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Haloperidol for the treatment of nausea and vomiting in palliative care patients (Review)

Murray-Brown F, Dorman S

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[Intervention Review]

Haloperidol for the treatment of nausea and vomiting in palliative care patients

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ABSTRACT

Background

Nausea and vomiting are common symptoms in patients with terminal, incurable illnesses. Both nausea and vomiting can be distressing. Haloperidol is commonly prescribed to relieve these symptoms. This is an updated version of the original Cochrane review published in Issue 2, 2009, of Haloperidol for the treatment of nausea and vomiting in palliative care patients.

Objectives

To evaluate the efficacy and adverse events associated with the use of haloperidol for the treatment of nausea and vomiting in palliative care patients.

Search methods

For this updated review, we performed updated searches of CENTRAL, EMBASE and MEDLINE in November 2013 and in November 2014. We searched controlled trials registers in March 2015 to identify any ongoing or unpublished trials. We imposed no language restrictions. For the original review, we performed database searching in August 2007, including CENTRAL, MEDLINE, EMBASE, CINAHL and AMED, using relevant search terms and synonyms. Handsearching complemented the electronic searches (using reference lists of included studies, relevant chapters and review articles) for the original review.

Selection criteria

We considered randomised controlled trials (RCTs) of haloperidol for the treatment of nausea or vomiting, or both, in any setting, for inclusion. The studies had to be conducted with adults receiving palliative care or suffering from an incurable progressive medical condition. We excluded studies where nausea or vomiting, or both, were thought to be secondary to pregnancy or surgery.

Data collection and analysis

We imported records from each of the electronic databases into a bibliographic package and merged them into a core database where we inspected titles, keywords and abstracts for relevance. If it was not possible to accept or reject an abstract with certainty, we obtained the full text of the article for further evaluation. The two review authors independently assessed studies in accordance with the inclusion criteria. There were no differences in opinion between the authors with regard to the assessment of studies.

Main results

We considered 27 studies from the 2007 search. In this update we considered a further 38 studies from the 2013 search, and two in the 2014 search. We identified one RCT of moderate quality with low risk of bias overall which met the inclusion criteria for this update, comparing ABH (Ativan®, Benadryl®, Haldol®) gel, applied to the wrist, with placebo for the relief of nausea in 22 participants. ABH gel

includes haloperidol as well as diphenhydramine and lorazepam. The gel was not significantly better than placebo in this small study; however haloperidol is reported not to be absorbed significantly when applied topically, therefore the trial does not address the issue of whether haloperidol is effective or well-tolerated when administered by other routes (e.g. by mouth, subcutaneously or intravenously). We identified one ongoing trial of haloperidol for the management of nausea and vomiting in patients with cancer, with initial results published in a conference abstract suggesting that haloperidol is effective for 65% of patients. The trial had not been fully published at the time of our review. A further trial has opened, comparing oral haloperidol with oral methotrimeprazine (levomepromazine) for patients with cancer and nausea unrelated to their treatment, which we aim to include in the next review update.

Authors' conclusions

Since the last version of this review, we found one new study for inclusion but the conclusion remains unchanged. There is incomplete evidence from published RCTs to determine the effectiveness of haloperidol for nausea and vomiting in palliative care. Other than the trial of ABH gel vs placebo, we did not identify any fully published RCTs exploring the effectiveness of haloperidol for nausea and vomiting in palliative care patients for this update, but two trials are underway.

PLAIN LANGUAGE SUMMARY

Haloperidol for the treatment of nausea and vomiting in palliative care patients

Haloperidol is often used to help control nausea (feeling sick) or vomiting (being sick), both of which are common problems for patients with serious life-threatening illnesses. Haloperidol can be given by mouth or by injection. There has been some research looking at how this drug works in nausea and vomiting caused by surgery and when trying to prevent nausea and vomiting caused by anti-cancer treatments.

This is an update of the original review published in 2009 for which no studies met the inclusion criteria. For this update, in a search of the published literature in November 2014 we found one moderate quality randomised controlled trial which compared ABH (Ativan®, Benadryl®, Haldol®) gel, containing haloperidol and two other medications, to placebo.

The trial showed no difference between ABH gel and placebo. However it has previously been shown that haloperidol is not absorbed after applying ABH gel, so this result is not surprising. We identified a trial of haloperidol for nausea and vomiting in patients with cancer, with initial results presented at a conference. This suggests that haloperidol is effective in 65% of patients, but the results were not fully published at the time of our review. A further trial has opened in Australia, comparing haloperidol with another medication used for nausea, methotrimeprazine (levomepromazine).

BACKGROUND

This is an updated version of the original Cochrane review published in Issue 2, 2009, of Haloperidol for the treatment of nausea and vomiting in palliative care patients.

All patients with terminal illness should have access to palliative care, independent of their diagnosis, and we wanted to reflect this in our review. Defining this population has been identified as a problem in previous reviews. We used the same definition as Hirst 2001 to give some consistency with other Cochrane reviews: "adult patients in any setting, receiving palliative care or suffering an incurable progressive medical condition".

Description of the condition

Nausea and vomiting are common symptoms for patients with terminal, incurable illnesses. Both symptoms can be distressing. Between 6% and 68% of patients with advanced cancer are troubled by nausea (Solano 2006), and nausea and vomiting are also common in other conditions, for example long-term lung conditions and heart failure (Edmonds 2001; Klinkenberg 2004; Solano 2006). There are many potential causes in patients with terminal illness, including biochemical abnormalities (for example, kidney failure, high calcium salts in the blood), drugs (for example, iron supplements or morphine), or the underlying illness (for example, cancer deposits in the liver or brain). Anxiety can also be associated with nausea. Medications used to improve nausea and vomiting are called antiemetics. Antiemetics can help control symptoms while actions are taken to try and treat the underlying cause (Twycross 1998; Bentley 2001; Mannix 2004; Reuben 1986).

Description of the intervention

Haloperidol is in the butyrophenone class of drugs and acts as an antagonist on dopamine receptors. Haloperidol is used alone or in combination with other antiemetics orally, subcutaneously, intravenously or intramuscularly and can also be used intranasally (Miller 2008). It is also available in a compound gel including lorazepam and diphenhydramine, although it is reported not to be absorbed by this route (Smith 2012a).

Possible side effects of haloperidol include sedation, movement disturbance and arrhythmias (Twycross 2014). Neuroleptic malignant syndrome is a more serious but less common adverse event. This has numerous features including fever, altered consciousness and muscle rigidity, and can be fatal (Susman 2001).

How the intervention might work

Dopamine is an important neurotransmitter in the vomiting centre in the brain. Haloperidol acts as an antagonist at dopamine receptors in the brain (Smith 2012b; Twycross 2014).

Why it is important to do this review

There is little evidence from published randomised trials for many of the drugs used for these symptoms in this patient group (for example, cyclizine, haloperidol or levomepromazine) (Glare 2004). Haloperidol is commonly used in this setting to treat nausea and vomiting (Critchley 2001; Smith 2012b; To 2014). A small uncontrolled study (42 participants with cancer and nausea or vomiting unrelated to cancer treatment) suggests some evidence for effectiveness in the setting: 61% of evaluable participants had partial or complete control of nausea at day two (47% of all participants) and 74% at day five (40% of all participants) (Hardy 2010). We felt it important to update the previous systematic review to establish the current evidence base from randomised trials (Perkins 2009).

OBJECTIVES

To evaluate the efficacy and adverse events associated with the use of haloperidol for the treatment of nausea and vomiting in palliative care patients.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of haloperidol for the treatment of nausea or vomiting, or both, in any setting.

Types of participants

Inclusion criteria

Adults receiving palliative care or suffering from an incurable progressive medical condition. Adults suffering from nausea or vomiting, or both.

Exclusion criteria

Nausea or vomiting, or both, thought to be secondary to pregnancy or surgery.

Types of interventions

Studies where haloperidol was used as an antiemetic (alone or in addition to other agents) including any dose of haloperidol, via any route, over any duration of follow-up.

Acceptable comparators

- Placebo.
- Other drug.
- Non-pharmacological intervention.

Types of outcome measures

Primary outcomes

- Patient-reported nausea severity.
- Patient-reported vomiting severity.

As there is a wide variety of instruments to measure these symptoms, we accepted any measure.

Secondary outcomes

- Quality of life measurement.
- Acceptability of treatment.
- Need for rescue antiemetic medication.
- Adverse events.
- Withdrawal from study because of side effects.

Ideally, valid outcome measures would have been used but we would not have excluded studies on the basis of their outcome measures.

Search methods for identification of studies

For the original review we searched the electronic databases including CENTRAL, MEDLINE (1950 to August 2007), EMBASE (1980 to August 2007), CINAHL (1981 to August 2007) and AMED (1985 to August 2007), using relevant search terms and synonyms. The basic search strategy was ("haloperidol" OR "butyrophenone") AND ("nausea" OR "vomiting"), modified for each database. For the original review, handsearching complemented the electronic searches (using reference lists of included studies, relevant chapters and review articles). We did not impose a language restriction on studies. See Appendix 1 for the MEDLINE search strategy. We performed database searching in August 2007. For this update, we performed updated electronic searches of CENTRAL, MEDLINE and EMBASE in September 2012 and again in November 2013 and in November 2014.

We also searched clinical trials registers, the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), ClinicalTrials.gov, Current Controlled Trials (www.controlled-trials.com/) and the EU Clinical Trials Register (clinicaltrialsregister.eu) for this update on 06 March 2015, using the search term "haloperidol".

Electronic searches

We searched the following databases without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via *The Cochrane Library*, 2007) for the previous version, and (Issue 10 of 12, 2014) for this update.
- MEDLINE (via Ovid) 1946 to August 2007 for the previous version, and November 2014 for this update.
- EMBASE (via Ovid) 1974 to August 2007 for the previous version, and November 2014 for this update.
- CINAHL (via EBSCO) 1981 to August 2007 for the previous version.
- AMED (via Ovid) 1985 to August 2007 for the previous version.

We used medical subject headings (MeSH) or equivalent and text word terms. There were no language or date restrictions. The search strategies for CENTRAL, MEDLINE, EMBASE, CINAHL and AMED are in Appendix 1.

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) on 06 March 2015 to identify additional completed or ongoing studies.

Data collection and analysis

For the original review, records were imported from each of the above electronic databases into the bibliographic package EndNote 9 and merged into a core database where titles, keywords and abstracts were inspected for relevance. If it was not possible to accept or reject an abstract with certainty, the full text of the article was obtained for further evaluation. We reviewed the updated searches from 2013 and 2014 in a Word document including title, keywords and abstracts.

Selection of studies

Two review authors independently assessed abstracts and possible studies for inclusion in accordance with the above inclusion criteria (PP and SD for the review published in 2009 (Perkins 2009) and FM-B and SD for this updated review). There were no differences in opinion between review authors with regards to assessment of studies.

Data extraction and management

Data were entered into RevMan 5.3 (RevMan 2014).

We planned to assess studies for treatment effect (see Types of outcome measures above), specifying numbers needed to treat for an additional beneficial outcome (NNTB) and numbers needed to treat for an additional harmful outcome (NNTH).

Assessment of risk of bias in included studies

We graded studies that met the inclusion criteria in the Risk of bias table below (see Characteristics of included studies).

Measures of treatment effect

Treatment effect was given as the mean difference in the change in nausea scores from baseline (Fletcher 2014). Other estimations of treatment effect would also have been considered.

Unit of analysis issues

We accepted randomisation of the individual patient.

Dealing with missing data

Had missing data been potentially relevant to the findings of the review, we would have contacted the authors to include the missing data if available; if unavailable, we would have used imputation (e.g. last outcome value carried forward).

Assessment of heterogeneity

Palliative care populations can be diverse, including a range of diagnoses as well as demographic characteristics. We did not exclude studies on the basis of scales used, raising the possibility of several different outcome measures being used. If the heterogeneity of studies allowed we would have performed a meta-analysis. If the I^2 statistic value was > 50% we would have used a random-effects model (Higgins 2003).

Assessment of reporting biases

We planned to assess heterogeneity using L'Abbé plots (L'Abbé 1987), a visual method for assessing differences in results of individual studies.

Data synthesis

Quantiative meta-analysis would only be used if studies were sufficiently similar to do so on the basis of I^2 statistical test to assess heterogeneity (Higgins 2003). In the qualitative synthesis, risk of bias is noted.

Subgroup analysis and investigation of heterogeneity

If there had been sufficient data we had planned to perform subgroup analyses using the following subgroups identified a priori:

Population subgroups

- Diagnoses of patients.
- Likely mechanism of nausea/vomiting.
- Prognoses of patients.
- Age of patients.
- Gender of patients.

Intervention subgroups

- Route of administration.
- Drug dose (< 2 mg/24 hours; 2 mg to 5 mg/24 hours; > 5 mg/24 hours),

Outcome subgroups

- Nausea.
- Vomiting.

Sensitivity analysis

Sensitivity analysis was not undertaken as there were insufficient studies identified to warrant it.

RESULTS

Description of studies

Results of the search

We obtained 27 full studies (one in German) as potentially fitting the inclusion criteria for the 2009 review; we obtained a further 38 studies in 2013 as potentially fitting the inclusion criteria. None of these studies met the criteria for inclusion (see Figure 1). A further two studies were obtained from the search in November 2014 including one randomised study (Fletcher 2014) and one published as a conference abstract (ACTRN12610000481077).

Figure 1. Study flow diagram.

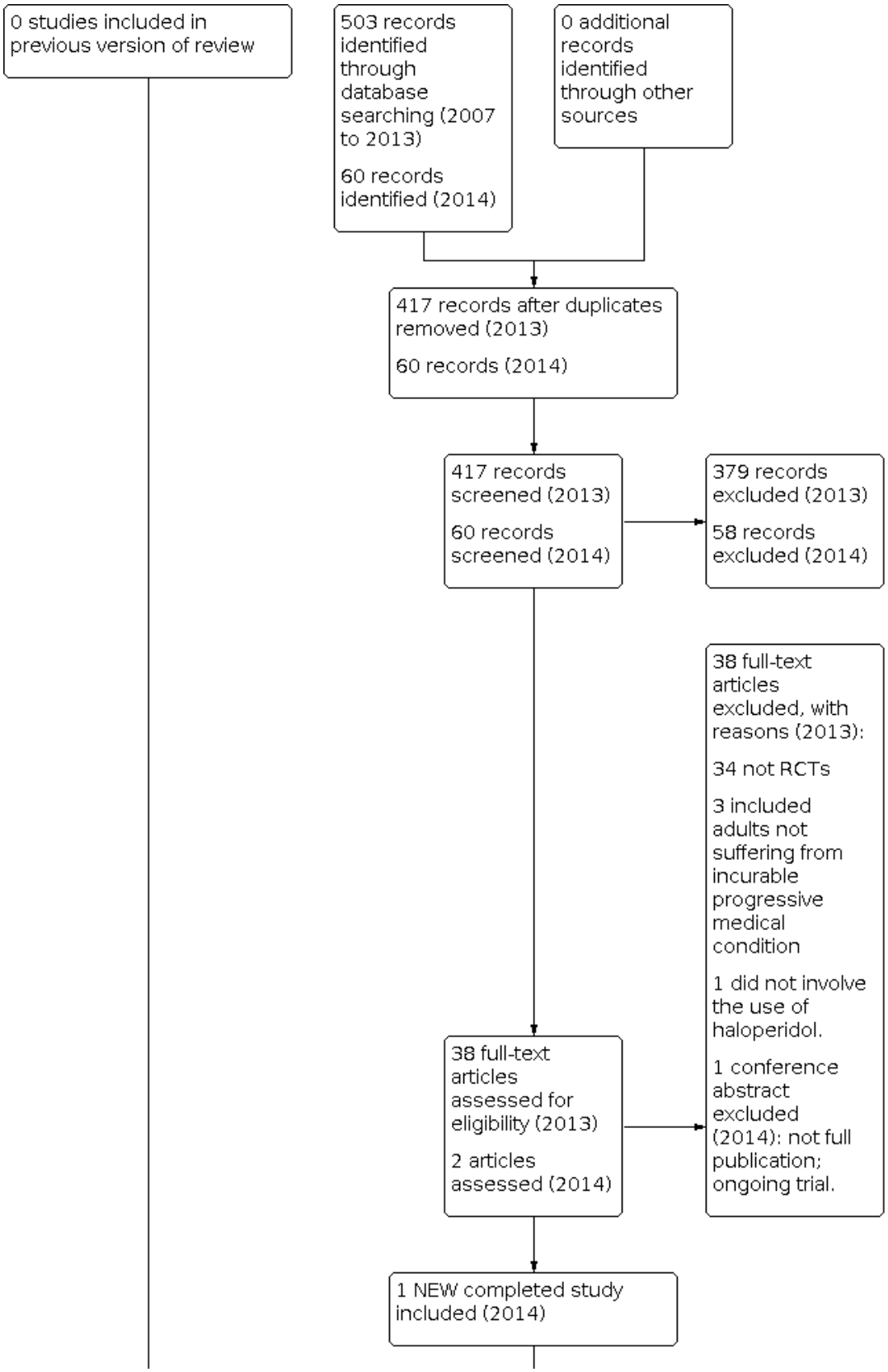
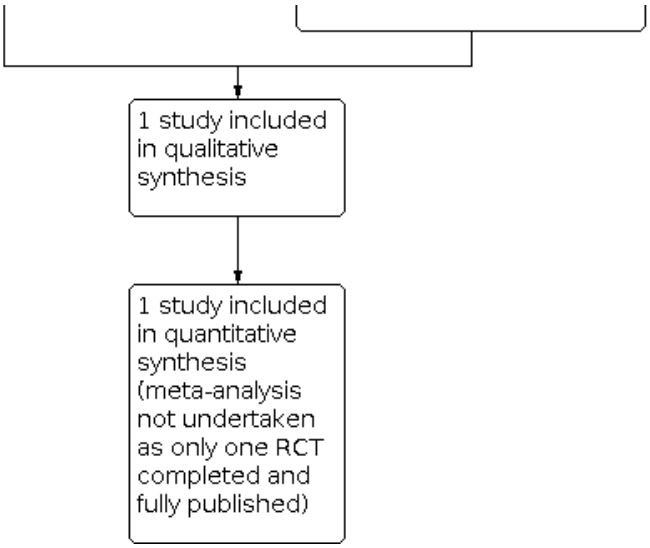


Figure 1. (Continued)



We also identified the two ongoing trials and one uncompleted trial below in trials registers, from 190 records (163 trials) in the WHO International Clinical Trials Registry Platform, 137 records in ClinicalTrials.gov, 18 records in Current Controlled Trials and 33 records in the EU Clinical Trials Register (date of searches 06 March 2015):

Trials in progress

- A two-stage trial of response to antiemetic therapy in patients with cancer and nausea not related to anticancer therapy. Study 1 is a randomised, open-label study of guideline-driven, targeted antiemetic therapy versus single-agent antiemetic therapy (ACTRN12610000481077). Haloperidol is the treatment in arm 2 of this study (escalated in a three-step schedule from 1 mg/24 hours to 3 mg/24hours orally or subcutaneously). It is also used in combination with dexamethasone for a subset of arm 1 (participants with mechanical bowel obstruction). Preliminary results have been published as a conference abstract (ACTRN12610000481077). The authors conclude that haloperidol is effective for 65% of patients, with no significant difference between haloperidol or targeted antiemetic therapy, however the full results were not published at the time of our review.
- A study for participants with cancer who experience ongoing nausea, not related to their treatment, despite taking standard and usual medications, that studies the effectiveness of oral methotrimeprazine (levomepromazine) versus oral haloperidol. This study was registered 23 February 2015, with a target sample size of 126. Patients will be randomised to receive blinded encapsulated oral methotrimeprazine (6.25mg) or oral haloperidol (1.5mg) given once daily for three days, with a potential to increase to twice daily if there is no response at 24 hours or 48 hours. Responses will be assessed using a 0 to 10 numeric rating scale of nausea (ACTRN12615000177550).

Trial stopped early

- A study of olanzapine versus haloperidol for the relief of nausea and vomiting in patients with advanced cancer (registered 7 June 2005 but stopped early due to poor recruitment on 30 June 2008; Pereira 2012).

Included studies

Fletcher 2014 compared topical "ABH Gel" (Ativan® (lorazepam), Benadryl® (diphenhydramine) and Haldol® (haloperidol)) with placebo gel in 22 patients with nausea. Participants had cancer, or had a consultation with the palliative care team; patients receiving chemotherapy were excluded. The study sample size was reported to be large enough to detect a significant change in nausea (two points on a ten point scale), with a power of 80%. Patients were randomised to a sequence of treatments: one group that applied the ABH gel initially and then the placebo; the other group applied the placebo first followed by ABH gel. Twenty patients completed both treatments. It is unclear which arm was completed by the two participants who dropped out, ABH gel or placebo. The study is of moderate quality overall (GRADE criteria, Schünemann 2011).

See Characteristics of included studies.

Excluded studies

In total 27 studies were excluded in the initial review (Perkins 2009) with a further 37 studies excluded in this update (Excluded studies, with reasons shown below in Characteristics of excluded studies).

Risk of bias in included studies

The comparison of ABH gel with placebo (Fletcher 2014) recruited 22 participants of whom 20 completed the trial. The study sample size was calculated using a paired t-test to be adequate to show that placebo was not inferior to ABH gel (power 80%, common standard deviation 1.5 at a one-sided significance level of 5%). Risk of bias is summarised in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

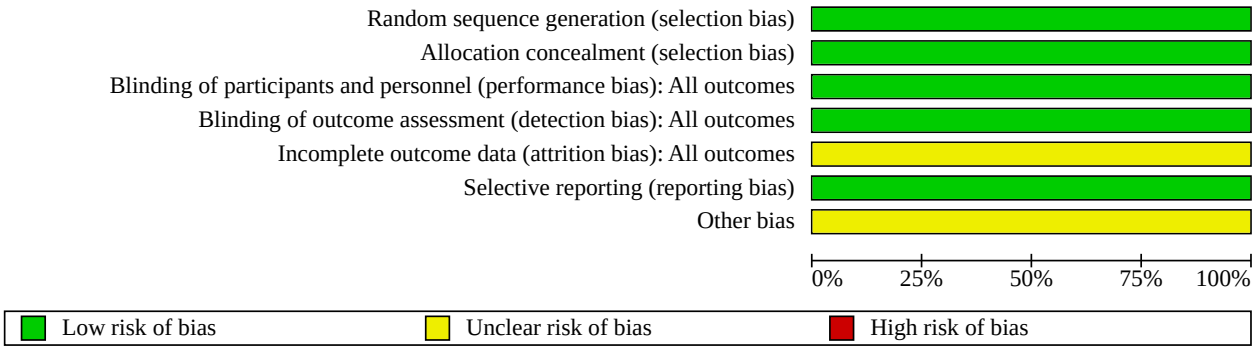
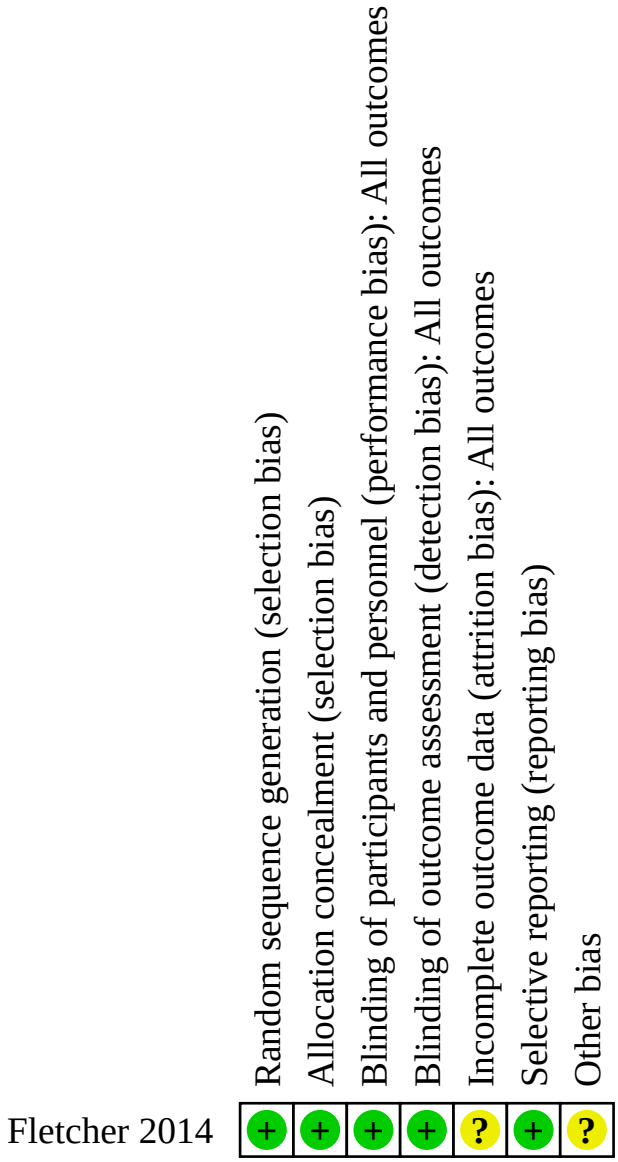


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In the study of ABH gel (Fletcher 2014), participants were allocated a sequence of treatments randomly, using a randomisation list generated by the study statistician.

Blinding

The study of ABH gel (Fletcher 2014) is described as double-blind. Participants received ABH gel or placebo gel in randomised order. Participants and investigators were not aware of which treatment was being used.

Incomplete outcome data

Two of the 22 participants did not complete the study (Fletcher 2014). It is not clear which arm of the study they were in. This is unlikely to affect the overall results of the study.

Selective reporting

Placebo is reported to be non-inferior to ABH gel (Fletcher 2014). Reporting bias appears unlikely in this instance.

Other potential sources of bias

There is some risk of recruitment bias in Fletcher 2014: all participants were reported to have an active cancer diagnosis, and some were recruited from a bone marrow transplant clinic. The study population may not therefore fully reflect the heterogeneity of patients seen by palliative care services. Also, some potential participants with more severe nausea may have chosen not to take part in the study because they preferred a subcutaneous or intravenous injection of medication for nausea, with a likely more rapid onset of action.

Effects of interventions

Haloperidol in the form of ABH topical gel did not reduce nausea or vomiting any more than placebo.

The primary study outcome was nausea which was self-assessed using a 0–10 scale, with zero being no nausea and 10 being the worst possible nausea. The number of episodes of vomiting over time was recorded and participants completed the Memorial Symptom Assessment Scale-Condensed which was used to determine the secondary outcomes and side effects. Participants were also asked at the end of each treatment period, "Did you feel the treatment was effective?," and “Did you have any side effects from the drug?” On completion of both arms of the study, participants were asked, “Which drug helped you more?,” “Which drug did you think was the real ABH gel?,” and “Which was the placebo?” (Fletcher 2014)

Primary review outcomes

Patient-reported nausea: no significant difference was found between placebo and ABH gel rubbed into the wrists, with both treatments showing a small reduction in nausea scores at 60 minutes (1.7+/- 2.05 for ABH gel, 0.9 +/- 2.45 for placebo; not statistically significant P value = 0.42).

Patient-reported vomiting: observed episodes of vomiting were recorded rather than patient-reported. ABH gel did not reduce vomiting more than placebo (not statistically significant P value = 0.34), but most patients did not have episodes of vomiting in any case.

Secondary review outcomes

Quality of life: not measured (note short term study).

Acceptability of treatment: of the 21 participants answering the question, seven thought the ABH gel was effective and 14 thought it was not. One reported a side effect of drowsiness.

Need for rescue antiemetic medication: not reported.

Adverse events: of 21 participants answering the question "Did you have any side effects from the drug?", 20 said they had no side effects from the drug and one said they did (drowsiness). One participant did not answer the question.

Withdrawal from study because of side effects: none (two participants did not complete both arms of the study, said to be because they did not want to wait to complete the study; they denied side effects) (Fletcher 2014).

DISCUSSION

This is an updated version of the original Cochrane review published in Issue 2, 2009, on Haloperidol for the treatment of nausea and vomiting in palliative care patients.

For this update, we identified one small RCT of moderate quality which compared ABH gel, containing haloperidol, diphenhydramine and lorazepam, with placebo (Fletcher 2014). However haloperidol is not absorbed significantly from application of ABH gel (Smith 2012a) so this study does not add to the evidence base for the effectiveness of haloperidol as an antiemetic. Other than this (Fletcher 2014) there are no fully published randomised controlled trials of haloperidol for nausea or vomiting in a palliative care population, although it is frequently used by palliative care physicians (Prommer 2012; Smith 2012b; To 2014).

A previous systematic review of haloperidol in this context retrieved case reports and case series only (Critchley 2001). In a systematic review of antiemetics in the treatment of nausea in far-advanced cancer only case series were found to support the use of haloperidol (Glare 2004). A review of the management of nausea and vomiting in people with cancer and other chronic diseases described haloperidol as "likely to be beneficial" based on consensus (Keeley 2007). Indeed haloperidol is thought by some to be one of four essential drugs for the management of symptoms at the end of life (Lindqvist 2013).

However, initial results from a trial comparing haloperidol with a targeted antiemetic approach suggests that either approach is effective for 65% of patients (ACTRN12610000481077); the full results were not published at the time of our review. This is similar to the findings from a previous uncontrolled study which suggested a response rate of 61% at day two (47% on intention to treat analysis (Hardy 2010). It is encouraging that despite the difficulties encountered by some researchers trying to conduct RCTs of the effectiveness of haloperidol, two randomised studies are currently underway (ACTRN12610000481077; ACTRN12615000177550).

There are RCTs of haloperidol in post-operative nausea and vomiting (Barton 1975), gastrointestinal disorders (Christman 1974; Robbins 1975), prophylaxis against nausea and vomiting associated with radiotherapy (Cole 1974) and chemotherapy (Neidhart 1981). A meta-analysis calculated that the number needed to treat for an additional beneficial outcome (NNTB) (with 2 mg) to prevent postoperative nausea or vomiting compared with placebo was four (Buttner 2004). It is not clear to what extent these studies are applicable to palliative care populations, although they may help to inform practice (McLean 2013). The causes and mechanisms of nausea and vomiting may be somewhat different in palliative care. This may have an impact on the effectiveness of interventions.

Summary of main results

For this update, we identified one RCT which compared ABH gel, containing haloperidol, diphenhydramine and lorazepam, with placebo (Fletcher 2014). However haloperidol is not absorbed significantly from topical application of ABH gel (Smith 2012a) so this study does not add to the evidence base for the effectiveness of haloperidol as an antiemetic. Other than Fletcher 2014 there are no fully published randomised controlled trials of haloperidol for nausea or vomiting in a palliative care

population, although two randomised studies are currently underway (ACTRN12610000481077; ACTRN12615000177550).

Overall completeness and applicability of evidence

There is incomplete evidence from published RCTs to determine the effectiveness of haloperidol for nausea and vomiting in palliative care. The study of ABH gel (Fletcher 2014) does not refute the apparent anti-emetic effect of haloperidol in clinical practice and studies in other settings (Christman 1974; Cole 1974; Barton 1975; Robbins 1975; Neidhart 1981; Buttner 2004; McLean 2013) since haloperidol is not absorbed by this route (Smith 2012a).

Haloperidol remains frequently prescribed as an antiemetic by palliative care physicians (Prommer 2012; Smith 2012b; To 2014).

Quality of the evidence

Only one published RCT of moderate quality has been identified in this updated review (Fletcher 2014). This is a small study of ABH gel (applied topically) compared with placebo. Since haloperidol is not absorbed via this route (Smith 2012a), this study neither supports nor refutes the role of haloperidol as an antiemetic.

Potential biases in the review process

The review methods sought to minimise bias by conducting a thorough search of the published literature to identify relevant studies, using predefined criteria to select studies for inclusion, and independent review by two authors. The review authors sometimes prescribe haloperidol as an antiemetic in palliative care settings.

Agreements and disagreements with other studies or reviews

A previous systematic review of haloperidol in this context retrieved case reports and case series only (Critchley 2001). In a systematic review of antiemetics in the treatment of nausea in far-advanced cancer only case series were found to support the use of haloperidol (Glare 2004). A review of the management of nausea and vomiting in people with cancer and other chronic diseases described haloperidol as "likely to be beneficial" based on consensus (Keeley 2007). Indeed haloperidol is thought by some to be one of four essential drugs for the management of symptoms at the end of life (Lindqvist 2013).

Although we did not systematically review the evidence in other contexts, we found RCTs of haloperidol in post-operative nausea and vomiting (Barton 1975), gastrointestinal disorders (Christman 1974; Robbins 1975), prophylaxis against nausea and vomiting associated with radiotherapy (Cole 1974) and chemotherapy (Neidhart 1981). A meta-analysis calculated that the number needed to treat for a beneficial outcome (NNTB) (with 2 mg) to prevent postoperative nausea or vomiting compared with placebo was four (Buttner 2004). It is not clear to what extent these studies are applicable to palliative care populations, although they may help to inform practice (McLean 2013). The causes and mechanisms of nausea and vomiting may be somewhat different in palliative care. This may have an impact on the effectiveness of interventions.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review, we found one new study for inclusion (Fletcher 2014) but the conclusions remain unchanged.

There is a lack of published evidence for the use of haloperidol for nausea and vomiting in palliative care. A study comparing ABH gel (containing haloperidol, diphenhydramine and lorazepam) to placebo showed no significant difference (Fletcher 2014). However haloperidol is not absorbed significantly following application of the gel (Smith 2012a). No other RCTs of haloperidol in this setting have been fully published but two trials are underway (ACTRN12610000481077; ACTRN12615000177550).

Implications for people with nausea or vomiting in the context of advanced disease

Haloperidol is often used to help control nausea (feeling sick) or vomiting (being sick). The evidence to support this is largely from other settings - for example, haloperidol to control sickness after surgical operations, chemotherapy or radiotherapy. There are no published randomised trials of haloperidol to control nausea and vomiting in people with advanced disease, other than a small study of a gel containing haloperidol (ABH gel) compared with placebo. No significant difference was found between ABH gel and placebo, which is not surprising as haloperidol is not absorbed by this route. Two randomised studies are underway to compare haloperidol with other medications for nausea and vomiting.

Implications for clinicians

Haloperidol may still be used as an antiemetic, though there is no evidence from RCTs in the palliative care context to quantify its effectiveness used orally or by injection. A small study of a gel containing haloperidol (ABH gel) compared with placebo found no significant difference (Fletcher 2014), which is not surprising as haloperidol is not absorbed by this route (Smith 2012a). Initial results from a trial which is underway suggest that it may be effective in 65% of patients (ACTRN12610000481077). Further results from this ACTRN12610000481077 and another ongoing study, ACTRN12615000177550, will help to inform practice which so far has been guided by clinical experience, consensus (Keeley 2007), an uncontrolled study (Hardy 2010) and research in other settings (McLean 2013).

Implications for policy makers

Haloperidol is frequently prescribed as an antiemetic (Prommer 2012; Smith 2012b; To 2014), although there is no evidence from RCTs in the palliative care context to quantify its effectiveness used orally or by injection. A small study of a topically applied gel containing haloperidol (ABH gel) compared with placebo found no significant difference (Fletcher 2014), which is not surprising as haloperidol is not absorbed by this route (Smith 2012a). Initial results from a trial which is underway suggest that it may be effective in 65% of patients (ACTRN12610000481077). Further results from ACTRN12610000481077 and another ongoing study, ACTRN12615000177550, will help to inform practice which so far has been guided by clinical experience, consensus (Keeley 2007) and research in other settings (McLean 2013).

Implications for funders

There is limited evidence for the use of haloperidol as an antiemetic in palliative care although it is commonly prescribed. Current clinical practice is guided by clinical experience, consensus and research in other settings. Some research to compare haloperidol with other antiemetics is underway, however this is a relatively under-researched area. Nausea and vomiting are common, distressing symptoms with a profound impact on quality of life. Further studies are needed to determine the most effective strategies for managing these symptoms.

Implications for research

Much has been written about methodological challenges when conducting research in palliative medicine (Jordhoy 1999; Ewing 2004). Nevertheless, two trials of haloperidol compared with other antiemetics are underway (ACTRN12610000481077; ACTRN12615000177550).

There is scope to build on this evidence further, using variations in intervention (e.g. dose, route of administration) and variations in trial design.

For instance, a randomised controlled trial could be conducted with participants with advanced disease who have nausea or vomiting, not associated with surgery, chemotherapy, radiotherapy or pregnancy, using an intervention of haloperidol, compared with another antiemetic, for example levomepromazine. Oral or subcutaneous routes of administration could be appropriate as these are often used in palliative care settings. Suggested outcomes include relief from nausea and from vomiting, anxiety, sedation, and extrapyramidal side effects. The duration of the study would be likely to have an impact on recruitment and attrition rates, but some side effects may only be apparent after weeks or months of use.

The pros and cons of placebo-controlled studies have been debated (Hardy 1997; Kirkham 1997; Sanderson 2013). Placebo effects are likely to be significant, particularly in the context of a therapeutic relationship and environment (Sanderson 2013). Kris et al recommended that further trials of antiemetics in the context of chemotherapy should be conducted using active agents rather than placebo as comparator (Kris 1996). However a recent study of antiemetics in the emergency department compared metoclopramide, ondansetron and placebo and found no significant difference; most participants were satisfied with the treatment of their nausea (Egerton-Warburton 2014). The feasibility and ethical acceptability of a placebo arm may in part depend on the participants' perception of the severity of their symptoms and the urgency of the need for treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fletcher 2014

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled non-inferiority crossover trial.
Participants	Adults with active cancer and self-reported nausea at least 4 out of 10 (n=22 enrolled, 20 of whom completed the study). Many participants (unspecified) were attending the bone marrow transplant clinic, some were enrolled from the palliative care clinic or palliative care in-patient setting. For full inclusion and exclusion criteria see Fletcher 2014.
Interventions	ABH gel (contains lorazepam, diphenhydramine and haloperidol) or placebo gel rubbed on the wrist.

Fletcher 2014 *(Continued)*

	ABH gel contains lorazepam 20mg, diphenhydramine 250mg, haloperidol 20mg, lecithin organogel 2mL, ethoxydiglycol 0.83mL, water 0.2mL, pluronic gel 20% (sufficient to make 10mL). These 10mL were divided into ten doses of 1mL. Placebo was 1mL pluronic lecithin organogel alone. If no effect (up to 1 point on 0 to 10 scale) was seen after one hour, the participant was offered other medication for nausea and was considered to have completed the trial. Otherwise the participant crossed over to the other treatment after four hours.
Outcomes	Primary outcome: difference in nausea score from baseline to 60 minutes after intervention. A change of 2 points on a 0 to 10 scale was thought to be significant. Secondary outcomes: difference in vomiting episodes and side effects determined by the Memorial Symptom Assessment Scale - Condensed. Assessments were made at baseline (before administration of gel), 30, 60, 90, 120, 180, 240 minutes. Participants were also asked questions about the perceived effectiveness of each gel.
Notes	There was no significant difference in the change in nausea scores for each group (1.7 +/- 2.05 for the ABH gel group and 0.9 +/- 2.45 for the placebo group on a 0 to10 scale; P = 0.42). Authors concluded that placebo was non-inferior to ABH gel. A previous study had shown that there was no significant absorption of haloperidol via this route (Smith 2012a).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The study biostatistician generated the randomisation list."
Allocation concealment (selection bias)	Low risk	"Randomisation was done in the investigational drug pharmacy with allocation concealed by the use of sealed opaque envelopes not accessible to investigators."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind. Participants received ABH gel or placebo gel in randomised order.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and investigators not aware of which treatment was being used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two of the 22 participants did not complete both arms of the study, because they "did not feel like waiting the length of the study but denied side effects from the medications". It is not clear which treatments were completed for the two who did not complete the study.
Selective reporting (reporting bias)	Low risk	Placebo is reported to be non-inferior to ABH gel in this study.
Other bias	Unclear risk	This is a relatively small study. Participants were enrolled from the bone marrow transplant clinic, inpatient palliative care unit or seen as an inpatient by the palliative care team. The study authors state that, "Many patients were bone marrow transplant patients" but it is not clear what proportion. The study participants may not be fully representative of patients receiving pallia-

Fletcher 2014 *(Continued)*	tive care in other settings. However, this is unlikely to have been a significant cause of bias for the study findings.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abdelsayed 2007	Review article - not a RCT
Bleicher 2008	Pilot retrospective study - not a RCT; unclear whether population is palliative; unable to isolate effectiveness of haloperidol as given with other agents
Bregni 1991	Not a RCT; prophylaxis not treatment; bone marrow transplantation rather than palliative context
Buttner 2004	Review article - not a RCT
Casey 2011	Review article - not a RCT; unclear whether population is palliative
Cerchietti 2000	RCT but not of haloperidol
Cheung 2011	Review article - not a RCT
Chiu 2007	Review article - not a RCT; focus on antiemetics other than haloperidol
Chow 2010	Review article - not a RCT; not a palliative population (acute gastroenteritis); no mention of haloperidol
Christman 1974	Not a palliative population
Christo 2003	Review article - not a RCT
Clary 2009	Review article - not a RCT
Cole 1974	Unclear whether patient group restricted to palliative care patients
Cole 1994	Case report
Davis 2010	Systematic review, but no RCTs including haloperidol described
De Vries 1969	Not a palliative population (mixed - with diagnosis of "functional gastrointestinal disorders" with "an evident psychosomatic component")
DiVall 2007	Review article - not a RCT
Ettinger 2007	Review article - not a RCT
Ettinger 2009	Review article - not a RCT
Feyer 2011	Review article - not a RCT; no mention of haloperidol
Findlay 1993	Unable to isolate effectiveness of haloperidol as given with other agents; not a palliative care population
Fischberg 2007	RCT but not of haloperidol (droperidol), and not restricted to palliative care patients

Study	Reason for exclusion
Getto 2011	Review article - not a RCT; not a palliative population
Glare 2004	Review article - not a RCT
Glare 2011	Review article - not a RCT
Gonzales 2011	Review article - not a RCT
Grunberg 1984	Randomised controlled trial but not restricted to palliative care patients
Grunberg 2010	Review article - not a RCT; no mention of haloperidol
Hardy 2010	Prospective, open-label, uncontrolled study - not a RCT
Herndon 2002	Review article - not a RCT
Herrstedt 2008	Review article - not a RCT
Jordan 2007	Review article - not a RCT
Kohara 2005	Retrospective notes review
Ladabaum 1999	Review - no mention of haloperidol
Liem-Moolenar 2010	Not a palliative population - healthy male volunteers
Lohr 2008	Review article - not a RCT
McHugh 2011	Review article - not a RCT
McNicol 2003	Review article - not a RCT
Mercadante 2007	Systematic review but no mention of haloperidol
Naeim 2008	Review article - not a RCT; no mention of haloperidol
Navari 2007	Review article - not a RCT
Neidhart 1981	Prophylaxis rather than treatment of emesis; unclear whether population is palliative
O'Connor 2011	Review article - not a RCT
Owens 1984	Prophylaxis rather than treatment of emesis; unclear whether population is palliative
Perkins 2009	Cochrane systematic review - not a RCT
Pleuvry 2009	Review article - not a RCT
Porreca 2009	Review article - not a RCT; not a palliative population (patients with chronic pain)
Ripamonti 2001	Review article - not a RCT
Robbins 1975	Population not necessarily palliative; treatment of symptoms of gastritis/gastroenteritis
Roeland 2010	Review article - not a RCT; stem cell transplant rather than palliative context

Study	Reason for exclusion
Saller 1985	Prophylaxis not treatment of chemotherapy-associated nausea and vomiting
Siden 2008	Case report - not a RCT; child
Silvey 1988	Prophylaxis rather than treatment of emesis; unclear whether population is palliative
Smith 2011	Population not palliative (volunteers)
Smith 2012a	Population not palliative (volunteers)
Sperry 2007	Review article - not a RCT
Stapleton 2009	Review article - not a RCT; not a palliative population (patients with gastroparesis from any cause)
Tatum 2009	Review article - not a RCT
Tornetta 1971	Postoperative nausea and vomiting
Tornetta 1972	Prophylaxis of postoperative nausea and vomiting
Trigg 2008	Review article - not a RCT; stem cell transplant rather than palliative context
Trigg 2010	Review article - not a RCT
Weschules 2005	Not a RCT - retrospective notes review; haloperidol given with other agents
White 2006	Case study - not a RCT

RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12610000481077

Study name	The effectiveness of guideline-driven antiemetic therapy versus single agent antiemetic therapy in patients with cancer and nausea not related to cancer therapy. A two-stage trial of response to antiemetic therapy in patients with cancer and nausea not related to anticancer therapy. Study 1: a randomised open label study of guideline-driven targeted antiemetic therapy versus single agent antiemetic therapy.
Methods	Randomised Controlled Trial Multi-centre, open-label randomised parallel arm trial. Participants are randomised to active treatment arms 1 or 2.
Participants	Patients with cancer and nausea not related to anticancer therapy.
Interventions	Arm 1: targeted guideline-driven antiemetic therapy dependent on presumed cause of nausea. Arm 2: haloperidol in a three-step dose escalation schedule from 1mg over 24 hours to 3mg over 24 hours given orally or parenterally (subcutaneously).
Outcomes	Primary outcome: response to treatment at 72 hours. Response defined as at least a two-point improvement in average nausea score from baseline and final score less than 3 on an 11-point numeric rating scale.

ACTRN12610000481077 *(Continued)*

Starting date	First enrolment 15 June 2010.
Contact information	Professor Patsy Yates Head of School, Faculty of Health, School - Nursing Queensland University of Technology, Brisbane QLD 4001 Australia
Notes	Preliminary results of this study were published as a conference abstract in 2014 (see Yates 2010 secondary reference).

ACTRN12615000177550

Study name	A randomised, controlled, double blind study of oral methotrimeprazine versus oral haloperidol in patients with cancer and nausea not related to anticancer therapy (Nausea study 3), to compare the effectiveness of oral methotrimeprazine versus oral haloperidol in improving the management of nausea in patients with cancer and nausea not related to anticancer therapy.
Methods	Randomised controlled trial.
Participants	Patients with cancer and nausea not related to anticancer therapy, with nausea severity of at least 3 on an 11 point numeric rating scale (0 no nausea to 10 worst possible nausea).
Interventions	Blinded encapsulated oral methotrimeprazine (6.25mg) or haloperidol (1.5mg) given once daily for three intervention days. If no response at 24 or 48 hours, the dose of the study drug can be increased to twice daily. Rescue medication of metoclopramide or domperidone will be available.
Outcomes	Primary outcome: response to treatment at 72 hours from first study drug administration. Response defined as more than or equal to a two point improvement from baseline for average nausea over the preceding 24 hours on an 11 point numeric rating scale. Secondary outcomes: best nausea score over the preceding 24 hours; complete response (defined as at least two-point improvement from baseline and a score of less than 3 for average nausea over preceding 24 hours, on 0 to 10 numeric rating scale; response; number of episodes of vomiting, not including retching; number of rescue antiemetic doses; toxicity.
Starting date	First enrolment 02 March 2015
Contact information	Prof Janet R Hardy, Director of Palliative Care Mater Health Services, Raymond Terrace, South Brisbane QLD 4101 Australia +617 31632775 janet.hardy@mater.org.au
Notes	http://www.anzctr.org.au/ACTRN12615000177550.aspx

APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Vomiting] explode all trees

#2 MeSH descriptor: [Nausea] explode all trees

#3 vomit*:ti,ab,kw (Word variations have been searched)

#4 nause*:ti,ab,kw (Word variations have been searched)

#5 (emesis or emet*):ti,ab,kw (Word variations have been searched)

#6 (antiemet* or anti-emet*):ti,ab,kw (Word variations have been searched)

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Haloperidol] this term only

#9 (haloperidol or enabran* or halopidol* or halozen* or limerix* or neupram* or zetoridal* or haldol* or serenace* or haloper* or loperidol* or "uni haloper*" or novo-peridol* or peridol* or alternus* or serenase* or buteridol* or duraperidol* or elaubat* or haloneural* or sigaperidol* or aloperidin* or sevium$.mp. or cizoren* or pericate* or peridor* or bioperidol* or kepsidol* or pulsit* or serenelfi*):ti,ab,kw (Word variations have been searched)

#10 (senorm* or cereen* or h-tab* or halo-p or halomed* or halopol* or haricon* or haridol* or perida* or polyhadon* or schizopol* or tensidol* or dozic* or fortunan* or halperon*):ti,ab,kw (Word variations have been searched)

#11 butyrophenone*:ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Butyrophenones] explode all trees

#13 #8 or #9 or #10 or #11 or #12

MEDLINE

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.sh.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE BLIND METHOD.sh.
7. 1 or 2 or 3 or 4 or 5 or 6
8. (ANIMALS not HUMAN).sh.
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. exp CLINICAL TRIALS/
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. PLACEBOS.sh.
15. placebo$.ti,ab.
16. random$.ti,ab.
17. RESEARCH DESIGN.sh.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. 21 or 22 or 23 or 24 or 25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. nause$.mp.
31. vomit$.mp.
32. emesis.mp.
33. emet$.mp.

34. anti-eme$.mp.
35. antieme$.mp.
36. antiemetics.sh.
37. nausea.sh.
38. vomiting.sh.
39. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. haloperidol.mp.
41. enabran$.mp.
42. halopidol$.mp.
43. halozen$.mp.
44. limerix$.mp.
45. neupram$.mp.
46. zetoridal$.mp.
47. haldol$.mp.
48. serenace$.mp.
49. haloper$.mp.
50. loperidol$.mp.
51. "uni haloper$".mp.
52. novo-peridol$.mp.
53. peridol$.mp.
54. alternus$.mp.
55. serenase$.mp.
56. buteridol$.mp.
57. duraperidol$.mp.
58. elaubat$.mp.
59. haloneural$.mp.
60. sigaperidol$.mp.
61. aloperidin$.mp.
62. sevium$.mp.
63. cizoren$.mp.
64. pericate$.mp.
65. peridor$.mp.
66. bioperidol$.mp.
67. avant$.mp.
68. kepsidol$.mp.
69. pulsit$.mp.
70. serenelfi$.mp.
71. senorm$.mp.
72. cereen$.mp.
73. h-tab$.mp.
74. halo-p.mp.
75. halomed$.mp.
76. halopol$.mp.
77. haricon$.mp.
78. haridol$.mp.
79. perida$.mp.
80. polyhadon$.mp.
81. schizopol$.mp.
82. tensidol$.mp.
83. dozic$.mp.
84. fortunan$.mp.
85. halperon$.mp.
86. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85
87. butyrophenone$.mp.
88. exp butyrophenones/
89. 87 or 88
90. 86 or 89
91. 29 and 39 and 90

EMBASE

1 exp Vomiting/ (131250)
2 exp Nausea/ (152267)
3 vomit*.tw. (73323)
4 nause*.tw. (66297)
5 (emesis or emet*).tw. (12303)
6 (antiemet* or anti-emet*).tw. (9283)
7 or/1-6 (248098)
8 exp Butyrophenones/ (66670)
9 butyrophenone*.tw. (961)
10 (senorm* or cereen* or h-tab* or halo-p or halomed* or halopol* or haricon* or haridol* or perida* or polyhadon* or schizopol* or tensidol* or dozic* or fortunan* or halperon*).tw. (178)
11 (haloperidol or enabran* or halopidol* or halozen* or limerix* or neupram* or zetoridal* or haldol* or serenace* or haloper* or loperidol* or "uni haloper*" or novo-peridol* or peridol* or alternus* or serenase* or buteridol* or duraperidol* or elaubat* or haloneural* or sigaperidol* or aloperidin* or sevium* or cizoren* or pericate* or peridor* or bioperidol* or kepsidol* or pulsit* or serenelfi*).tw. (22865)
12 or/8-11 (68762)
13 random$.tw. (927492)
14 factorial$.tw. (24183)
15 crossover$.tw. (50980)
16 cross over$.tw. (22914)
17 cross-over$.tw. (22914)
18 placebo$.tw. (209888)
19 (doubl$ adj blind$).tw. (151391)
20 (singl$ adj blind$).tw. (15179)
21 assign$.tw. (249822)
22 allocat$.tw. (88369)
23 volunteer$.tw. (186012)
24 Crossover Procedure/ (40652)
25 double-blind procedure.tw. (222)
26 Randomized Controlled Trial/ (355913)
27 Single Blind Procedure/ (19061)
28 or/13-27 (1477437)
29 (animal/ or nonhuman/) not human/ (4687675)
30 28 not 29 (1306909)
31 7 and 12 and 30 (1217)
32 (201311* or 201312* or 2014*).dd. (1574688)
33 31 and 32 (34)

CINAHL

S13 S7 AND S12

S12 S8 OR S9 OR S10 OR S11

S11 (haloperidol or enabran* or halopidol* or halozen* or limerix* or neupram* or zetoridal* or haldol* or serenace* or haloper* or loperidol* or "uni haloper*" or novo-peridol* or peridol* or alternus* or serenase* or buteridol* or duraperidol* or elaubat* or haloneural* or sigaperidol* or aloperidin* or sevium* or cizoren* or pericate* or peridor* or bioperidol* or kepsidol* or pulsit* or serenelfi*)

S10 (senorm* or cereen* or h-tab* or halo-p or halomed* OR halopol* OR haricon* or haridol* or perida* or polyhadon* or schizopol* or tensidol* or dozic* or fortunan* or halperon*)

S9 butyrophenone*

S8 (MH "Antipsychotic Agents, Butyrophenone+")

S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6

S6 (antiemet* or anti-emet*)

S5 (emesis or emet*)

S4 nause*

S3 vomit*

S2 (MH "Nausea")

S1 (MH "Vomiting+")

AMED

1. exp Vomiting/

2. exp Nausea/

3. vomit*.tw.

4. nause*.tw.

5. (emesis or emet*).tw.

6. (antiemet* or anti-emet*).tw.

7. or/1-6

8. butyrophenone*.tw.

9. (senorm* or cereen* or h-tab* or halo-p or halomed* or halopol* or haricon* or haridol* or perida* or polyhadon* or schizopol* or tensidol* or dozic* or fortunan* or halperon*).tw.

10. (haloperidol or enabran* or halopidol* or halozen* or limerix* or neupram* or zetoridal* or haldol* or serenace* or haloper* or loperidol* or "uni haloper*" or novo-peridol* or peridol* or alternus* or serenase* or buteridol* or duraperidol* or elaubat* or haloneural* or sigaperidol* or aloperidin* or sevium* or cizoren* or pericate* or peridor* or bioperidol* or kepsidol* or pulsit* or serenelfi*).tw.

11. or/8-10

12. 7 and 11

WHAT'S NEW

Date	Event	Description
27 October 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 2, 2009

Date	Event	Description
4 May 2017	Review declared as stable	See Published notes.
6 March 2015	New search has been performed	This review has been updated; a risk of bias table has been added and a PRISMA flowchart have been included for this update. Two ongoing studies have been identified in trials registers.
15 October 2014	New citation required but conclusions have not changed	One new study has been identified for inclusion, but the conclusions remain unchanged.
8 June 2014	Amended	Edited by authors

Date	Event	Description
24 March 2014	New search has been performed	Review updated
24 March 2014	Amended	Change of author
9 November 2009	Amended	Contact details updated.
30 June 2008	Amended	Protocol converted to new review format.

CONTRIBUTIONS OF AUTHORS

Paul Perkins and SD designed the original systematic review and wrote the protocol. SD developed the search strategy with comments from PP and advice from Sylvia Bickley. Both authors independently reviewed all titles and abstracts yielded by the search strategy for inclusion or exclusion and achieved a consensus by discussion (PP and SD for the original review, FM-B and SD for the updated review). FM-B and SD updated the text of the full review, which was originally written by PP and SD. SD is responsible for further updates.

DECLARATIONS OF INTEREST

FMB has no known conflicts of interest to declare that are relevant to the development of this review.

SD has no known conflicts of interest to declare that are relevant to the development of this review.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had planned to use the Jadad score (Jadad 1996) to assess risk of bias but used the Cochrane risk of bias table instead, as recommended by the Cochrane Collaboration.

NOTES

Assessed for updating in 2017

A restricted search in May 2017 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. We are aware of one relevant ongoing study, which we will assess when available. We will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Assessed for updating in 2019/20

We updated the searches in full in June 2019 with the intention of completing a full update; unfortunately the author team is no longer available. The current version of this review has been permanently stabilised. We are currently undertaking a priority setting process for palliative care titles. If this topic is prioritised, a new protocol will be required for this title.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiemetics [*therapeutic use]; Diphenhydramine [therapeutic use]; Gels; Haloperidol [*therapeutic use]; Lorazepam [therapeutic use]; Nausea [*drug therapy]; *Palliative Care; Randomized Controlled Trials as Topic; Vomiting [*drug therapy]

MeSH check words

Humans