

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 oncology² and postoperative nausea and vomiting³ 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

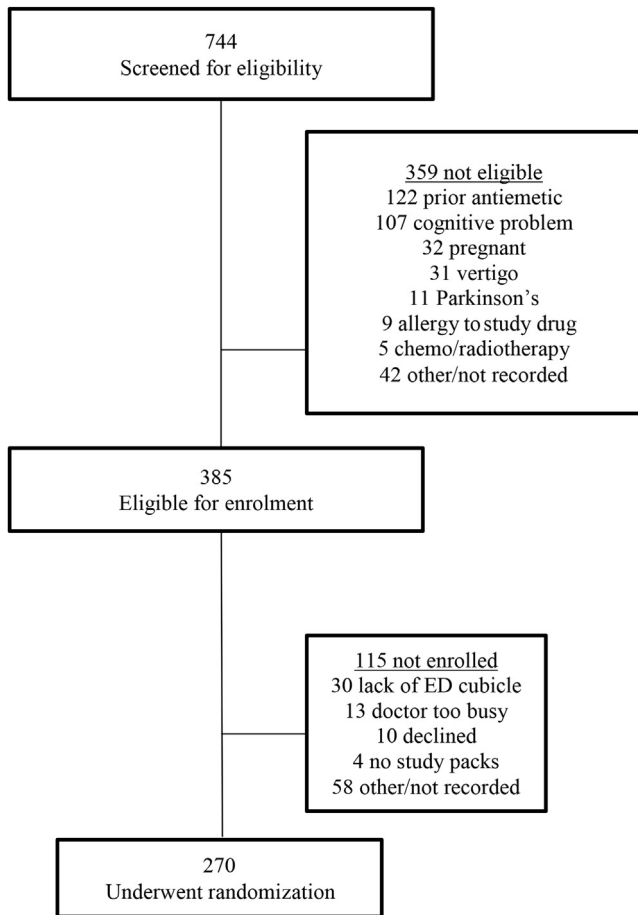


Figure 1. CONSORT diagram of patient flow.

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. (%) [95% CI]	56 (64.4) [53.9-73.9]	58 (65.9) [55.6-75.2]	55 (66.3) [55.6-75.8]
Main clinical causes, No. (%) [95 CI]			
Opioid induced	23/72 (31.9) [22.0-43.4]	19/65 (29.2) (19.2-41.1)	16/63 (25.4) (15.8-37.2)
Gastroenteritis	19/72 (26.4) [17.2-37.5]	10/65 (15.4) [8.1-25.7]	14/63 (22.2) [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

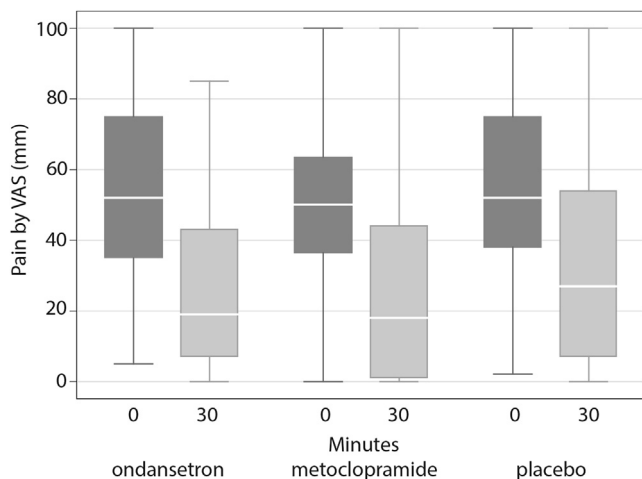


Figure 2. Box and whisker plot of enrollment (VAS1) and 30-minute (VAS2) severity ratings for each treatment group.

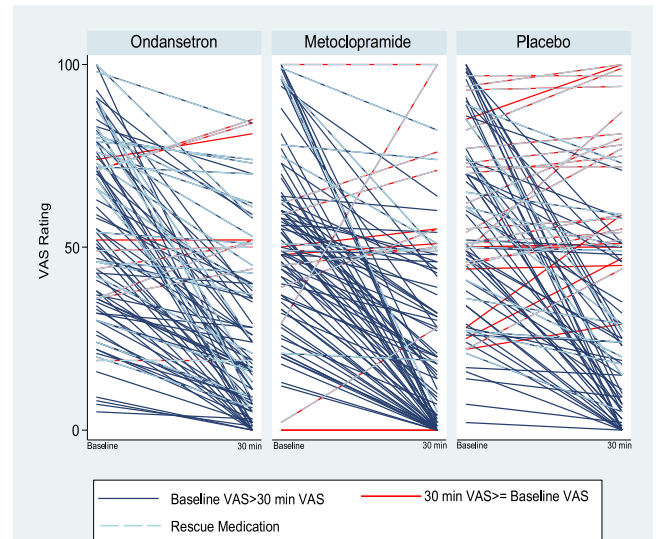


Figure 3. Change in rating from baseline to 30 minutes for all patients in each treatment group. Patients with increased severity ratings and who received rescue antiemetic are highlighted.

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.

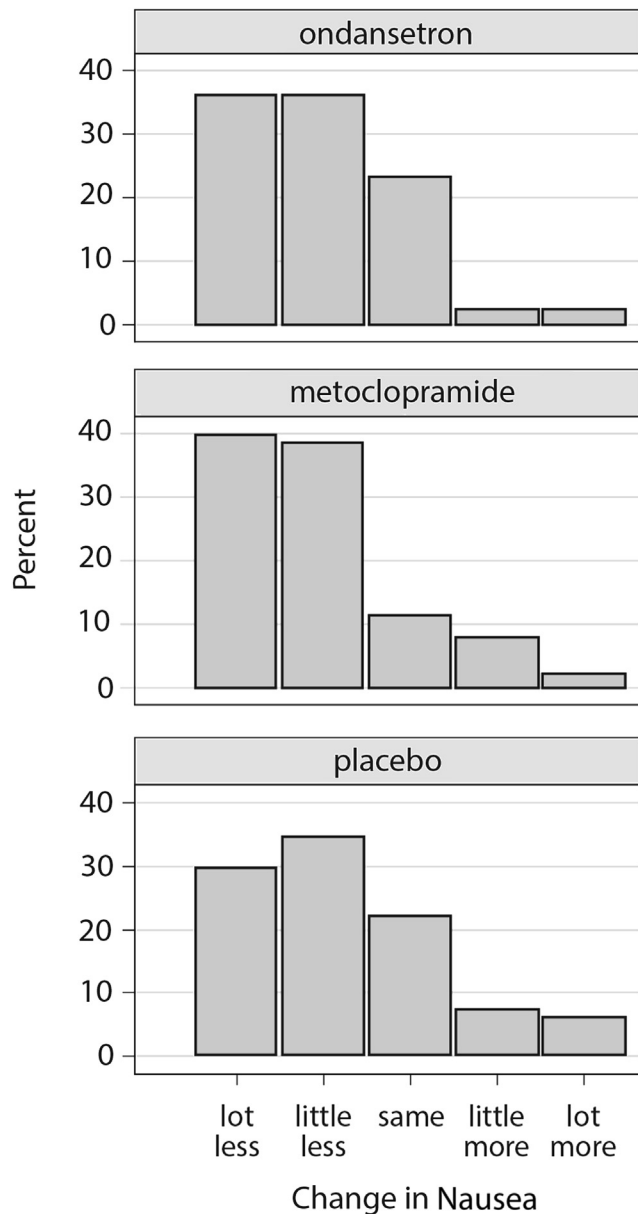


Figure 4. Distribution of change in severity descriptions from enrollment to 30 minutes for each treatment group. 1="a lot less," 2="a little less," 3="the same," 4="a little more," and 5="a lot more."

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 al⁴ 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 al⁴ 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 al⁴ and Barrett et al⁵ 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 al⁴ 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 oncology² and postoperative nausea and vomiting³ 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)
	Ondansetron 4 mg (n=60)	34 (SD 29)
Braude, 2008 ⁶	Promethazine 25 mg (n=60)	36 (SD 28)
	Tropisetron 5 mg (n=50)	25 (SD 25)
Chae, 2011 ⁷	Metoclopramide 10 mg (n=50)	26 (SD 20)