± 12.6; treatment group 2: 38.9 ± 11.5; treatment group 3: 36.3 ± 11.0; control group: 38.2 ± 12.5 Sex (M/W): treatment group 1: 7/15; treatment group 2: 8/17; treatment group 3: 17/7; control group: 10/16
Interventions	Treatment group 1: droperidol 1.25 mg IV Treatment group 2: metoclopramide 10 mg IV Treatment group 3: prochlorperazine 10 mg IV Control group: placebo All interventions were administered as a single push All groups received IV fluid over the 30-min study period

Braude 2006 (*Continued*)

Outcomes	Primary outcome: change in nausea severity score at 30 min Secondary outcomes: proportion of participants requiring rescue medication, participant satisfaction, adverse reactions (akathisia and sedation)
Notes	All groups received IV fluid with a mean (± SD) 739 ± 445 mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Low risk	Drug supplied by pharmacy, allocation known only to them
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs appeared identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Appeared to be adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/100 participants failed to provide 30-min rating. Unlikely to influence results
Selective reporting (reporting bias)	Low risk	No indication of selective reporting
Other bias	Low risk	No other issues identified

Braude 2008

Methods	Study design: randomized, double-blind, non-inferiority trial Study duration: August 2003 to November 2005 Follow-up: 30 min
Participants	Country: USA Setting: single urban university teaching hospital ED Annual census: 75,000 Inclusion criteria: aged ≥ 18 years, chief or secondary complaint of nausea or vomiting Exclusion criteria: aged < 18 or > 65 years, unable to provide informed consent, received antiemetic drug in prior 24 hours, nausea VAS severity < 40 mm, known or suspected pregnancy, given > 1000 mL IV fluid prior to enrolment Number: total 120; treatment 1: 60; treatment group 2: 60 Mean age ± SD (years): treatment group 1: 36 ± 11.2; treatment group 2: 39 ± 14.2 Sex (M/W): treatment group 1: 24/36; treatment group 2: 14/46

Braude 2008 (*Continued*)

Interventions	Treatment group 1: ondansetron 4 mg IV Treatment group 2: promethazine 25 mg IV Both interventions diluted to 10 mL, and administered as a single push over 2 min Both groups received similar amounts of IV fluid
Outcomes	Primary outcome: change in nausea severity score at 30 min Secondary outcomes: proportion of participants requiring rescue medication, adverse reactions (change in self reported anxiety and sedation)
Notes	At 30 min, both groups received a similar amount of IV fluid mean (± SD): promethazine 497 ± 360 mL and ondansetron 460 ± 356 mL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomized in blocks of 10" but method of sequence generation not described in published report, clarified with authors as computer generated
Allocation concealment (selection bias)	Low risk	Identical appearing vials, prepared by pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "study drugs appeared identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clearly stated that allocations were not revealed until after all analyses were complete
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up for primary outcome. Some attrition for 24-hour follow-up (equal in groups)
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Convenience sample, and slow recruitment. Effect of potential bias low. Funded by GlaxoSmithKline (GSK), makers of ondansetron. Stated that GSK not involved in study design, data collection, analysis, writing the manuscript or approval of final manuscript

Chae 2011

Methods	Study design: randomized, double-blind superiority trial Study duration: October 2009 to March 2010 Follow-up: 180 min
Participants	Country: Australia Setting: single centre, urban teaching hospital ED Annual census: 70,000 Inclusion criteria: aged ≥ 18 years, with nausea or vomiting and ED doctor recommended antiemetic Exclusion criteria: received antiemetic drug in prior 6 hours, unable to provide informed consent, allergy, symptoms associated with migraine Number: total 100; treatment group 1: 50; treatment group 2: 50 Mean age ± SD (years): treatment group 1: 53 ± 21.0; treatment group 2: 56.7 ± 19.2 Sex (M/W): treatment group 1: 21/29; treatment group 2: 21/29
Interventions	Treatment group 1: tropisetron 5 mg IV Treatment group 2: metoclopramide 10 mg IV Both interventions administered as a single bolus
Outcomes	Primary outcome: number of vomiting episodes (vomits per person-hours) Secondary outcomes: change in nausea severity score at 30 min, proportion of participants requiring rescue medication, adverse reactions (akathisia score - modified Prince Henry's scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated by an independent pharmacist
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as "double-blind". Drugs were prepared and administered from usual ward stock by "independent" nurses, with the participant and doctor blinded. Although there is the potential for this process to be compromised, we thought this was unlikely to have occurred, and hence judged the study domain to be low risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above, while there was potential for the blinding to be compromised, we determined it was unlikely and hence judged the domain to be low risk of bias

Chae 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data of relevance to this review well reported. Some minor inaccuracies in reporting exact numbers at each time point, but unlikely to lead to systematic bias
Selective reporting (reporting bias)	Low risk	Change in nausea VAS listed as primary outcome on clinical trial registry, secondary outcome in report. Time point 240 min (not relevant to this review) listed on Clinical Trial Registry but not reported in published paper (these are unlikely to substantially affect the review)
Other bias	Low risk	Convenience sample, not likely to have impact on results

Cham 2004

Methods	Study design: prospective, single-blind, randomized trial Study duration: October 2001 to July 2003 Follow-up: 30 min
Participants	Country: Australia Setting: 2 urban teaching hospital EDs Annual census: 75,000 (combined) Inclusion criteria: aged $\geq$ 18 year, who required treatment for nausea or vomiting, or both Exclusion criteria: known allergy; previous dystonic reaction; suspected gastrointestinal obstruction; gastrointestinal haemorrhage; having received any antiemetic, narcotic or phenothiazine in the last 24 hours; treatment with chemotherapy; pregnancy and a history of epilepsy Number: total 58; treatment 1 (24); treatment group 2 (34) Median age, range (years): treatment group 1 (42, 21-83); treatment group 2 (34, 18-76) Sex (M/W): treatment group 1 (8/16); treatment group 2 (9/25)
Interventions	Treatment group 1: metoclopramide 0.4 mg/kg to a maximum of 32 mg Treatment group 2: metoclopramide 10 mg IV Both interventions administered as a single bolus
Outcomes	Primary outcome: change in nausea severity score at 30 min Secondary outcomes: proportion of participants requiring rescue medication, adverse reactions
Notes	
Risk of bias	

Cham 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by random number allocation (note groups were unevenly balanced)
Allocation concealment (selection bias)	Low risk	Dose regimen contained in numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported as single blind, but no attempt made to blind clinical staff. Not elaborated further
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes were self reported; however, staff aware of treatment allocation may have led to bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported loss to follow-up
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Other reporting issues included: no planned sample size presented, a very low recruitment rate, unknown if this sample is representative and the groups were unbalanced. Unlikely to have led to systematic bias

Egerton-Warburton 2014

Methods	Study design: double-blind, randomized controlled trial Study duration: September 2009 to April 2010 Follow-up: 30 min
Participants	Country: Australia Setting: 2 EDs, 1 urban district and 1 tertiary referral Annual census: 57,000 (urban district) and 59,000 (tertiary referral) Inclusion criteria: aged $\geq$ 18 years, and nausea or vomiting (or both) during their ED episode of care for which the attending doctor recommended IV Exclusion criteria: haemodynamic instability or primary diagnosis requiring time critical intervention; pregnancy or lactation, Parkinson's disease or restless leg syndrome; use of any antiemetic drug in the previous 8 hours or prior IV fluid in ED, ED nausea or vomiting that was motion related or associated with vertigo; currently undergoing chemotherapy or radiotherapy; inability to understand study explanation of outcome measures; known allergy or previous adverse reaction to study drugs Number: total 258; treatment group 1 (87); treatment group 2 (88); control group (83) Median age, IQR (years): treatment group 1 (42, 27-61); treatment group 2 (42, 27-67)

	; control group (42, 28-62) Sex (M/W): treatment group 1 (31/56); treatment group 2 (30/58); control group (28/55)
Interventions	Treatment group 1: ondansetron 4 mg IV Treatment group 2: metoclopramide 10 mg IV Control group: placebo All interventions were administered as a single push over 2 min All groups received IV fluid over the 30-min study period
Outcomes	Primary outcome: change in nausea severity score at 30 min Secondary outcomes: proportion of participants requiring rescue medication, adverse reactions, participant satisfaction
Notes	Median (IQR) IV fluid received: group 1 180 (125-250); group 2 200 (125-300); control group 200 (125-250) Additional data provided by author - means and SD for treatment groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number sequence in blocks of 6 by independent trial pharmacist
Allocation concealment (selection bias)	Low risk	Study drug prepared and packed in sequentially numbered packs by independent pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All 3 study drugs prepared to look identical as 2 x 2 mL syringes of clear fluid, labelled only as study medications
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Code not broken until after all data entry and analysis complete
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete data for 12/270 participants. Small likelihood of bias
Selective reporting (reporting bias)	Low risk	No indication of selective reporting
Other bias	Low risk	No other biases

Ernst 2000

Methods	Study design: randomized, double-blind parallel trial Study duration: not stated Follow-up: 60 min
Participants	Country: USA Setting: 2 university Hospital EDs Annual census: not stated Inclusion criteria: uncomplicated gastritis or gastroenteritis, aged ≥ 18 years, reported inability to drink fluids without recurrence of nausea or vomiting and required IV hydration and administration of antiemetic Exclusion criteria: another possible source of the nausea, vomiting and diarrhoea; significant abdominal pain in association with other causes; any underlying serious illness such as diabetes or renal failure, or altered sensorium; people who had received prior antiemetics; inability to understand English; drug or alcohol use; pregnancy; refusal to participate and inability to perform VAS ratings Number: total 84; treatment group 1 (42); treatment group 2 (42) Mean age ± SD (years): treatment group 1 (29 ± 11); treatment group 2 (30 ± 14) Sex (M/W): treatment group 1 (14/28); treatment group 2 (11/31)
Interventions	Treatment group 1: prochlorperazine 10 mg IV Treatment group 2: promethazine 25 mg IV All interventions were administered as a stat dose Both groups received IV fluid administration
Outcomes	Primary outcome: change in nausea severity score at 30 and 60 min Secondary outcomes: proportion of participants requiring rescue medication, proportion of participants who required hospital admission, adverse effects
Notes	Mean ± SD of IV fluid: group 1 1300 ± 700 mL; group 2 1100 ± 600 mL

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	Low risk	1 investigator mixed solutions according to the randomization table, but did not participate in obtaining VAS data or administration. Together with "convenience sampling" the process has the potential to compromise allocation concealment; however, we thought that this was unlikely to have occurred to the extent to systematically bias results, and judged the domain to be low risk of bias

Ernst 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Efforts made to blind participants and investigators. 2 medications were prepared to appear identical as 10 mL of clear fluid in a syringe
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Efforts made to blind participants and investigators. Another investigator, blinded to the allocation and not involved in the data collection, performed the data entry and analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	No reported attrition
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other source of bias

Patka 2011

Methods	Study design: prospective, randomized, active controlled, double-blinded study Study duration: not stated Follow-up: 120 min
Participants	Country: not stated Setting: not stated Annual census: not stated Inclusion criteria: if admitted to ED with nausea or vomiting, or both Exclusion criteria: previous treatment in the ED with antiemetics; missed last menstrual period or pregnancy; aged < 18 years; conditions with impaired gastrointestinal tract function (i.e. irritable bowel syndrome); impaired mental status; treatment with antineoplastic agents within 7 days prior to randomization; people unable to read English language; people leaving the ED against medical advice Number: total 64; treatment group 1 (32); treatment group 2 (32) Mean age (years) (SD not reported): treatment group 1 (41); treatment group 2 (40) Sex (M/W): treatment group 1 (15/17); treatment group 2 (14/18)
Interventions	Treatment group 1: prochlorperazine 10 mg IV Treatment group 2: ondansetron 4 mg IV Prochlorperazine administered as single pushed dose over 2 min and ondansetron administered pushed over 2-5 min
Outcomes	Primary outcome: number of vomiting episodes. Secondary outcomes: change in nausea severity score at 30 (60 and 120 min), proportion of participants requiring rescue medication, adverse effects (sedation, headache, akathisia)
Notes	Additional data provided by author - means and SD for treatment groups, and clarifications about methodology

Patka 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were assigned to treatment using a 1 : 1 random numbers table
Allocation concealment (selection bias)	Unclear risk	Mechanism for allocation concealment not elucidated in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Mechanism for blinding not reported. Inconsistency with "blinding" in reporting, e.g. reported as double blind, however reported interventions differed in their administration times 2 vs. 2-5 min
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were self reported; however' mechanism for blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data for some outcomes, but unlikely to have substantial effect on results
Selective reporting (reporting bias)	Low risk	Primary outcome of review reported satisfactorily. Secondary outcomes incompletely reported, e.g. VAS scores for headache and sedation reported divided into quartiles only. Unlikely to substantially influence results
Other bias	Unclear risk	Generally poor reporting, no reasons given for non-recruitment substantial numbers screened

CCF: congestive cardiac failure; ED: emergency department; IQR: interquartile range; IV: intravenous; M: men; min: minute; SD: standard deviation; VAS: visual analogue scale; W: women.

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

Study	Reason for exclusion
Agorastos 1981	Setting not clearly identified as ED
Cohen 1999	Not identified as ED study, "outpatient setting". Exclusion criteria included requirement for intravenous treatment
Ordog 1984	Not a randomized trial, no comparator group
Roy 1991	Setting not ED (general practice), outcomes measured beyond the time frame considered for this review
Sussman 1999	Setting not clearly identified as ED (quote: "many of the centres conducting the study in an ED"), outcomes reported only at 24 hours, therefore not relevant to this review

ED: emergency department.

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

Friedland 2008

Methods	Study design: prospective, randomized, double-blind, controlled clinical trial Study duration: December 2004 to April 2006 Follow-up: 60 min
Participants	Country: not stated Setting: single urban ED Annual census: 80,000 Inclusion criteria: aged ≥ 18 years, acute nausea or vomiting Exclusion criteria: hepatic disease, head trauma, small bowel obstruction, fever > 100.2 °F (37.2 °C), severe abdominal pain, gastrointestinal bleed, hernia Number: treatment group 1: 32; treatment group 2: 35 Median age, IQR (years): combined both groups 33 (IQR not reported) Sex (M/W): combined both groups 72% women
Interventions	Treatment group 1: granisetron 0.1 mg IV Treatment group 2: prochlorperazine 10 mg IV
Outcomes	Main outcomes: change in nausea VAS at 30 and 60 min, rescue medication use
Notes	Data reported in abstract only Results: change in nausea VAS at 30 min was group 1 -34.6 mm (95% CI -43.2 to -26.1), group 2 -35.5 mm (95% CI -44.3 to -26.7), at 60 min was -47.6 mm (95% CI -57.7 to -37.4) and -45.6 mm (95% CI -54.5 to -36.8). "No difference in rescue medication use"

Haensel 2007

Methods	Study design: prospective, randomized, double-blind study Study duration: 12 months in 2005-2006 Follow-up: 30 min
Participants	Country: not stated Setting: adult ED Annual census: not stated Inclusion criteria: nausea and at least 1 episode of vomiting within 12 hours of presentation Exclusion criteria: not stated Number: total 132 participants (not reported separately) Mean age, SD (years): not reported Sex (M/W): not reported
Interventions	Treatment group 1: ondansetron 4 mg Treatment group 2: ondansetron 2 mg Treatment group 3: metoclopramide 10 mg At least 500 mL of IV saline
Outcomes	Primary outcome: nausea VAS at 30 min Secondary outcomes: complete relief of nausea, subjective change in nausea, adverse effects
Notes	Reported in abstract only Results: "all 3 groups had significant and similar reduction in VAS" from 66.4 mm to 33.6 mm (not reported separately. No reported adverse events

Thacker 2003

Methods	Study design: prospective, randomized study Study duration: not stated Follow-up: 60 min
Participants	Country: not stated Setting: not stated Annual census: not stated Inclusion criteria: adults undergoing treatment for nausea Exclusion criteria: pregnancy Number: treatment group 1: 16; treatment group 2: 12 Mean age (years): total 33.8 (95% CI 29.3 to 38.4), not reported separately Sex (M/W): 63% women, not reported separately
Interventions	Treatment group 1: droperidol 1.25 mg IV Treatment group 2: metoclopramide 10 mg IV
Outcomes	Outcomes: nausea VAS, somnolence VAS, adverse effects, QTc
Notes	Abstract only available Results: mean change in nausea VAS: group 1 (-46.9 mm, 95% CI -55.3 to -38.5); group 2 (-45.2 mm, 95% CI -62.6 to -27.9). Akathisia reported in 2 (12.5%) participants in group 1 and 1 (9.1%) participants in group 2

Thacker 2004

Methods	Study design: prospective, randomized, study Study duration: not stated Follow-up: 60 min
Participants	Country: not stated Setting: not stated Annual census: 100,000 Inclusion criteria: adults presenting with nausea and vomiting who were to receive an IV antiemetic Exclusion criteria: pregnancy, mental disabilities, and QTc > 440 m seconds Number: treatment group 1: 6; treatment group 2: 15; treatment group 3: 5 Mean age, SD (years): not reported Sex (M/W): not reported
Interventions	Treatment group 1: droperidol 0.625 mg IV Treatment group 2: droperidol 1.25 mg IV Treatment group 3: droperidol 2.5 mg IV
Outcomes	Outcomes: nausea and somnolence VAS at 0 and 60 min, and any extrapyramidal reactions and dysrhythmias
Notes	Abstract only available Results: mean change in nausea VAS, for group 1: -44.2 mm, 95% CI 9.9 to 78.4; group 2: -30.4 mm, 95% CI 19.0 to 41.7; group 3: -45.0 mm, 95% CI 20.2 to 69.8. Mean change in somnolence VAS for group 1: 0.0 mm, 95% CI -26.5 to 26.5; group 2: 4.8 mm, 95% CI -12.6 to 22.5; group 3: 20.0 mm, 95% CI -56.5 to 60.5. No significant difference in QTc or adverse events

CI: confidence interval; ED: emergency department; IQR: interquartile range; IV: intravenous; M: men; min: minute; SD: standard deviation; VAS: visual analogue scale; W: women.

DATA AND ANALYSES

Comparison 1. Metoclopramide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	3	301	Mean Difference (IV, Random, 95% CI)	-5.27 [-11.33, 0.80]
2 Proportion of participants requiring rescue medication	3	299	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.17, 0.53]
3 Participant satisfaction	2	216	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.60, 1.91]

Comparison 2. Ondansetron versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	2	250	Mean Difference (IV, Random, 95% CI)	-4.32 [-11.20, 2.56]
2 Proportion of participants requiring rescue medication	2	247	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.37]

Comparison 3. Metoclopramide versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	4	470	Mean Difference (IV, Random, 95% CI)	-0.00 [-4.50, 4.49]
2 Proportion of participants requiring rescue medication	4	469	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.21, 1.73]
3 Participant satisfaction	2	242	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.71, 2.17]

Comparison 4. Metoclopramide versus 5HT3 antagonist

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	3	356	Mean Difference (IV, Random, 95% CI)	-1.74 [-6.88, 3.40]
2 Proportion of participants requiring rescue medication	3	353	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.20, 2.50]

Comparison 5. Metoclopramide versus ondansetron

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	2	256	Mean Difference (IV, Random, 95% CI)	-2.00 [-8.30, 4.29]
2 Proportion of participants requiring rescue medication	2	253	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.22, 0.68]

Comparison 6. 5HT3 Antagonists versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	5	583	Mean Difference (IV, Fixed, 95% CI)	2.28 [-2.03, 6.59]
2 Proportion of participants requiring rescue medication	5	582	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.72, 3.01]
3 Proportion of participants who required hospital admission	2	184	Odds Ratio (M-H, Random, 95% CI)	1.84 [0.35, 9.60]

Comparison 7. Ondansetron versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	4	483	Mean Difference (IV, Random, 95% CI)	2.61 [-2.31, 7.53]
2 Proportion of participants requiring rescue medication	4	482	Odds Ratio (M-H, Random, 95% CI)	2.00 [1.29, 3.09]
3 Participant satisfaction	2	263	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.36, 4.22]

Comparison 8. Ondansetron versus promethazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	2	204	Mean Difference (IV, Random, 95% CI)	3.16 [-4.29, 10.60]
2 Proportion of participants requiring rescue medication	2	207	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.70, 2.37]

Comparison 9. Prochlorperazine versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	2	135	Mean Difference (IV, Random, 95% CI)	0.93 [-11.57, 13.42]
2 Proportion of participants requiring rescue medication	3	219	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.07, 8.74]
3 Proportion of participants who required hospital admission	2	148	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.05, 0.95]

Comparison 10. Promethazine versus active control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in nausea severity at 30 minutes	2	244	Mean Difference (IV, Random, 95% CI)	-2.17 [-8.99, 4.66]
2 Proportion of participants requiring rescue medication	3	334	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.58, 4.14]
3 Proportion of participants who required hospital admission	2	204	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.51, 2.70]

Analysis 1.1. Comparison 1 Metoclopramide versus placebo, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 1 Metoclopramide versus placebo

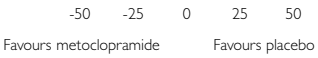
Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	Metoclopramide N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barrett 2011	40	-31.8 (21.7)	39	-23.46 (26.7)		31.8 %	-8.34 [-19.08, 2.40]
Braude 2006	25	-40.2 (23.8)	26	-38.7 (21.1)		24.0 %	-1.50 [-13.86, 10.86]
Egerton-Warburton 2014	88	-27.8 (28.8)	83	-22.7 (31.9)		44.1 %	-5.10 [-14.23, 4.03]
Total (95% CI)	**153**		**148**			**100.0 %**	**-5.27 [-11.33, 0.80]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.67$, df = 2 (P = 0.71); $I^2 = 0.0\%$

Test for overall effect: Z = 1.70 (P = 0.089)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Metoclopramide versus placebo, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 1 Metoclopramide versus placebo

Outcome: 2 Proportion of participants requiring rescue medication

Study or subgroup	Metoclopramide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	9/43	23/41		33.9 %	0.21 [0.08, 0.54]
Braude 2006	1/25	4/26		6.1 %	0.23 [0.02, 2.21]
Egerton-Warburton 2014	15/84	29/80		60.0 %	0.38 [0.19, 0.79]
Total (95% CI)	**152**	**147**		**100.0 %**	**0.30 [0.17, 0.53]**

Total events: 25 (Metoclopramide), 56 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.06$, df = 2 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 4.21 (P = 0.000025)

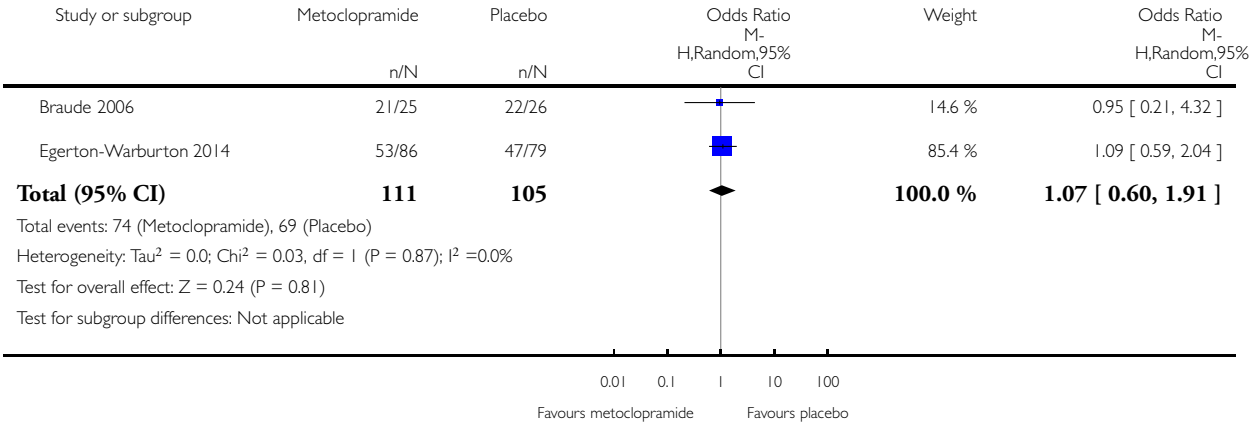
Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Metoclopramide versus placebo, Outcome 3 Participant satisfaction.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 1 Metoclopramide versus placebo

Outcome: 3 Participant satisfaction

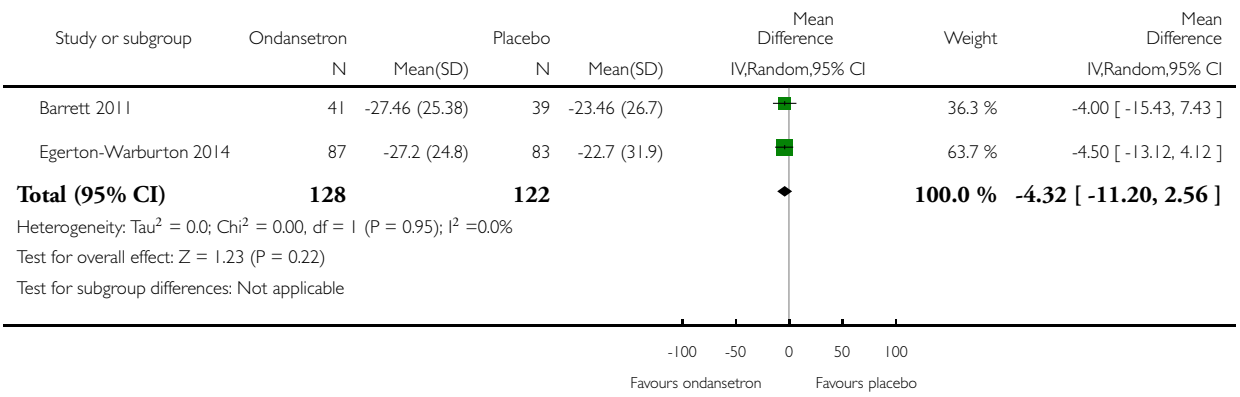


Analysis 2.1. Comparison 2 Ondansetron versus placebo, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 2 Ondansetron versus placebo

Outcome: 1 Change in nausea severity at 30 minutes

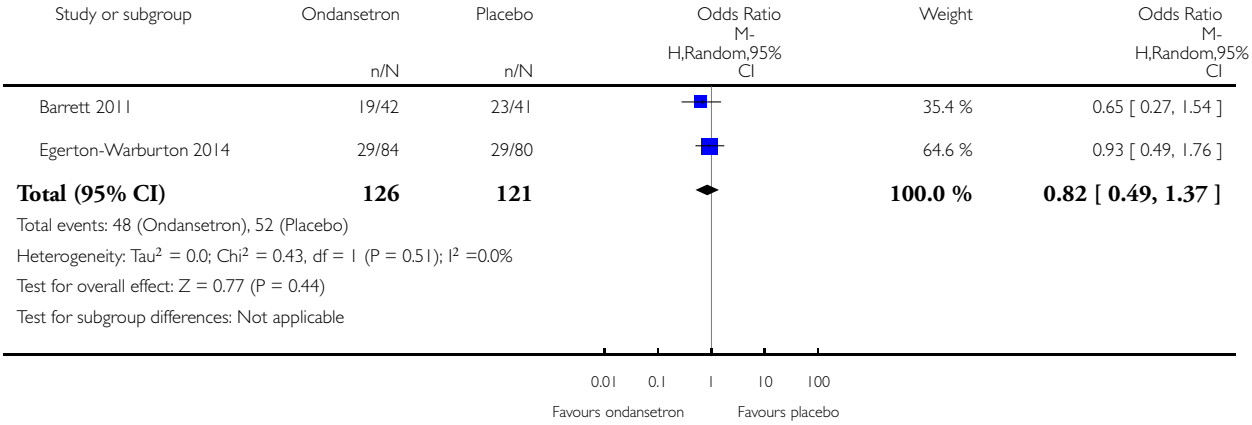


Analysis 2.2. Comparison 2 Ondansetron versus placebo, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 2 Ondansetron versus placebo

Outcome: 2 Proportion of participants requiring rescue medication



Analysis 3.1. Comparison 3 Metoclopramide versus active control, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 3 Metoclopramide versus active control

Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	Metoclopramide N	Mean(SD)	Active control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barrett 2011	40	-31.8 (21.7)	84	-29.75 (25.58)		26.9 %	-2.05 [-10.72, 6.62]
Braude 2006	25	-40.2 (23.8)	46	-47.2 (22.47)		15.7 %	7.00 [-4.37, 18.37]
Chae 2011	50	-26.4 (19.7)	50	-25 (25.4)		25.5 %	-1.40 [-10.31, 7.51]
Egerton-Warburton 2014	88	-27.8 (28.8)	87	-27.2 (24.8)		31.9 %	-0.60 [-8.56, 7.36]
Total (95% CI)	**203**		**267**			**100.0 %**	**0.00 [-4.50, 4.49]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.79$, df = 3 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.00 (P = 1.0)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Metoclopramide versus active control, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 3 Metoclopramide versus active control

Outcome: 2 Proportion of participants requiring rescue medication

Study or subgroup	Metoclopramide n/N	Active control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	9/43	38/87		29.2 %	0.34 [0.15, 0.80]
Braude 2006	1/25	7/46		14.3 %	0.23 [0.03, 2.01]
Chae 2011	13/50	5/50		25.6 %	3.16 [1.03, 9.69]
Egerton-Warburton 2014	15/84	29/84		30.9 %	0.41 [0.20, 0.84]
Total (95% CI)	**202**	**267**		**100.0 %**	**0.61 [0.21, 1.73]**

Total events: 38 (Metoclopramide), 79 (Active control)

Heterogeneity: $Tau^2 = 0.80$; $Chi^2 = 11.84$, df = 3 (P = 0.01); $I^2 = 75\%$

Test for overall effect: Z = 0.94 (P = 0.35)

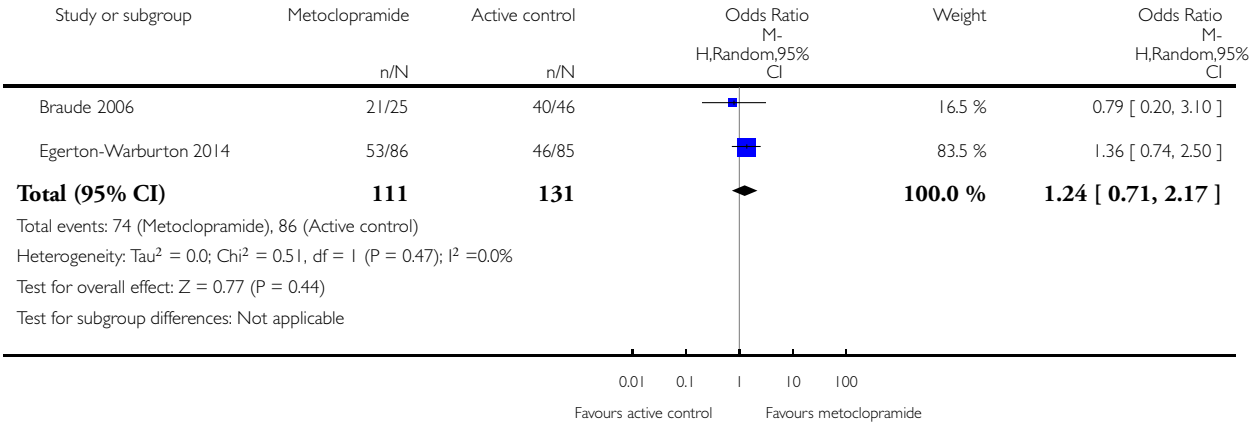
Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Metoclopramide versus active control, Outcome 3 Participant satisfaction.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 3 Metoclopramide versus active control

Outcome: 3 Participant satisfaction

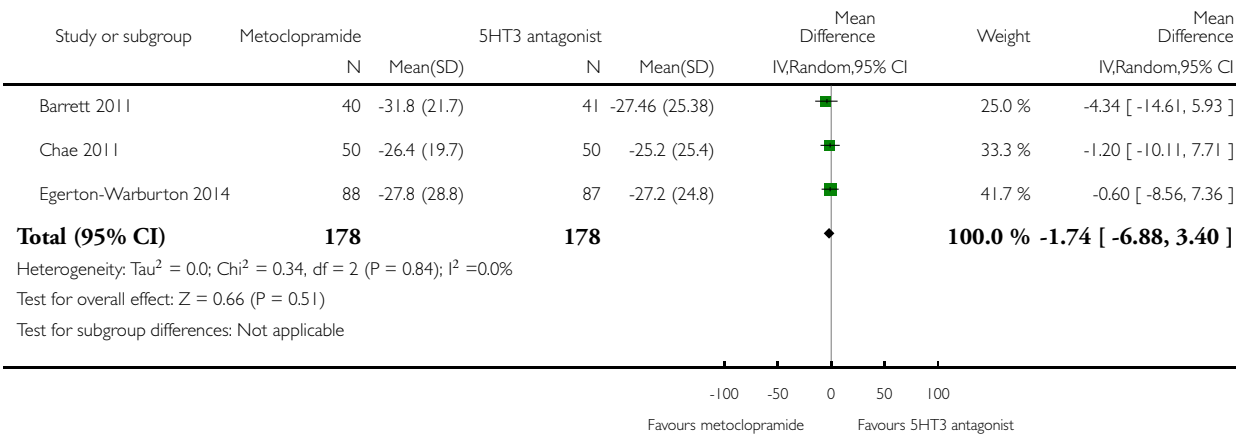


Analysis 4.1. Comparison 4 Metoclopramide versus 5HT3 antagonist, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 4 Metoclopramide versus 5HT3 antagonist

Outcome: 1 Change in nausea severity at 30 minutes

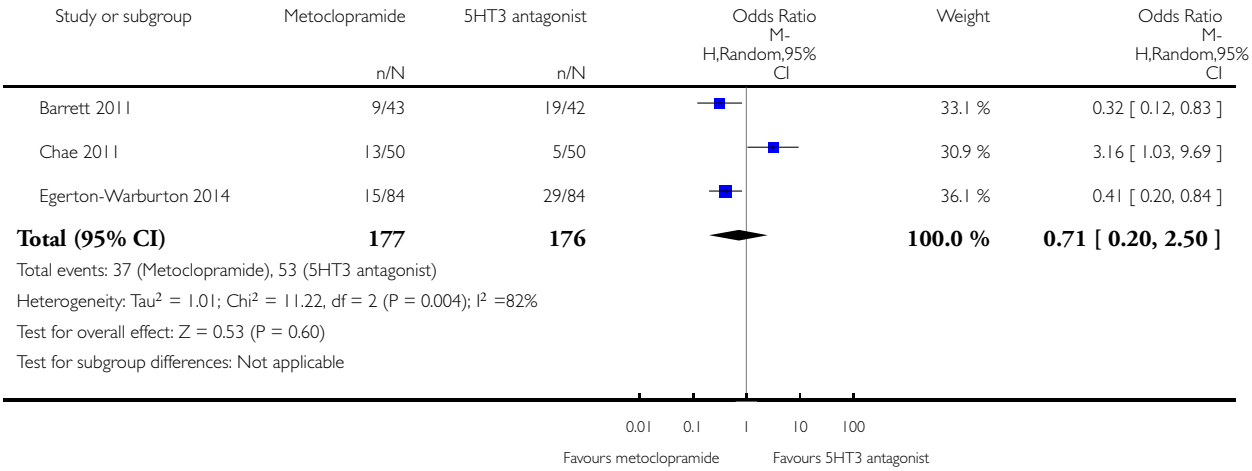


Analysis 4.2. Comparison 4 Metoclopramide versus 5HT3 antagonist, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 4 Metoclopramide versus 5HT3 antagonist

Outcome: 2 Proportion of participants requiring rescue medication



Analysis 5.1. Comparison 5 Metoclopramide versus ondansetron, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 5 Metoclopramide versus ondansetron

Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	Metoclopramide N	Mean(SD)	Ondansetron N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barrett 2011	40	-31.8 (21.7)	41	-27.46 (25.38)		37.5 %	-4.34 [-14.61, 5.93]
Egerton-Warburton 2014	88	-27.8 (28.8)	87	-27.2 (24.8)		62.5 %	-0.60 [-8.56, 7.36]
Total (95% CI)	**128**		**128**			**100.0 %**	**-2.00 [-8.30, 4.29]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.32$, df = 1 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 5.2. Comparison 5 Metoclopramide versus ondansetron, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 5 Metoclopramide versus ondansetron

Outcome: 2 Proportion of participants requiring rescue medication

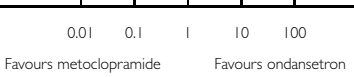
Study or subgroup	Metoclopramide n/N	Ondansetron n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	9/42	19/43		36.2 %	0.34 [0.13, 0.89]
Egerton-Warburton 2014	15/84	29/84		63.8 %	0.41 [0.20, 0.84]
Total (95% CI)	**126**	**127**		**100.0 %**	**0.39 [0.22, 0.68]**

Total events: 24 (Metoclopramide), 48 (Ondansetron)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 1 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 3.26 (P = 0.0011)

Test for subgroup differences: Not applicable



Analysis 6.1. Comparison 6 5HT3 Antagonists versus active control, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 6 5HT3 Antagonists versus active control

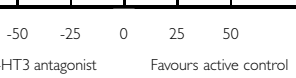
Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	5-HT3 antagonist N	Mean(SD)	Active control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Barrett 2011	41	-27.5 (25.4)	83	-31.9 (23.6)		21.5 %	4.40 [-4.89, 13.69]
Braude 2008	60	-34 (29)	60	-36 (28)		17.8 %	2.00 [-8.20, 12.20]
Chae 2011	50	-25.2 (25.4)	50	-26.4 (19.7)		23.4 %	1.20 [-7.71, 10.11]
Egerton-Warburton 2014	87	-27.2 (24.8)	88	-27.8 (28.8)		29.3 %	0.60 [-7.36, 8.56]
Patka 2011	32	-21.4 (22.1)	32	-27.9 (37.9)		8.0 %	6.50 [-8.70, 21.70]
Total (95% CI)	**270**		**313**			**100.0 %**	**2.28 [-2.03, 6.59]**

Heterogeneity: $Chi^2 = 0.73$, df = 4 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6 5HT3 Antagonists versus active control, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 6 5HT3 Antagonists versus active control

Outcome: 2 Proportion of participants requiring rescue medication

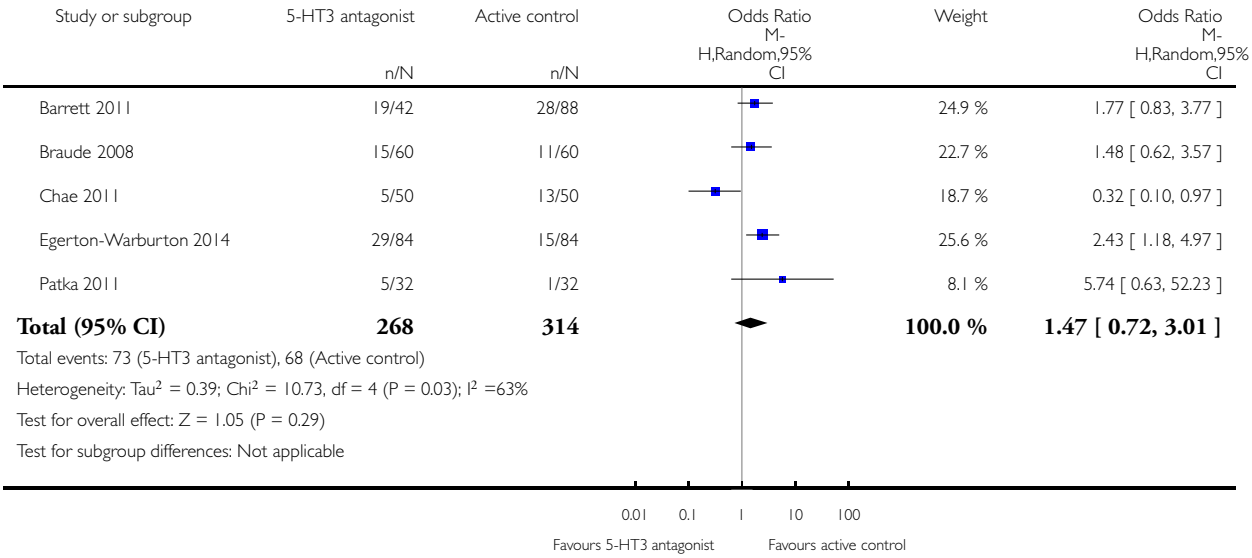
Study or subgroup	5-HT3 antagonist n/N	Active control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	19/42	28/88		24.9 %	1.77 [0.83, 3.77]
Braude 2008	15/60	11/60		22.7 %	1.48 [0.62, 3.57]
Chae 2011	5/50	13/50		18.7 %	0.32 [0.10, 0.97]
Egerton-Warburton 2014	29/84	15/84		25.6 %	2.43 [1.18, 4.97]
Patka 2011	5/32	1/32		8.1 %	5.74 [0.63, 52.23]
Total (95% CI)	**268**	**314**		**100.0 %**	**1.47 [0.72, 3.01]**

Total events: 73 (5-HT3 antagonist), 68 (Active control)

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 10.73$, df = 4 (P = 0.03); $I^2 = 63\%$

Test for overall effect: Z = 1.05 (P = 0.29)

Test for subgroup differences: Not applicable

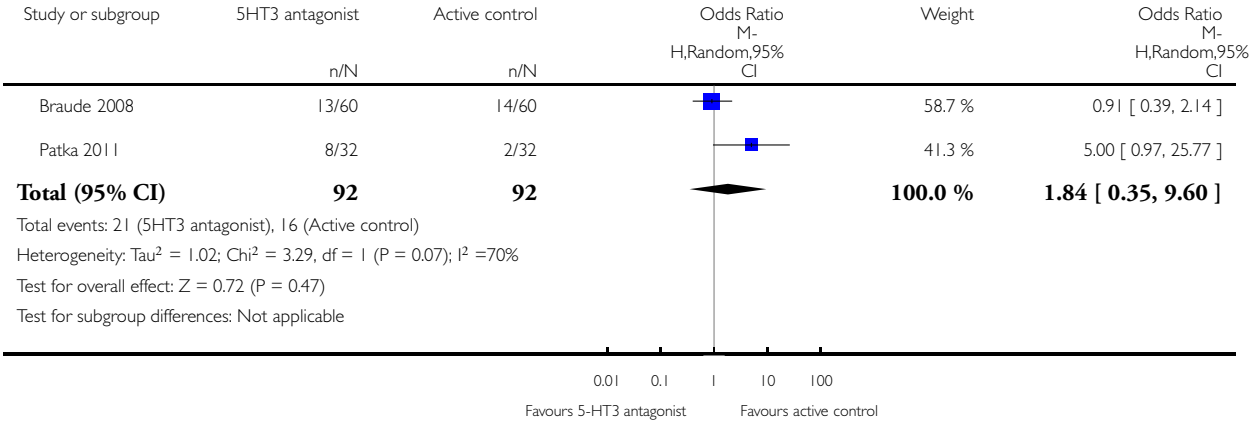


Analysis 6.3. Comparison 6 5HT3 Antagonists versus active control, Outcome 3 Proportion of participants who required hospital admission.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 6 5HT3 Antagonists versus active control

Outcome: 3 Proportion of participants who required hospital admission



Analysis 7.1. Comparison 7 Ondansetron versus active control, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 7 Ondansetron versus active control

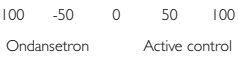
Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	Ondansetron		Active control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Barrett 2011	41	-27.5 (25.4)	83	-31.9 (23.6)		28.1 %	4.40 [-4.89, 13.69]
Braude 2008	60	-34 (29)	60	-36 (28)		23.3 %	2.00 [-8.20, 12.20]
Egerton-Warburton 2014	87	-27.2 (24.8)	88	-27.8 (28.8)		38.2 %	0.60 [-7.36, 8.56]
Patka 2011	32	-21.4 (22.1)	32	-27.9 (37.9)		10.5 %	6.50 [-8.70, 21.70]
Total (95% CI)	**220**		**263**			**100.0 %**	**2.61 [-2.31, 7.53]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.65$, df = 3 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7 Ondansetron versus active control, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 7 Ondansetron versus active control

Outcome: 2 Proportion of participants requiring rescue medication

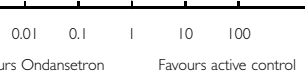
Study or subgroup	Ondansetron n/N	Active control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	19/42	28/88		33.7 %	1.77 [0.83, 3.77]
Braude 2008	15/60	11/60		25.0 %	1.48 [0.62, 3.57]
Egerton-Warburton 2014	29/84	15/84		37.4 %	2.43 [1.18, 4.97]
Patka 2011	5/32	1/32		3.9 %	5.74 [0.63, 52.23]
Total (95% CI)	**218**	**264**		**100.0 %**	**2.00 [1.29, 3.09]**

Total events: 68 (Ondansetron), 55 (Active control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.70$, df = 3 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 3.09 (P = 0.0020)

Test for subgroup differences: Not applicable

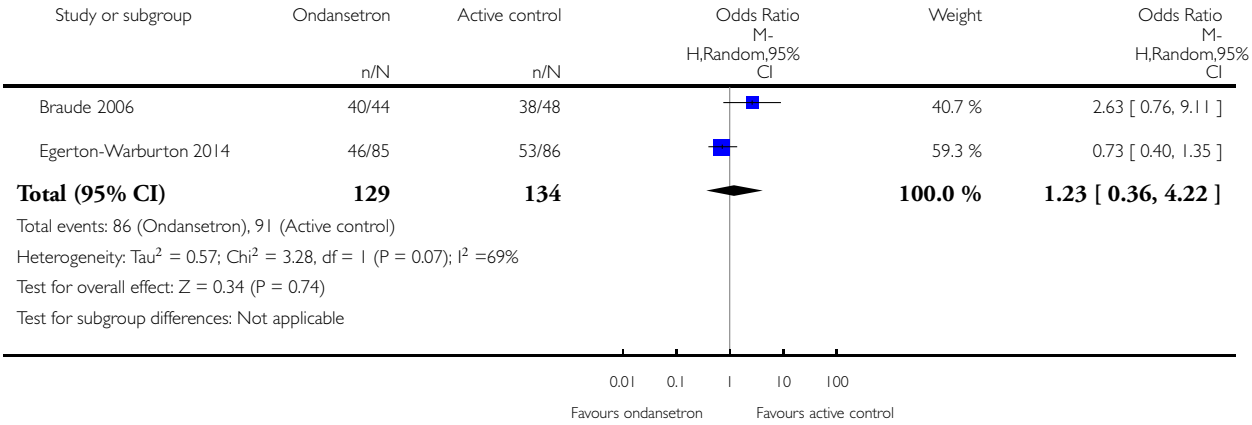


Analysis 7.3. Comparison 7 Ondansetron versus active control, Outcome 3 Participant satisfaction.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 7 Ondansetron versus active control

Outcome: 3 Participant satisfaction

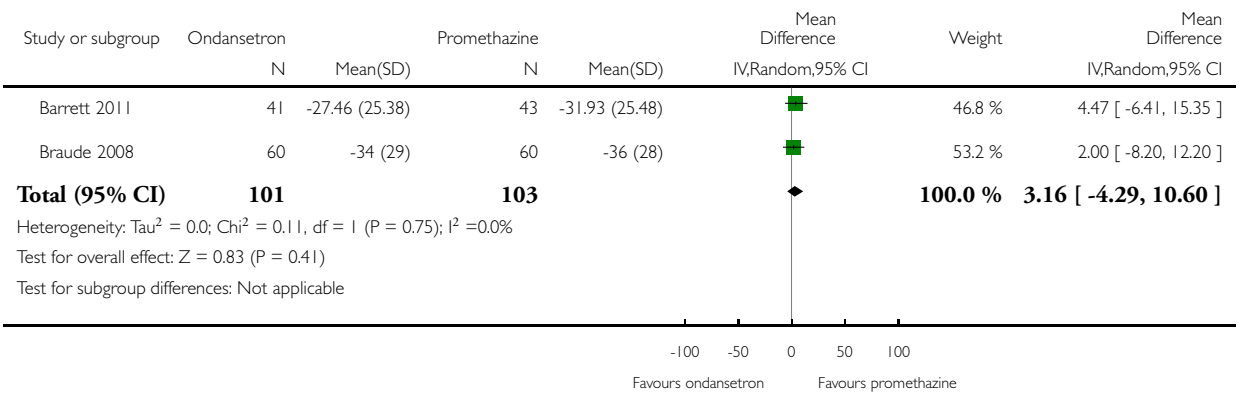


Analysis 8.1. Comparison 8 Ondansetron versus promethazine, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 8 Ondansetron versus promethazine

Outcome: 1 Change in nausea severity at 30 minutes



Analysis 8.2. Comparison 8 Ondansetron versus promethazine, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 8 Ondansetron versus promethazine

Outcome: 2 Proportion of participants requiring rescue medication

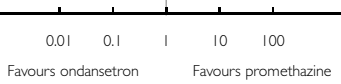
Study or subgroup	Ondansetron n/N	Promethazine n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	19/42	19/45		51.7 %	1.13 [0.48, 2.64]
Braude 2008	15/60	11/60		48.3 %	1.48 [0.62, 3.57]
Total (95% CI)	**102**	**105**		**100.0 %**	**1.29 [0.70, 2.37]**

Total events: 34 (Ondansetron), 30 (Promethazine)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 1 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Test for subgroup differences: Not applicable



Analysis 9.1. Comparison 9 Prochlorperazine versus active control, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 9 Prochlorperazine versus active control

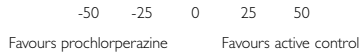
Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	Prochlorperazine N	Mean(SD)	Active control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Braude 2006	24	-40.5 (24.1)	47	-46.9 (22.4)		57.6 %	6.40 [-5.17, 17.97]
Patka 2011	32	-27.9 (37.9)	32	-21.4 (22.1)		42.4 %	-6.50 [-21.70, 8.70]
Total (95% CI)	**56**		**79**			**100.0 %**	**0.93 [-11.57, 13.42]**

Heterogeneity: Tau² = 35.69; Chi² = 1.75, df = 1 (P = 0.19); I² =43%

Test for overall effect: Z = 0.15 (P = 0.88)

Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9 Prochlorperazine versus active control, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 9 Prochlorperazine versus active control

Outcome: 2 Proportion of participants requiring rescue medication

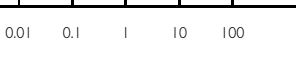
Study or subgroup	Prochloperazine n/N	Active control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Braude 2006	6/24	2/47		34.1 %	7.50 [1.38, 40.69]
Ernst 2000	3/42	12/42		36.2 %	0.19 [0.05, 0.74]
Patka 2011	1/32	3/32		29.7 %	0.31 [0.03, 3.17]
Total (95% CI)	**98**	**121**		**100.0 %**	**0.77 [0.07, 8.74]**

Total events: 10 (Prochloperazine), 17 (Active control)

Heterogeneity: Tau² = 3.75; Chi² = 11.53, df = 2 (P = 0.003); I² =83%

Test for overall effect: Z = 0.21 (P = 0.84)

Test for subgroup differences: Not applicable

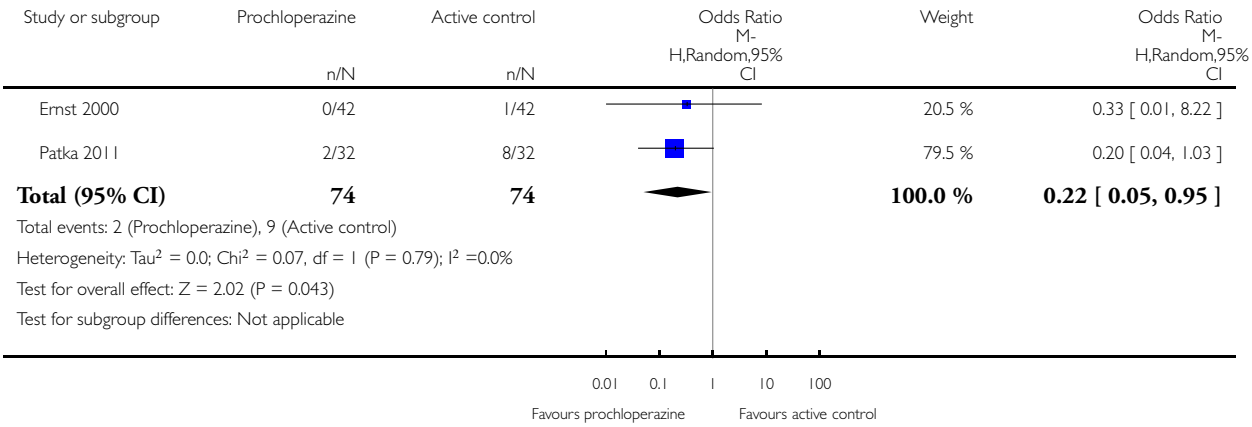


Analysis 9.3. Comparison 9 Prochlorperazine versus active control, Outcome 3 Proportion of participants who required hospital admission.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 9 Prochlorperazine versus active control

Outcome: 3 Proportion of participants who required hospital admission



Analysis 10.1. Comparison 10 Promethazine versus active control, Outcome 1 Change in nausea severity at 30 minutes.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 10 Promethazine versus active control

Outcome: 1 Change in nausea severity at 30 minutes

Study or subgroup	Promethazine N	Mean(SD)	Active control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Barrett 2011	43	-31.9 (25.5)	81	-29.6 (23.6)		55.2 %	-2.30 [-11.49, 6.89]
Braude 2008	60	-36 (28)	60	-34 (29)		44.8 %	-2.00 [-12.20, 8.20]
Total (95% CI)	**103**		**141**			**100.0 %**	**-2.17 [-8.99, 4.66]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 10.2. Comparison 10 Promethazine versus active control, Outcome 2 Proportion of participants requiring rescue medication.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 10 Promethazine versus active control

Outcome: 2 Proportion of participants requiring rescue medication

Study or subgroup	Promethazine n/N	Active control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Barrett 2011	19/45	28/85		38.7 %	1.49 [0.71, 3.13]
Braude 2008	11/60	15/60		35.6 %	0.67 [0.28, 1.62]
Ernst 2000	12/42	3/42		25.7 %	5.20 [1.35, 20.09]
Total (95% CI)	**147**	**187**		**100.0 %**	**1.55 [0.58, 4.14]**

Total events: 42 (Promethazine), 46 (Active control)

Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 6.33$, df = 2 (P = 0.04); $I^2 = 68\%$

Test for overall effect: Z = 0.87 (P = 0.39)

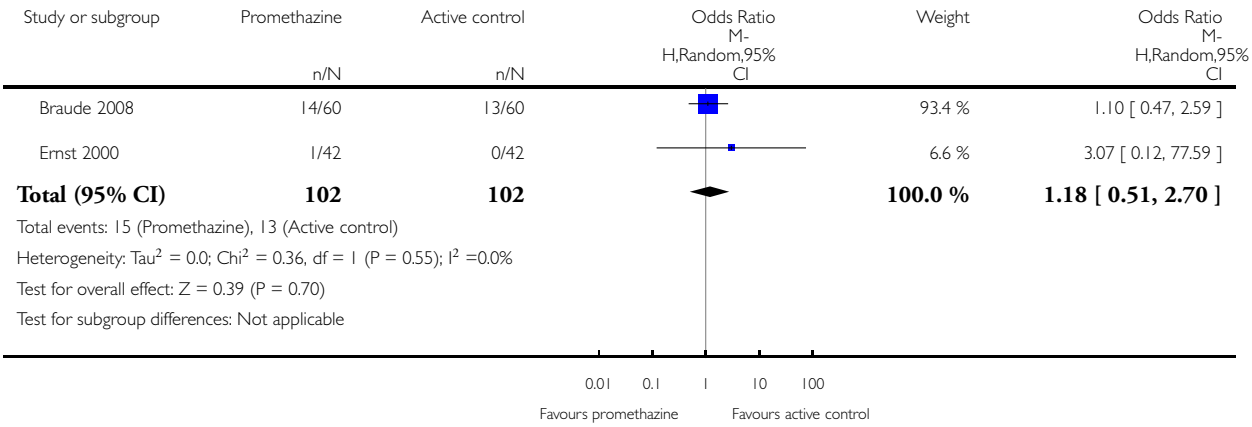
Test for subgroup differences: Not applicable

Analysis 10.3. Comparison 10 Promethazine versus active control, Outcome 3 Proportion of participants who required hospital admission.

Review: Drugs for the treatment of nausea and vomiting in adults in the emergency department setting

Comparison: 10 Promethazine versus active control

Outcome: 3 Proportion of participants who required hospital admission



ADDITIONAL TABLES

Table 1. Prochlorperazine versus placebo

Outcome	Participants	Statistical methods	Effect estimate
Change in nausea severity at 30 minutes	50	Mean Difference (IV, Random, 95% CI [mm])	-1.80 [-14.40, 10.80]
Proportion of participants requiring rescue medication	50	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.45, 7.51]
Participant satisfaction	50	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.20, 4.13]

Data from single trial comparing prochlorperazine versus placebo (Braude 2006).
CI: confidence interval.

Table 2. Promethazine versus placebo

Outcome	Participants	Statistical methods	Effect estimate
Change in nausea severity at 30 minutes	82	Mean Difference (IV, Random, 95% CI [mm])	-8.47 [-19.79, 2.85]
Proportion of participants requiring rescue medication	86	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.24, 1.34]

Data from single trial comparing promethazine versus placebo (Barrett 2011).
CI: confidence interval.

Table 3. Droperidol versus placebo

Outcome	Participants	Statistical methods	Effect estimate
Change in nausea severity at 30 minutes	48	Mean Difference (IV, Random, 95% CI [mm])	-15.80 [-26.98, -4.62]
Proportion of participants requiring rescue medication	48	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.03, 2.54]
Participant satisfaction	48	Odds Ratio (M-H, Random, 95% CI)	1.82 [0.30, 11.02]

Data from single trial comparing droperidol versus placebo (Braude 2006).
CI: confidence interval.

Table 4. Ondansetron versus placebo

Outcome	Participants	Statistical methods	Effect estimate
Participant satisfaction	164	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.43, 1.49]

Data from single trials comparing drug versus placebo.
CI: confidence interval.

Table 5. Metoclopramide versus tropisetron

Outcome	Participants	Statistical method	Effect estimate
Change in nausea severity at 30 minutes	100	Mean Difference (IV, Random, 95% CI [mm])	-1.20 [-10.11, 7.71]

Table 5. Metoclopramide versus tropisetron (*Continued*)

Proportion of participants requiring rescue medication	100	Odds Ratio (M-H, Random, 95% CI)	3.16 [1.03, 9.69]

Data from single trials comparing metoclopramide versus active control.
CI: confidence interval.

Table 6. Metoclopramide versus promethazine

Outcome	Participants	Statistical method	Effect estimate
Change in nausea severity at 30 minutes	83	Mean Difference (IV, Random, 95% CI [mm])	0.10 [-10.06, 10.26]
Proportion of participants requiring rescue medication	88	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.93]

Data from single trials comparing metoclopramide versus active control.
CI: confidence interval.

Table 7. Metoclopramide versus prochlorperazine

Outcome	Participants	Statistical method	Effect estimate
Change in nausea severity at 30 minutes	49	Mean Difference (IV, Random, 95% CI [mm])	0.30 [-13.12, 13.72]
Proportion of participants requiring rescue medication	49	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.01, 1.13]
Participant satisfaction	49	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.23, 4.78]

Data from single trials comparing metoclopramide versus active control.
CI: confidence interval.

Table 8. Metoclopramide versus droperidol

Outcome	Participants	Statistical method	Effect estimate
Change in nausea severity at 30 minutes	47	Mean Difference (IV, Random, 95% CI [mm])	14.30 [2.21, 26.39]
Proportion of participants requiring rescue medication	47	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.05, 14.87]

Table 8. Metoclopramide versus droperidol (*Continued*)

Participant satisfaction	47	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.09, 3.19]

Data from single trials comparing metoclopramide versus active control.
CI: confidence interval.

Table 9. Metoclopramide versus ondansetron

Outcome	Participants	Statistical method	Effect estimate
Participant satisfaction	171	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.74, 2.50]

Data from single trials comparing metoclopramide versus active control.
CI: confidence interval.

Table 10. Ondansetron versus prochlorperazine

Outcome	Participants	Statistical methods	Effect estimate
Change in nausea severity at 30 minutes	64	Mean Difference (IV, Random, 95% CI [mm])	6.50 [-8.70, 21.70]
Proportion of participants requiring rescue medication	64	Odds Ratio (M-H, Random, 95% CI)	5.74 [0.63, 52.23]
Proportion of participants who required hospital admission	64	Odds Ratio (M-H, Fixed, 95% CI)	5.00 [0.97, 25.77]

Data from single trial comparing ondansetron versus prochlorperazine (Patka 2011).
CI: confidence interval.

Table 11. Ondansetron versus promethazine

Outcome	Participants	Statistical methods	Effect estimate
Proportion of participants who required hospital admission	120	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.39, 2.14]
Participant satisfaction	92	Odds Ratio (M-H, Random, 95% CI)	2.63 [0.76, 9.11]

Data from single trials comparing ondansetron versus active control.
CI: confidence interval.

Table 12. Prochlorperazine versus droperidol

Outcome	Participants	Statistical methods	Effect estimate
Change in nausea severity at 30 minutes	46	Mean Difference (IV, Random, 95% CI [mm])	14.00 [1.67, 26.33]
Proportion of participants requiring rescue medication	46	Odds Ratio (M-H, Random, 95% CI)	1.91 [0.16, 22.66]
Participant satisfaction	46	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.08, 3.05]

Data from single trials comparing prochlorperazine versus droperidol.
CI: confidence interval.

Table 13. Prochlorperazine versus promethazine

Outcome	Participants	Statistical method	Effect estimate
Proportion of participants requiring rescue medication	84	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.05, 0.74]
Proportion of participants who required hospital admission	84	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.22]

Data from single trials comparing prochlorperazine versus promethazine.
CI: confidence interval.

Table 14. Prochlorperazine versus active control

Outcome	Participants	Statistical method	Effect estimate
Participant satisfaction	71	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.19, 2.89]

Data from single trials comparing prochlorperazine versus active control.
CI: confidence interval.

Table 15. Droperidol versus active control

Outcome	Participants	Statistical method	Effect estimate
Change in nausea severity at 30 minutes	71	Mean Difference (IV, Random, 95% CI [mm])	-14.10 [-24.26, -3.94]
Proportion of participants requiring rescue medication	71	Odds Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.48]

Table 15. Droperidol versus active control (*Continued*)

Participant satisfaction	69	Odds Ratio (M-H, Random, 95% CI)	3.41 [0.39, 29.68]

Data from single trial by Braude 2006.
CI: confidence interval.

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1. antiemetics/ or antiemesis.ti,ab. or antiemetic*.ti,ab. or antiemetogenic.ti,ab. or dopamine antagonists/ or (dopamine$ adj2 antagonists).ti,ab. or (chlorpromazine or droperidol or domperidone or metoclopramide or haloperidol or prochlorperazine or promethazine or alizapride).ti,ab. or serotonin antagonists/ or (serotonin adj2 antagonist$).ti,ab. or (dolasetron or granisetron or ondansetron or tropisetron or palonosetron).ti,ab. or cholinergic antagonists/ or (anticholinergic agents or scopolamine or hyoscine).ti,ab. or histamine H1 antagonists/ or antihistamines.ti,ab. or buclizine.ti,ab. or cyclizine.ti,ab. or dimenhydrinate.ti,ab. or trimethobenzamide.ti,ab. or meclizine.ti,ab. or pheniramine.ti,ab. or piphenhydramine.ti,ab. or benzodiazepines/ or lorazepam.ti,ab. or diazepam.ti,ab. or adrenal cortex hormones/ or corticosteroids.ti,ab. or dexamethasone.ti,ab. or methylprednisolone.ti,ab. or betamethasone.ti,ab. or cannabinoids/ or cannabinoid$.ti,ab. or marijuana.ti,ab. or marinol.ti,ab. or dronabinol.ti,ab.
2. nausea/ or vomiting/ or nausea*.ti,ab. or vomit*.ti,ab. or emesis.ti,ab. or emet*.ti,ab. or emergency service, hospital/ or emergency medical services/ or (emergency adj3 (medic* or servic* or ward*)).ti,ab. or (intensive adj3 care).ti,ab.
3. 1 and 2
4. (randomized controlled trial.pt. or randomized.ab. or random*.ti.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 2. Search strategy for EMBASE (OvidSP)

1. exp antiemetic agent/ or exp dopamine receptor blocking agent/ or exp serotonin antagonist/ or exp cholinergic receptor blocking agent/ or exp histamine H1 receptor antagonist/ or exp benzodiazepine derivative/ or exp corticosteroid/ or exp cannabinoid/ or anti?eme*.mp. or ((serotonin or dopamine* or cholinergic) adj3 antagonist*).ti,ab. or (chlorpromazine or droperidol or domperidone or metoclopramide or haloperidol or prochlorperazine or promethazine or alizapride or dolasetron or granisetron or ondansetron or tropisetron or palonosetron or anticholinergic agent* or scopolamine or hyoscine or antihistamin* or buclizine or cyclizine or dimenhydrinate or trimethobenzamide or meclizine or pheniramine or piphenhydramine or lorazepam or diazepam or corticosteroid* or dexamethasone or methylprednisolone or betamethasone or cannabinoid* or marijuana or marinol or dronabinol).mp.
2. exp nausea/ or exp vomiting/ or exp "nausea and vomiting"/ or (nausea* or vomit* or emesis or emet*).mp.
3. exp emergency health service/ or exp emergency medicine/ or exp emergency care/ or exp emergency ward/ or exp evidence based emergency medicine/ or exp intensive care/ or (emergency adj3 (medic* or servic* or ward*)).mp. or (intensive adj3 care).mp.
4. 1 and 2 and 3
5. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.
6. 4 and 5

Appendix 3. Search strategy for CENTRAL, *The Cochrane Library*

#1 MeSH descriptor Antiemetics explode all trees
#2 MeSH descriptor Dopamine Antagonists explode all trees
#3 MeSH descriptor Serotonin Antagonists explode all trees
#4 MeSH descriptor Cholinergic Antagonists explode all trees
#5 MeSH descriptor Histamine H1 Antagonists explode all trees
#6 MeSH descriptor Adrenal Cortex Hormones explode all trees
#7 MeSH descriptor Benzodiazepines explode all trees
#8 MeSH descriptor Cannabinoids explode all trees
#9 anti?eme* or chlorpromazine or droperidol or domperidone or metoclopramide or haloperidol or prochlorperazine or promethazine or alizapride or dolasetron or granisetron or ondansetron or tropisetron or palonosetron or anticholinergic agent* or scopolamine or hyoscine or antihistamin* or buclizine or cyclizine or dimenhydrinate or trimethobenzamide or meclizine or pheniramine or piphenhydramine or lorazepam or diazepam or corticosteroid* or dexamethasone or methylprednisolone or betamethasone or cannabinoid* or marijuana or marinol or dronabinol
#10 (serotonin or dopamine* or cholinergic) near antagonist*
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Nausea explode all trees
#13 MeSH descriptor Vomiting explode all trees
#14 nausea* or vomit* or emesis or emet*
#15 (#12 OR #13 OR #14)
#16 MeSH descriptor Emergency Medical Services explode all trees
#17 MeSH descriptor Intensive Care explode all trees
#18 emergency near (medic* or servic* or ward*)
#19 intensive near care
#20 (#16 OR #17 OR #18 OR #19)
#21 (#11 AND #15 AND #20)

Appendix 4. ISI Web of Science search strategy

#1 TI=antieme* or TS=(dopamine antagonist* or chlorpromazine or droperidol or domperidone or metoclopramide or haloperidol or prochlorperazine or promethazine or alizapride or serotonin antagonist* or dolasetron or granisetron or ondansetron or tropisetron or palonosetron or cholinergic antagonist*or anticholinergic agent* or scopolamine or hyoscine or histamine H1 antagonist* or antihistamin*or buclizine or cyclizine or dimenhydrinate or trimethobenzamide or meclizine or pheniramine or piphenhydramine or benzodiazepine* or lorazepam or diazepam or adrenal cortex hormone* or corticosteroid* or dexamethasone or methylprednisolone or betamethasone or cannabinoid* or marijuana or marinol or dronabinol)
#2 TI=(nausea or vomiting or emesis or emet*) or TS=(emergency SAME (medic* or servic* or ward*)) or TS=(intensive SAME care)
#3 TS=(random* or ((control*or clinical) SAME trial)) not TS=(animal* not (human* and animals*))
#4 #3 AND #2 AND #1

Appendix 5. Data Collection Form

Review author initials (completing form):
Study ID (surname of author and year):
Report ID (created by review author):
Citation and contact details:
First Author:
Journal/Conference proceeding etc:
Date:
Contact details:
NOTES:

Eligibility Verification

1. Identified as Randomized Controlled trial**:** **[ ]** Yes [ ] No [ ] Unclear

2. Emergency Department setting: **[ ]** Yes [ ] No [ ] Unclear

3. Adults (> 80% Participants ≥16 years): **[ ]** Yes [ ] No [ ] Unclear

4. Undifferentiated Nausea and Vomiting: **[ ]** Yes [ ] No [ ] Unclear

5. Pharmacological agent and appropriate comparator: **[ ]** Yes [ ] No [ ] Unclear
(Appropriate comparators are placebo, no treatment or active control)

6. Relevant outcomes: **[ ]** Yes [ ] No [ ] Unclear
(Nausea any scale and/or vomiting episodes)

Note: If answered no to any of the above questions the study should not be included in the review. If study is to be included in "excluded studies" section of the review, record information to be inserted into "Table of excluded studies"

EXCLUDED STUDY DETAILS:

Participant characteristics

	Details
Age (mean, median, range, etc.)	
Sex of participants (numbers/%)	
Other	

Trial Characteristics

	Further details
Single centre / Multicentre	
Country / Countries	
Setting (e.g. Emergency Department)	
How was participant eligibility defined?	

(*Continued*)

How many people were randomized?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Drug treatment(s) used	
Comparator	
Dose / frequency of administration	
Duration of treatment	
Median (range) length of follow-up reported in this paper	
Time-points when measurements were taken during the study	
Time-points reported in the study	
Time-points you are using in RevMan	
Trial design	
Outcomes measured (units)	
Other	

Risk of Bias Assessment

Selection Bias

Domain	Random sequence generation
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Domain	Allocation concealment
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Performance Bias

Domain	Blinding of participants and personnel
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Detection Bias

Domain	Blinding of outcome assessment
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Attrition Bias

Domain	Incomplete outcome data
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Reporting Bias

Domain	Selective reporting
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Other Bias

Domain	Other sources of Bias
Review authors' judgement:	[ ] Low risk [ ] High risk [ ] Unclear risk
Support for judgement:	

Results

Outcomes relevant to review	
	Reported in paper (circle)
Primary outcome - Nausea severity	Yes / No
Primary outcome - Complete resolution of nausea	Yes/No
Primary outcome - Number of vomits	Yes / No
Primary outcome - Adverse events	Yes / No
Secondary outcomes	
Outcome 1 - Requiring rescue medication	Yes / No
Outcome 2 - Proportion requiring admission	Yes / No

(*Continued*)

Outcome 3 - Emergency length of stay	Yes / No
Outcome 4 - Patient satisfaction	Yes / No

For Continuous data

Code of paper	Outcomes	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (SD)	n	Mean (SD)	
	Primary Outcome - Nausea severity						
	Primary outcome - Number of vomits						
	Secondary outcome 3 - Emergency department LOS						

For Dichotomous data

Code of paper	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events

(*Continued*)

	Primary outcome - Adverse events reported		
	Primary outcome - Complete resolution of nausea		
	Secondary outcome 1 - requiring rescue medication		
	Secondary outcome 2 - requiring admission		
	Secondary outcome 4 - Patient satisfaction		

Other information which you feel is relevant to the results

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

Freehand space for writing actions such as contact with study authors and changes

Additional information.

Funding Source	
Key conclusions of study authors	
Clarifications with study authors	

References to other trials

Did this report include any references to published reports of potentially eligible trials not already identified for this review?		
First author	Journal / Conference	Year of publication
Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details		

CONTRIBUTIONS OF AUTHORS

Jeremy S Furyk (JF), Robert A Meek (RM), Diana Egerton-Warburton (DEW).

Conceiving the review: JF.

Co-ordinating the review: JF.

Undertaking manual searches: JF, RM.

Screening search results: JF, RM.

Organizing retrieval of papers: JF.

Screening retrieved papers against inclusion criteria: JF, RM.

Appraising quality of papers: JF, RM.

Abstracting data from papers: JF, RM.

Writing to authors of papers for additional information: JF.

Providing additional data about papers: JF.

Obtaining and screening data on unpublished studies: JF.

Data management for the review: JF.

Entering data into Review Manager (RevMan 2014): JF.

RevMan statistical data: JF.

Other statistical analysis not using RevMan: JF.

Interpretation of data: JF, RM, DEW.

Statistical inferences: JF, RM, DEW.

Writing the review: JF, RM, DEW.

Securing funding for the review: JF.

Performing previous work that was the foundation of the present study: JF, RM, DEW.

Guarantor for the review (one author): JF.

Person responsible for reading and checking review before submission: JF.

DECLARATIONS OF INTEREST

Jeremy S Furyk: none known.

Robert Meek and Diana Egerton-Warburton are authors of one of the trials included in this review (Egerton-Warburton 2014).

JF and RM independently appraised the study for inclusion, risk of bias and data extraction.

There were no disagreements in this process, or need for independent arbiter.

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Internal sources

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External sources

- Queensland Emergency Medicine Research Foundation (QEMRF), Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. The search strategy of the review differed from the published protocol with the omission of the LILACS database (Furyk 2012).

2. The search identified trials with multiple intervention groups, therefore, we combined groups to create single pair-wise comparisons as outlined in Section 16.5.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

3. For dichotomous outcomes, we summed both the sample sizes and the numbers of people with events across groups, and for continuous outcomes, we combined means and standard deviations using methods described in Section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

4. The protocol stipulated use of risk ratios to measure treatment effect of dichotomous outcomes, whereas in the review we have reported results as odds ratios.

5. Missing data for the primary outcome of change in nausea severity was not an issue, therefore, there was no requirement to use imputation methods for 'worst-case', 'best-case' and 'average-case' scenarios or to perform sensitivity analyses.

6. In addition to assessing for statistical heterogeneity as described in the protocol (Furyk 2012), we assessed for clinical heterogeneity, with consideration to the characteristics of included studies regarding participants, interventions and outcome measures.

7. Planned subgroup analysis on nausea and vomiting associated with pregnancy, opiate administration and chemotherapy was not possible due to no data.

8. For our 'Summary of findings' table, we presented the data for the comparison of metoclopramide versus placebo, as it was the most commonly evaluated drug. We could not include outcomes of time to treatment success, intravenous fluid volume and admission rate as stated in the protocol due to a lack of data (Furyk 2012). We also included outcomes of the requirement for rescue medication and participant satisfaction in the 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

*Emergency Service, Hospital; Antiemetics [*therapeutic use]; Droperidol [therapeutic use]; Metoclopramide [therapeutic use]; Nausea [*drug therapy]; Ondansetron [therapeutic use]; Prochlorperazine [therapeutic use]; Promethazine [therapeutic use]; Randomized Controlled Trials as Topic; Visual Analog Scale; Vomiting [*drug therapy]

MeSH check words

Adult; Female; Humans; Male