

BMJ Open Methotrimeprazine versus haloperidol in palliative care patients with cancer-related nausea: a randomised, double-blind controlled trial

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ABSTRACT

Objectives Methotrimeprazine is commonly used for the management of nausea but never tested formally against other drugs used in this setting. The aim was to demonstrate superior antiemetic efficacy.

Design Double-blind, randomised, controlled trial of methotrimeprazine versus haloperidol.

Setting 11 palliative care sites in Australia.

Participants Participants were >18 years, had cancer, an average nausea score of $\geq 3/10$ and able to tolerate oral medications. Ineligible patients had acute nausea related to treatment, nausea for which a specific antiemetic was indicated, were about to undergo a procedure or had received either of the study drugs or a change in glucocorticoid dose within the previous 48 hours.

Interventions Based on previous studies, haloperidol was used as the control. Participants were randomised to encapsulated methotrimeprazine 6-25 mg or haloperidol 1.5 mg one time or two times per day and assessed every 24 hours for 72 hours.

Main outcome measures A \geq two-point reduction in nausea score at 72 hours from baseline. Secondary outcome measures were as follows: complete response at 72 hours (end nausea score less than 3), response at 24 and 48 hours, vomiting episodes, use of rescue antiemetics, harms and global impression of change.

Results Response to treatment at 72 hours was 75% (44/59) in the haloperidol (H) arm and 63% (36/57) in the methotrimeprazine (M) arm with no difference between groups (intention-to-treat analysis). Complete response rates were 56% (H) and 51% (M). In the *per protocol* analysis, there was no difference in response rates: 85% (44/52) (H) and 74% (36/49) (M). Complete *per protocol* response rates were 64% (H) and 59% (M). Toxicity worse than baseline was minimal with a trend towards greater sedation in the methotrimeprazine arm.

Conclusion This study did not demonstrate any difference in response rate between methotrimeprazine and haloperidol in the control of nausea.

Trial registration number ACTRN 12615000177550.

INTRODUCTION

Many people with cancer experience nausea not directly related to anticancer treatment.¹ This has a significant impact on quality of

Strength and limitations of this study

- This is one of very few quality multisite randomised controlled trials (RCTs) assessing the management of nausea and vomiting (N/V) in patients receiving palliative care.
- No other high-quality RCT of methotrimeprazine has been published to date.
- The study builds on previous work conducted by this group.
- It assesses only the short-term control of N/V.
- Haloperidol is not accepted as a standard antiemetic in many countries.

life (QoL), general activity and emotional well-being.² The focus of research in patients with cancer has centred on treatment-related emesis, for which there is good evidence of benefit for a number of agents.³ Nausea (and vomiting) unrelated to anticancer treatment remains an important and under-researched health problem, especially given the global burden of cancer.

Unlike chemotherapy-induced or radiation-induced nausea and vomiting (N/V), the evidence base for the treatment of cancer-related N/V is sparse and weak, and most of the recommendations are consensus-based. The most recent guidelines recommend metoclopramide as first-line treatment, with haloperidol, levomepromazine or olanzapine as alternative options.⁴ The evidence to support the use of other antiemetics commonly used in advanced cancer (eg, prochlorperazine, promethazine and cyclizine) is from uncontrolled or cohort studies.

As a consequence of multiple systematic reviews that have highlighted the need for randomised controlled studies (RCTs) of antiemetics in patients with cancer with nausea not related to treatment,⁴⁻⁶ our group has undertaken a series of RCTs in an attempt

to redress this knowledge deficit. In an initial study, we compared a mechanistic approach to nausea treatment (whereby the choice of a specific antiemetic drug was based on the aetiology of the nausea and knowledge of emetogenic pathways and receptors) with an empirical approach using a single agent,⁷ irrespective of the underlying cause of nausea. Haloperidol was used as the single agent comparator as metoclopramide was used frequently in the mechanistic arm. A high response rate (over 60%) was achieved in the *per protocol* analysis, with a more rapid response in the aetiology-based arm but no difference in the primary outcome measure at 72 hours between arms. The study demonstrated how currently available licensed drugs can lead to good nausea control if given regularly, at an appropriate dose by an appropriate route. The response rate for haloperidol, supported those found in our previous uncontrolled study⁸ and justified the use of haloperidol as our standard antiemetic for subsequent studies.

Haloperidol is a butyrophenone that exerts an antiemetic effect by blocking dopamine receptors in the chemoreceptor trigger zone of the brain.⁹ It is commonly used for the treatment of N/V in patients with cancer and several consensus-based guidelines endorse its use in the palliative care setting.^{4,10} Despite this, there remains resistance to the use of this drug outside the specialty, often because of concern regarding potential side effects, most frequently extrapyramidal movement disorders. A Cochrane review updated in 2015 concluded that there was incomplete evidence to determine the effectiveness of haloperidol for the control of N/V in palliative care.⁵

Another agent that has been used for the management of refractory nausea in the palliative care setting is a broad spectrum phenothiazine that acts at multiple receptor sites to cover a number of possible causes of nausea. Levomepromazine is the injectable form of this medication. The oral formulation is methotrimeprazine. There is consensus that phenothiazines including levomepromazine are likely to be beneficial in controlling N/V in patients with cancer, but despite wide use of this drug by clinicians, especially in the UK and Europe, there was a lack of evidence to support its effectiveness in palliative care patients. Uncontrolled trials have reported benefits in chemotherapy-induced and postoperative N/V.^{11,12} Two open label studies in patients with cancer receiving palliative care reported high rates of N/V control.^{13,14} For many years, it has been recognised that at higher doses, the sedative effects of this drug can be used to advantage in the management of terminal restlessness and agitation.¹⁵ A Cochrane review of levomepromazine updated in 2015 failed to identify any RCTs.⁶ The common off-label use of this drug led to the development of the current study. The null hypothesis was that there would be no difference in response rates of the two medications.

METHODS

Study design

This double-blind, RCT was undertaken in 11 sites within the Australian national Palliative Care Clinical Studies Collaborative. The study is reported in accordance with CONSORT guidance for RCTs. This study was part of a programme of work focused on the relief of nausea in cancer patients.⁷

Patients and public involvement

The experience of participants in the first study of this series⁷ contributed to the design of the subsequent studies.

Participants

Participants were known to a palliative care team, were >18 years, had a diagnosis of cancer and nausea with an average score over the past 24 hours of ≥ 3 on an 11 point (0–10) numerical rating scale (NRS). They had to be able to tolerate oral medications and comply with all trial requirements. Patients were ineligible if they had nausea related to the treatment of cancer (ie, surgery, chemotherapy) within 5 days of anticancer therapy, had nausea for which a specific antiemetic was indicated and randomisation to study medications alone would not be appropriate (such as dexamethasone for acutely raised intra-cranial pressure and 5HT₃ antagonists for chemotherapy-induced or radiotherapy-induced N/V), were to undergo a procedure or intervention with the potential to affect nausea during the 3-day study period (such as radiotherapy to a site likely to cause nausea), had received methotrimeprazine or haloperidol at study doses within the previous 48 hours, a change in glucocorticoid dose within 48 hours, or poor performance status.

Consent, randomisation and masking

Potentially eligible patients were given a patient information sheet as a basis for discussion and given time to consider and formulate questions. The consent form was signed by the participant and investigator in accordance with Good Clinical Practice requirements. Randomisation schedules were computer generated for each site at an independent central registry. There was no stratification. Schedules for each site were allocated in a 1:1 ratio in randomly allocated blocks of 2 and 4 and sent to each site pharmacy. Both study drugs were encapsulated and packed with an inert substance. All capsules were opaque and looked identical to preserve the blinding irrespective of the contents. Treatment allocation was not disclosed to study staff, treating clinicians or investigators until data cleaning was complete.

Treatments

Participants allocated to haloperidol received 1.5 mg and those allocated to methotrimeprazine 6.25 mg, both administered orally one time per day. Following daily review, the dose could be increased to 3 mg (H) and 12.5 mg (M)/24 hours in those patients with uncontrolled nausea. Oral metoclopramide 10 mg (or domperidone

for those intolerant of metoclopramide) was charted as a rescue antiemetic to be given four hourly as required (prn).

Outcome measures

Assessments of nausea severity and distress were undertaken daily using a NRS (0, 'no nausea' to 10, 'worst possible nausea').

Response was defined as at least a two-point reduction in average nausea score from baseline over the preceding 24 hours, measured at 72 hours on an 11-point NRS. Complete response was defined as at least a two-point reduction in average nausea score from baseline over the preceding 24 hours with a final score $<3/10$.

The primary outcome measure was a response to treatment at 72 hours (end day 3). Secondary outcomes included the following: average, best and worst nausea scores, nausea distress, rescue doses delivered, episodes of vomiting, need to increase dose, global impression of change (GIC)¹⁶ and adverse events. Other measures were as follows: performance status,¹⁷ symptom burden,¹⁸ QoL,¹⁹ comorbidities,²⁰ toxicity²¹ and extrapyramidal side effects.²²

Statistical analysis

The superiority of methotrimeprazine compared with haloperidol was tested by comparing the response to each drug after 72 hours, relative to baseline, using a χ^2 analysis of differences in response rates between treatments. Allowing 20% for attrition, and with estimated response rates of 85% for methotrimeprazine compared with 60% for haloperidol, it was anticipated that 126 participants (63 per treatment arm) should be randomised to achieve a sample size of 50 participants per arm, assuming 80% power, a simple random sampling scheme and a Type 1 error of 5% (two-tailed). An expert group of consultant colleagues confirmed our premise that any new unlicensed antiemetic should be at least 25% better than standard antiemetics to justify its use. No allowance was made for a design effect, assuming differences between clusters would be minimal.

Descriptive statistics and frequency distributions were generated from the patients' demographic and clinical characteristics. The primary endpoint of difference in response to treatment at 72 hours was assessed on an intention-to-treat (ITT) basis whereby eligible patients who withdrew after commencement were classified as non-responders. In a secondary ITT analysis, logistic regression was conducted to fit the binary outcome of response to treatment (yes/no) at 72 hours, adjusted for centre, although based on data from our previous study, we anticipated that the associated centre effect would be negligible. As almost half the participants came from one centre, 'centre' was dichotomised as 'large/others'. Adjustment was also made for place of care (whether treated in a hospital general ward, palliative care unit or at home/an aged care facility) and any covariates where an imbalance between groups was observed.

Other secondary analyses were conducted of participants administered treatment as randomised (*per protocol*) for response to treatment, number of vomiting episodes and GIC (worse, no change, better), using χ^2 tests at each time point. Using all available data in longitudinal analyses, change in nausea scores were analysed using mixed effects models and generalised linear models assessed change in GIC (dichotomised as improved/no change or worse) over time. All analyses were conducted using SPSS V.21 (Armonk, NY, USA: IBM Corp). There was no imputation for missing data.

Role of the funding source

The study funder had no role in the study design, collection, analysis and interpretation of data, the writing of the report or the decision to submit for publication. PY had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Of the 132 potential participants assessed for eligibility, 121 patients were randomised between March 2015 and February 2017. Five patients were subsequently proven to be ineligible, three for protocol violations determined by an independent review committee and were removed from the analysis. The ITT sample comprised 59 patients assigned to haloperidol treatment and 57 to methotrimeprazine (figure 1). At 72 hours, 52 patients had completed haloperidol treatment and 49 methotrimeprazine, *per protocol*, giving an attrition rate of 13%.

Randomisation achieved two groups that were similar with respect to baseline characteristics (table 1) except that participants assigned to methotrimeprazine were more likely to be women (70%) compared with the haloperidol arm (58%). The most common cancers in both arms were gynaecological, breast and lung. The average and worst nausea scores at baseline in each arm were 5.4 and 5.3/10 and 7.6 and 7.4/10 for the haloperidol and methotrimeprazine arms, respectively. Nausea distress was reflected by a mean nausea distress score of 6.1 and 5.9/10. Nausea was considered to be multi-factorial in origin in almost 80% in both arms. A dominant cause for nausea (most commonly central/CTZ stimulation and gastric stasis) could be determined in just over 40% of participants.

In the primary ITT analysis, the response to treatment at 72 hours was 75% (44/59) in the haloperidol arm and 63% (36/57) in the methotrimeprazine arm with no statistically significant difference between groups (-0.11 ; 95% CI: -0.30 to 0.07 ; $p=0.18$). Complete response rates were 56% (H) and 51% (M). In the *per protocol* analysis, there was no statistical difference in response rates; (85% (44/52) haloperidol and 74% (36/49) for methotrimeprazine (-0.11 ; 95% CI: -0.29 to 0.07 ; $p=0.59$). Complete *per protocol* response rates were 64% (H) and 59% (M) (table 2).

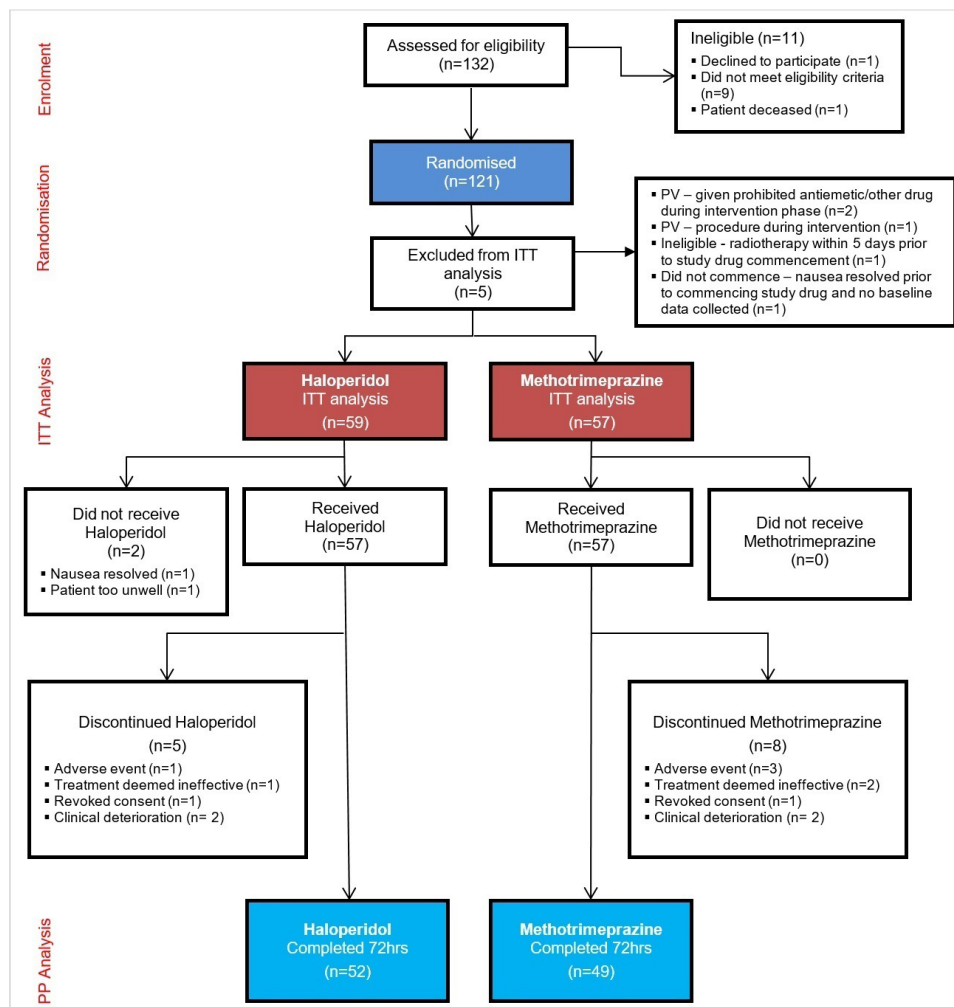


Figure 1 Patient flow. ITT, intention to treat; PV, protocol violation; PP, per protocol.

In a logistic regression analysis of response to treatment, adjusted for centre, place of care and female gender, there was no difference between arms. Longitudinal analyses of nausea scores (baseline to day 3; [figure 2](#)) showed reduction in all measures over time ($p < 0.001$), but no differences between treatment arms. After treatment completion (72 hours), patients in both arms were significantly less distressed by nausea, compared with baseline, with estimated mean scores of 2.0 (95% CI: 1.2 to 2.8) (H) and 2.2 (95% CI: 1.4 to 3.0) (M).

One-third of participants had been prescribed the higher dose at 72 hours (29% (H), 31% (M)). Episodes of vomiting decreased from over 30% at baseline to less than 15% in each arm at 72 hours. Rescue doses of metoclopramide (or domperidone) were given in around 40% of all participants at each time point ([table 3](#)), with a trend towards a greater use in the methotrimeprazine arm at 72 hours. In both arms, of those administered rescue medication, the majority of participants had one or two doses per day (85%, 85% and 74% on days 1–3) equating to ≤ 20 mg metoclopramide (or domperidone) per day.

More participants in the methotrimeprazine arm reported drowsiness worse at 72 hours than at baseline (20% vs 12%), but this difference was not significant.

Otherwise, side effects worse than baseline were minimal, specifically those relating to extrapyramidal reactions ([table 4](#)).

At 72 hours, compared with 24 hours, the proportion of patients reporting improvement in GIC increased from 72% at 24 hours to over 80% at 72 hours. A longitudinal analysis confirmed the increased proportion reporting improved GIC, but with no statistically significant difference over time or between treatment arms. Secondary outcomes by time are shown in a supplementary table ([online supplementary table S1](#)).

DISCUSSION

Consistent with the findings of our previous studies,^{7 8} we have shown a high response rate to haloperidol with metoclopramide rescue doses when this drug is used for the management of cancer-related nausea that is not associated with anticancer treatment. This justifies the recommendations in several guidelines.^{4 9 10} Concerns that this drug is associated with unacceptable side effects, specifically extrapyramidal effects, do not seem to be justified at least in the short term, with very few reports of this from both studies, as well as pharmacovigilance audits.²³

Table 1 Baseline characteristics

Characteristic	Haloperidol (n=59)				Methotrimeprazine (n=57)			
	No.	%	Mean	SD	No.	%	Mean	SD
Age (years)			66.2	10.2			67.9	12.0
Female gender	34	57.6			40	70.2		
Place of care								
Inpatient palliative care	20	34.5			17	29.8		
Hospital general ward	20	33.3			18	31.6		
Private home	18	32.1			22	38.6		
Residential aged care	1	1.7			0	0.0		
Primary cancer diagnosis								
Breast	9	15.3			9	15.8		
Lung	7	11.9			12	21.1		
Colorectal	3	5.1			3	5.3		
Gynaecologic	9	15.3			9	15.8		
Gastrointestinal	3	5.1			6	10.6		
Pancreas	6	10.2			3	5.3		
Prostate	7	11.9			3	5.3		
Other	15	25.4			12	21.1		
Performance status* (0–100)								
Median (IQR)	50 (30–90)				50 (30–90)			
Quality of life† (1–7)			3.3	1.6			3.1	1.4
Symptom burden‡ (0–90)			42.8	16.4			41.2	15.5
Charlson Comorbidity Index			6.6	1.8			6.5	2.0
Vomited in last 24 hours (Yes)	26	44.1			19	33.3		
Number of vomiting episodes								
Median (range)	0	(0–12)			0	(0–5)		
Antiemetics post-screening (Y)	24	40.7			23	40.4		
Duration of current nausea								
<1 week	6	10.2			4	7.0		
1 up to 2 weeks	11	18.6			9	15.8		
2 up to 4 weeks	13	22.0			14	24.6		
1 up to 2 months	6	10.2			11	19.3		
≥2 months	23	39.0			19	33.3		
Nausea score (0–10)								
Worst			7.6	2.1			7.4	1.8
Best			2.9	2.5			2.7	2.3
Average			5.4	1.7			5.3	1.3
Distress			6.1	2.9			5.9	2.7
Nausea interference§ (0–100)			51.7	25.2			49.4	18.6
Nausea—multi-factorial	47	79.7			45	78.9		
Dominant cause of nausea								
Undetermined	34	57.6			31	54.4		
Central/CTZ stimulation	12	20.3			15	26.3		
Gastric stasis	6	10.2			8	14.0		
Other	7	11.9			3	5.3		
No. adverse events¶ (0–11)			4.8	2.6			5.1	1.9
Adverse event prior to study drug¶								
Fatigue	47	79.7			53	93.0		

Continued



Table 1 Continued

Characteristic	Haloperidol (n=59)				Methotrimeprazine (n=57)			
	No.	%	Mean	SD	No.	%	Mean	SD
Dry mouth	39	66.1			41	71.9		
Drowsiness	35	59.3			34	59.7		
Constipation	29	49.2			27	47.4		
Dyspepsia	20	33.9			18	31.6		
Bruising	20	33.9			15	26.3		
Dizziness	19	32.2			16	28.1		
Bowel colic	14	23.7			16	28.1		
Blurred vision	12	20.3			10	17.5		
Headache	10	17.0			13	22.8		
Hypertension	5	8.5			9	15.8		
Diarrhoea	7	11.9			7	12.3		
Sensitivity to light	3	5.1			6	10.5		
Voiding difficulty	5	8.5			5	8.8		
Hypotension	5	8.5			4	7.0		
Confusion	4	6.8			5	8.8		
Jaundice	3	5.1			3	5.3		
Extrapyramidal reactions	2	3.4			1	1.8		
Palpitations	1	1.7			4	7.0		
Allergic skin reaction	1	1.7			1	1.8		

*Australian-modified Karnofsky performance status scale.

†EORTC-QLQ-C15-PAL.

‡Edmonton Symptom Assessment Scale.

§Nausea Interference Scale.

¶Any grade.

CTZ, chemoreceptor trigger zone.

Contrary to expectations, we found no difference in response rate between methotrimeprazine and haloperidol in this setting. Methotrimeprazine is used widely in those countries in which it is readily available (eg, the UK) and often by clinicians in other countries with prior experience in its use. It is anecdotally considered by many to be superior to many other agents and is therefore used in refractory nausea when other agents have failed to result in adequate control. The sedative effects of this drug at higher doses can be used to advantage for

terminal sedation; thus, it is not infrequently used for this indication in dying patients. At the doses used in this study, there appeared to be a trend towards greater sedation in the methotrimeprazine arm, but the difference was not statistically significant.

In our previous study,⁷ we demonstrated high response rates in cancer-related nausea using freely available, inexpensive antiemetics when given regularly at adequate dose. Subsequently, we have shown that methotrimeprazine is not superior to haloperidol. In fact, our series of

Table 2 Primary and secondary response outcomes

Type of response (Yes) at 72 hours	Haloperidol		Methotrimeprazine		Total		P value*
	n	n (%)	n	n (%)	n	n (%)	
Intention-to-treat analysis							
Response†	59	44 (74.6)	57	36 (63.2)	116	80 (69.0)	0.18
Complete response‡	59	33 (55.9)	57	29 (50.9)	116	62 (53.4)	0.59
Per protocol analysis							
Response	52	44 (84.6)	49	36 (73.5)	101	80 (79.2)	0.17
Complete response	52	33 (63.5)	49	29 (59.2)	101	62 (61.4)	0.66

* χ^2 test of differences between treatment groups.

† ≥ 2 -point difference from baseline.

‡ 2-point difference from baseline and end score < 3

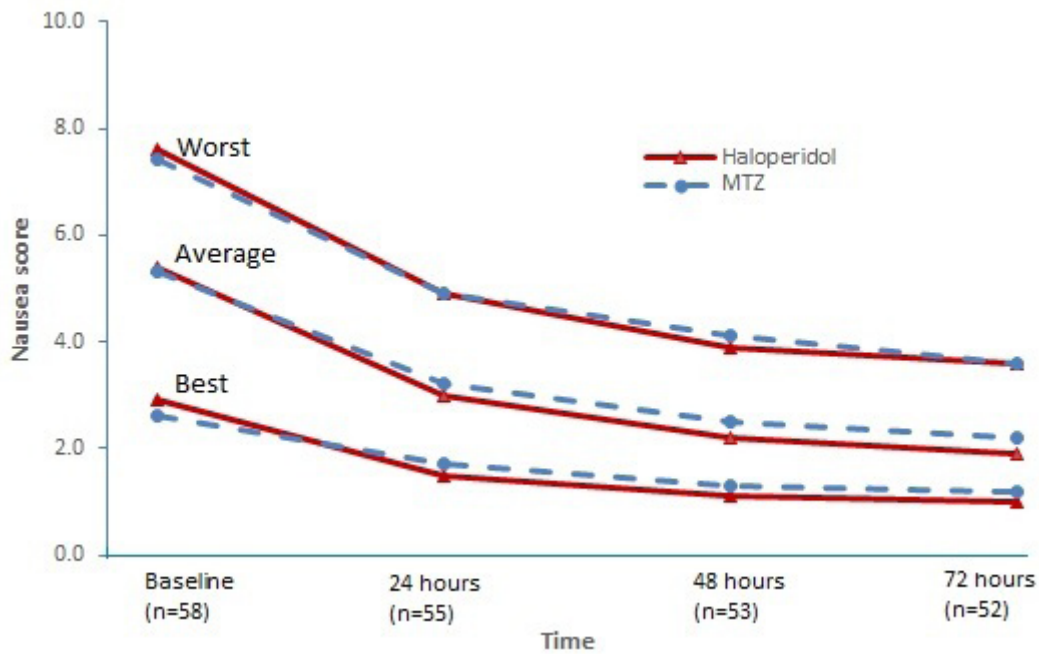


Figure 2 Nausea scores over time. MTZ, methotrimeprazine.

antiemetic studies has failed to show that any drug is superior to regular, low-dose haloperidol in this setting. This suggests that the newer, and often more expensive agents unlicensed for this indication (such as ondansetron, olanzapine as well as methotrimeprazine) should only be used second line and preferably within a monitored or trial context in the palliative care setting until further data are available.

The majority of participants in this study had nausea that was not associated with vomiting, illustrating once more that there is a need to consider nausea and vomiting separately.² Moreover, nausea is more frequently being considered in studies of chemotherapy-induced N/V where historically, control of emesis has always been the primary outcome measure.²⁴

Time	Number of doses	Haloperidol		Methotrimeprazine		N	
		Rescue medications administered		Rescue medications administered		Total	
		N	n (%)	N	n (%)	n (%)	
24 hours	1		13 (50.0)		17 (60.7)	30 (55.6)	
	2		10 (38.5)		6 (21.4)	16 (29.6)	
	3		2 (7.7)		5 (17.9)	7 (13.0)	
	4		1 (3.8)		0 (0.0)	1 (1.9)	
	Total	57	26 (45.6)	57	28 (49.1)	114	54 (47.4)
48 hours	1		10 (55.6)		16 (72.7)	26 (65.0)	
	2		5 (27.8)		3 (13.6)	8 (20.0)	
	3		2 (11.1)		3 (13.6)	5 (12.5)	
	4		1 (1.9)		0 (0.0)	1 (1.0)	
	Total	55	18 (32.7)	53	22 (41.5)	108	40 (37.0)
72 hours	1		10 (62.5)		13 (65.0)	23 (63.9)	
	2		1 (6.3)		3 (15.0)	4 (11.1)	
	3		4 (25.0)		3 (15.0)	7 (19.4)	
	4		1 (6.3)		1 (5.0)	2 (5.6)	
	Total	52	16 (30.8)	49	20 (40.8)	101	36 (35.6)

Table 4 Adverse events

Adverse event*	Haloperidol (n=52)		Methotrimeprazine (n=49)	
	Number	%†	Number	%†
Drowsiness	6	11.5	10	20.4
Fatigue	9	17.3	8	16.3
Constipation	7	13.5	6	12.2
Headache	6	11.5	4	8.2
Dry mouth	4	7.7	4	8.2
Hypotension	2	3.9	4	8.2
Dyspepsia	3	5.8	3	6.1
Hypertension	3	5.8	3	6.1
Diarrhoea	3	5.8	3	6.1
Bruising	1	1.9	3	6.1
Dizziness	3	5.8	2	4.1
Bowel colic	1	1.9	2	4.1
Blurred vision	0	0.0	2	4.1
Confusion	1	1.9	1	2.0
Sensitivity to light	0	0.0	1	2.0
Palpitations	0	0.0	1	2.0
Jaundice	0	0.0	1	2.0
Extrapyramidal reactions	1	1.9	0	0.0
Voiding difficulty	1	1.9	0	0.0
Total events	29		31	

*Any grade, worse at 72 hours than at baseline.

†% based on number of patients.

Limitations of this study include the use of breakthrough metoclopramide (or domperidone), although the dose per participant was ≤ 20 mg in the majority of participants with no difference between arms. Similarly, haloperidol is not considered as a standard antiemetic in some countries and the dose used may be considered higher than necessary, especially in elderly patients. Further work is needed to establish appropriate dosing for this indication.²⁵ Our primary outcome measure was at 72 hours; we have not assessed the longer-term benefit of these drugs nor the longer-term toxicity.

One of the main strengths of this study is that it was a multisite effectiveness study that enrolled participants frequently seen in palliative care services. The relatively rapid rate of recruitment confirms its acceptability to patients, their families and staff. The outcomes measures reflected factors that are important to patients.

It is now difficult to justify the use of a placebo arm in controlled clinical trials of patients with cancer with nausea unrelated to chemotherapy or radiotherapy given the weight of evidence that has been generated from our series of nausea studies.^{7 8} Future studies should consider regular haloperidol as the standard comparator. The optimal dose of haloperidol must be determined however, as it may be lower than that used in this

study. Furthermore, longer-term efficacy and toxicity data for this and other medications used for nausea must be defined. We have not tested haloperidol 'head to head' with metoclopramide, but the latter drug was present in many of the arms in our previous guideline versus single agent (haloperidol) study.⁷

In settings where people have ongoing nausea unrelated to anticancer treatment, low-dose haloperidol with metoclopramide rescue should be considered a first-line agent. This is widely available even in low-income and middle-income countries. Although there is a temptation to use new, more expensive agents in this setting, their benefit over and above haloperidol has yet to be established.

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Contributors All authors conceived and assisted in the study design. JH, PY, JP, GM and DC were members of the trials steering committee. JH wrote the first draft of the manuscript. HS was the trial statistician and designed and carried out the primary and subsequent statistical analyses. All authors (JH, HS, JP, PG, DC, GM, PY) were involved in the interpretation and critical review of the data, revising the manuscript and approval of the final version.

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