ClinicalEvidence

Nausea and vomiting in people with cancer and other chronic diseases

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ABSTRACT

INTRODUCTION: Nausea and vomiting occur in 40%–70% of people with cancer, and are also common in other chronic conditions such as hepatitis C and inflammatory bowel disease. Nausea and vomiting become more common as disease progresses. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer? What are the effects of treatments for nausea and vomiting occurring as a result of either the disease or its treatment in adults with chronic diseases other than cancer? We searched: Medline, Embase, The Cochrane Library, and other important databases up to April 2008 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found nine systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: $5HT_3$ antagonists, antihistamines, antimuscarinics, atypical antipsychotics, benzodiazepines, butyrophenones, cannabinoids, corticosteroids, haloperidol, metoclopramide, NK1 antagonists, phenothiazines, prokinetics, $5HT_3$ antagonists plus corticosteroids, and venting gastrostomy.

QUESTIONS

INTERVENTIONS

TREATING NAUSEA AND VOMITING IN CANCER

Beneficial

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

TREATING NAUSEA AND VOMITING IN OTHER CHRONIC DISEASES

Likely to be beneficial

Unknown effectiveness

To be covered in future updates	Footnote
Octreotide	*Based on consensus; RCTs unlikely to be conducted.

Key points

- Nausea and vomiting occur in 40%–70% of people with cancer, and are also common in other chronic conditions such as hepatitis C and inflammatory bowel disease. Nausea and vomiting become more common as disease progresses.
- Nausea and vomiting may occur as a result of the disease or its treatment.
- The evidence base for treatment-related causes of nausea and vomiting (chemotherapy and radiotherapy) is much greater and more robust than for disease-related causes.
- Metoclopramide is likely to be effective for reducing episodes of vomiting in people having chemotherapy.

  Dexamethasone, in combination with other antiemetics, reduces acute and delayed emesis compared with placebo in people receiving emetogenic chemotherapy, and it may be more effective than metoclopramide in this population.

  $5HT_3$ antagonists also reduce acute vomiting in people having chemotherapy compared with metoclopramide-based regimens, and this benefit is enhanced by the addition of dexamethasone.

  There is consensus that haloperidol, phenothiazines, and venting gastrostomy are effective for controlling nausea and vomiting in people with cancer.
- Cannabinoids are effective for nausea and vomiting in people receiving chemotherapy, but may be associated with a high and often unacceptable burden of adverse effects.
- We don't know whether antihistamines, antimuscarinics, antipsychotics, benzodiazepines, or NK1 antagonists are effective in people with cancer-related nausea and vomiting.
- We don't know whether $5HT_3$ antagonists alone reduce nausea and vomiting in people having radiotherapy. However, adding dexamethasone to $5HT_3$ antagonists seems more effective than $5HT_3$ antagonists alone.
- Despite the lack of robust RCT evidence, there is a consensus based on clinical experience that antihistamines have a place in the management of nausea and vomiting, especially that related to motion sickness, mechanical bowel obstruction, and raised intracranial pressure.

  We don't know whether any other interventions are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.

Clinical context

DEFINITION

Nausea and vomiting (emesis) are common in people with cancer and other chronic diseases. They may occur because of several factors, most easily categorised as disease-related and treatment-related. The evidence base for treatment-related causes of nausea and vomiting (chemotherapy and radiotherapy) is much greater and more robust than for disease-related causes. [1] [2] This review focuses on the management of nausea and vomiting in people with cancer or other chronic conditions, and does not include people with postoperative nausea and vomiting. For the purposes of this review, we have used the NICE definition of supportive care as follows: supportive care "helps the patient and their family to cope with cancer and treatment of it — from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness or death and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment." [3] This definition was written in relation to people with cancer but is applicable to all people with chronic or terminal illness: for example, heart failure or lung disease. We have used the WHO definition of palliative care as follows: "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." [4] Although this definition of palliative care does not specify incurable or terminal illness, there is consensus that palliative care applies to people approaching the end of life: that is, people with a prognosis of less than 1 year. Thus, both supportive and palliative care embrace the same priorities of maximising quality of life; but supportive care aims to do this in people who may live longer, become cured, or who are living in remission from their disease.

INCIDENCE/ PREVALENCE

Nausea and vomiting occur in 40%–70% of people with cancer [1] [2] and are also common in other chronic conditions such as hepatitis C [5] and inflammatory bowel disease. [6] Nausea and vomiting become more common as disease progresses.

AETIOLOGY/ RISK FACTORS

Nausea and vomiting are complex neurological and physical phenomena involving a range of areas of the central nervous system and gastrointestinal tract. In palliative and supportive care, nausea may be due to chemotherapy, especially platinum-based chemotherapy, [7] other drugs (opiates, antibiotics), [8] or radiotherapy. [9] It may also have disease-related causes: for example, metabolic (hypercalcaemia, uraemia), [10] cranial (raised intracranial pressure, VIIIth nerve tumours), gastrointestinal (gastric outflow obstruction, hepatomegaly constipation, bowel obstruction, or ileus), or psychogenic (anticipatory nausea and vomiting, anxiety, or fear). [11]

PROGNOSIS

In many cases, nausea will respond to treatment of the underlying cause: for example, nausea resulting from metabolic disturbance such as hypercalcaemia. Nausea resulting from emetogenic drugs such as opioids may resolve if the opioid is switched.

AIMS OF INTERVENTION

To reduce nausea and vomiting and improve quality of life, with minimal adverse effects of treatment.

OUTCOMES

Vomiting: number of episodes of nausea, retching, or vomiting, vomitus volume; **ability to remove nasogastric tube**; **quality of life**; **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal April 2008. The following databases were used to identify studies for this systematic review: Medline 1986 to April 2008, Embase 1986 to April 2008, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 1. An additional search was carried out of the NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single-blinded, and containing more than 20 individuals of whom more than 80% were followed up. We also searched for comparative cohort studies — both prospective and retrospective. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. We have searched for treatments for nausea and vomiting in people with advanced cancer or other chronic conditions being treated in the palliative-care setting and have included all RCTs of sufficient quality. We only evaluated interventions currently in common use (excluding, for example, triethylperazine and cisapride). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 34). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments for nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer?**

OPTION **CORTICOSTEROIDS IN THE CONTROL OF CHEMOTHERAPY-RELATED NAUSEA AND VOMITING**

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- Dexamethasone, in combination with other antiemetics, reduces acute and delayed emesis compared with placebo in people receiving emetogenic chemotherapy, and it may be more effective than metoclopramide in this population.
- $5HT_3$ antagonists also reduce acute vomiting in people having chemotherapy compared with metoclopramide-based regimens, and this benefit is enhanced by the addition of dexamethasone.

Benefits and harms

Dexamethasone versus placebo or no treatment in people receiving chemotherapy:

We found one systematic review (search date 1999) assessing dexamethasone in people receiving emetogenic chemotherapy (mainly cisplatin at doses of 50 mg/m^2) for both early and advanced cancer. [12]

Vomiting

Dexamethasone compared with placebo Dexamethasone reduces acute and delayed emesis in people receiving emetogenic chemotherapy. In almost all RCTs, all participants also received other antiemetics (primarily 5HT$_3$ antagonists) (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[12] Systematic review	5613 people receiving emetogenic chemotherapy (mainly cisplatin at doses of 50 mg/m^2) for both early and advanced cancer 25 RCTs in this analysis	**Proportion of people with no vomiting , within 24 hours of receiving chemotherapy** with dexamethasone given before chemotherapy with placebo or no treatment given before chemotherapy Absolute results not reported 25 RCTs in analysis	OR 2.22 95% CI 1.89 to 2.60 In all of the RCTs, all participants also received other antiemetics (primarily 5HT$_3$ antagonists)	●●○	dexamethasone
[12] Systematic review	2278 people receiving emetogenic chemotherapy (mainly cisplatin at doses of 50 mg/m^2) for both early and advanced cancer 16 RCTs in this analysis	**Vomiting , within 1–7 days of receiving chemotherapy** with dexamethasone given before chemotherapy with placebo or no treatment given before chemotherapy Absolute results not reported 16 RCTs in analysis	OR 2.04 95% CI 1.63 to 2.56 In all of the RCTs, all participants also received other antiemetics (primarily 5HT$_3$ antagonists)	●●○	dexamethasone

Ability to remove nasogastric tube

No data from the following reference on this outcome. [12]

Quality of life

No data from the following reference on this outcome. [12]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	People receiving emetogenic chemotherapy (mainly cisplatin at doses of 50 mg/m^2) for both	**Gastrointestinal adverse effects** with dexamethasone given before chemotherapy with placebo or no treatment given before chemotherapy	Statistical analysis not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	early and advanced cancer	Absolute results not reported The review stated that most RCTs found adverse effects "mild and tolerable"; several RCTs reported increased hiccups/gastrointestinal symptoms with dexamethasone (no further data reported). One person on dexamethasone had haematemesis			

Dexamethasone versus metoclopramide in people receiving chemotherapy:

We found one systematic review, which identified three RCTs (189 people receiving emetogenic chemotherapy for both early and advanced cancer). [12]

Vomiting

Dexamethasone compared with metoclopramide Dexamethasone may be more effective at reducing vomiting in this population (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[12] Systematic review	189 people receiving emetogenic chemotherapy for both early and advanced cancer 3 RCTs in this analysis	**Acute vomiting** with dexamethasone with metoclopramide	RR 1.11 95% CI 1.00 to 1.24 In one of the RCTs, all participants also received tropisetron (a $5HT_3$ antagonist). There was significant heterogeneity among RCTs. Result of borderline significance	●○○	dexamethasone
[12] Systematic review	189 people receiving emetogenic chemotherapy for both early and advanced cancer 3 RCTs in this analysis	**Delayed vomiting** with dexamethasone with metoclopramide	RR 1.16 95% CI 0.75 to 1.80 In one of the RCTs, all participants also received tropisetron (a $5HT_3$ antagonist). There was significant heterogeneity among RCTs	⟷	Not significant

Ability to remove nasogastric tube

No data from the following reference on this outcome. [12]

Quality of life

No data from the following reference on this outcome. [12]

Adverse effects

No data from the following reference on this outcome. [12]

Dexamethasone plus metoclopromide versus metoclopramide alone in people with nausea owing to disease, chemotherapy, or radiotherapy:

We found one RCT (51 people with advanced cancer with chronic nausea caused by the disease or chemotherapy). [13]

Vomiting

Dexamethasone plus metoclopramide compared with metoclopramide alone Adding dexamethasone to metoclopramide may be no more effective than metoclopramide alone at reducing vomiting (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[13] RCT	51 people with advanced cancer with chronic nausea caused by the disease or by chemotherapy or radiotherapy	**Mean nausea intensity at 3 days on a scale of 0–10 where 0 = symptom absent and 10 = worst possible symptom** 4.5 with dexamethasone plus metoclopramide 2.9 with placebo plus metoclopramide	P = 0.16 Note: although no significant difference between groups, nausea improved in both groups from baseline	⟷	Not significant
[13] RCT	51 people with advanced cancer with chronic nausea caused by the disease or by chemotherapy or radiotherapy	**Mean nausea intensity at 8 days on a scale of 0–10 where 0 = symptom absent and 10 = worst possible symptom** 5.9 with dexamethasone plus metoclopramide 5.7 with placebo plus metoclopramide	P = 0.85 Note: although no significant difference between groups, nausea improved in both groups from baseline	⟷	Not significant
[13] RCT	51 people with advanced cancer with chronic nausea caused by the disease or by chemotherapy or radiotherapy	**Vomiting** with dexamethasone plus metoclopramide with placebo plus metoclopramide Absolute results not reported	Reported as not significant P value not reported Note: although no significant difference between groups, nausea improved in both groups from baseline	⟷	Not significant

Ability to remove nasogastric tube

No data from the following reference on this outcome. [13]

Quality of life

Dexamethasone plus metoclopramide compared with metoclopramide alone We don't know how dexamethasone plus metoclopramide and metoclopramide alone compare at improving quality of life outcomes (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[13] RCT	51 people with advanced cancer with chronic nausea caused by the disease or by chemotherapy or radiotherapy	**Quality of life** with dexamethasone plus metoclopramide with placebo plus metoclopramide	Reported as not significant P value not reported Note: although no significant difference between groups, vomiting improved in both groups from baseline	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT	51 people with advanced cancer with chronic nausea caused by the disease or by chemotherapy or radiotherapy	**Adverse effects** with dexamethasone plus metoclopramide with placebo plus metoclopramide The RCT found that 14/51 (27%) people had adverse effects, including ankle oedema, insomnia, and restlessness, with similar rates in people taking dexamethasone and placebo	Significance between groups not assessed	○○○	

Dexamethasone plus $5HT_3$ antagonists versus $5HT_3$ antagonists alone in people receiving chemotherapy:
We found one systematic review (search date 1996, 11 RCTs, 10 RCTs included in another review), [12] which performed an analysis comparing adding dexamethasone to $5HT_3$ antagonists versus $5HT_3$ antagonists alone. [14]

Vomiting

Dexamethasone plus $5HT_3$ antagonists compared with $5HT_3$ antagonists alone Adding dexamethasone to $5HT_3$ antagonists is more effective than $5HT_3$ antagonists alone in controlling vomiting (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[14] Systematic review	People with early or advanced cancer receiving low to moderately emetogenic cisplatin-based chemotherapy regimens	**Proportion of people with vomiting** 272/1102 (25%) with dexamethasone plus $5HT_3$ antagonists 14/1017 (41%) with $5HT_3$ antagonists alone	OR 0.42 95% CI 0.34 to 0.51	●●○	dexamethasone plus $5HT_3$ antagonists

Ability to remove nasogastric tube

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

Further information on studies

Comment: None.

OPTION 5HT3 ANTAGONISTS IN PEOPLE WITH CHEMOTHERAPY-RELATED NAUSEA AND VOMITING

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- $5HT_3$ antagonists reduce acute vomiting in people having chemotherapy compared with metoclopramide-based regimens, and this benefit is enhanced by the addition of dexamethasone.

Benefits and harms

$5HT_3$ antagonists versus metoclopramide-based regimens in people receiving chemotherapy:

We found one systematic review (search date 1996) comparing $5HT_3$ antagonists versus high-dose metoclopramide alone or metoclopramide at any dose in combination with dexamethasone, lorazepam, or orphenadrine. [14]

Vomiting

$5HT_3$ antagonists compared with metoclopramide-based regimens $5HT_3$ antagonists are more effective at reducing acute vomiting in people receiving cisplatin-based chemotherapy (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[14] Systematic review	People receiving highly emetogenic cisplatin-based chemotherapy regimens for early or advanced cancer 15 RCTs in this analysis	**Proportion of people with acute vomiting** 531/1320 (40%) with $5HT_3$ antagonists 674/1314 (51%) with metoclopramide-based antiemitics 15 RCTs in analysis	OR 0.60 95% CI 0.51 to 0.70	●○○	$5HT_3$ antagonists
[14] Systematic review	People receiving low to moderately emetogenic cisplatin-based chemotherapy regimens for early or advanced cancer 15 RCTs in this analysis	**Proportion of people with vomiting** 293/924 (32%) with $5HT_3$ antagonists 450/924 (49%) with metoclopramide-based antiemitics	OR 0.47 95% CI 0.39 to 0.58	●●○	$5HT_3$ antagonists

Ability to remove nasogastric tube

No data from the following reference on this outcome. [14]

Quality of life

No data from the following reference on this outcome. [14]

Adverse effects

No data from the following reference on this outcome. [14]

5HT$_3$ antagonists in combination with dexamethasone in people receiving chemotherapy:
See option on dexamethasone, p 3 .

5HT$_3$ antagonists in people receiving radiotherapy:
See option on 5HT$_3$ antagonists in people receiving radiotherapy, p 23 .

Further information on studies

Comment: None.

OPTION BUTYROPHENONES

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- There is consensus that haloperidol is effective for controlling nausea and vomiting in people with cancer.
- We found no direct information whether haloperidol is better than no active treatment.
- A drug safety alert has been issued on cardiovascular adverse effects and sudden death associated with haloperidol (http://www.fda.gov).

Benefits and harms

Haloperidol versus cannabinoids in people receiving chemotherapy:
See option on cannabinoids, p 14 .

Other butyrophenones:
We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although haloperidol is almost universally used for nausea, especially where the cause is chemical or metabolic, there is no RCT evidence that it is beneficial. However, there is consensus, based largely on case series, that haloperidol is an effective antiemetic for chemical and metabolic causes of nausea and vomiting, such as opioid-induced nausea, renal failure, and hypercalcaemia. [15]

OPTION PROKINETICS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- Metoclopramide is likely to be effective for reducing episodes of vomiting in people having chemotherapy.
- Dexamethasone, in combination with other antiemetics, reduces acute and delayed emesis compared with placebo in people receiving emetogenic chemotherapy, and it may be more effective than metoclopramide in this population.
- $5HT_3$ antagonists also reduce acute vomiting in people having chemotherapy compared with metoclopramide-based regimens, and this benefit is enhanced by the addition of dexamethasone.
- The risk of tardive dyskinesia associated with long-term or high-dose use of metoclopramide has been highlighted by the FDA (http://www.fda.gov).

Benefits and harms

Metoclopramide versus placebo or versus prochlorperazine (a phenothiazine) in people receiving chemotherapy:

We found one paper reporting two RCTs undertaken in the same group of 41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer. [16] The first RCT compared metoclopramide 10 mg/kg 1.5–8.0 hours after chemotherapy versus placebo; the second RCT compared metoclopramide (at same dose and regimen) versus prochlorperazine 50 mg (see comment).

Vomiting

Metoclopramide compared with placebo or prochlorperazine Metoclopramide may be more effective than placebo or prochlorperazine (a phenothiazine) in reducing vomiting in people with advanced cancer having chemotherapy predominantly for lung and upper gastrointestinal cancer (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people	**Median number of episodes of vomiting** 1.0 with metoclopramide 10.5 with placebo	P = 0.001	○○○	metoclopramide
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer	**Median number of episodes of vomiting** 1.5 with metoclopramide 12.0 with prochlorperazine	P = 0.005	○○○	metoclopramide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people				
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people	**Volume of vomiting** 20 mL with metoclopramide 404 mL with placebo	P = 0.001	○○○	metoclopramide
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people	**Volume of vomiting** 15 mL with metoclopramide 208 mL with prochlorperazine	P = 0.022	○○○	metoclopramide
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people	**Median duration of nausea** 0 hours with metoclopramide 3.7 hours with placebo	P = 0.042	○○○	metoclopramide
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis	**Median duration of nausea** with metoclopramide with prochlorperazine Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	One paper reporting two RCTs undertaken in the same group of people				
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people	**Median duration of vomiting** 0.2 hours with metoclopramide 3.6 hours with placebo	P = 0.028	○○○	metoclopramide
[16] RCT	41 people with advanced cancer being treated with cisplatin-based chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people	**Median duration of vomiting** with metoclopramide with prochlorperazine Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Ability to remove nasogastric tube

No data from the following reference on this outcome. [16]

Quality of life

No data from the following reference on this outcome. [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] RCT	41 people with advanced cancer being treated with cisplatin-based	**Adverse effects** with metoclopramide with placebo/prochlorperazine	The RCTs found similar rates of adverse effects, including sedation, among groups (significance of difference among groups not	○○○	

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	chemotherapy, predominantly for lung and upper gastrointestinal cancer 2 RCTs in this analysis One paper reporting two RCTs undertaken in the same group of people		reported). See further information on studies for full details		

Metoclopramide versus dexamethasone in people receiving chemotherapy:

See option on dexamethasone, p 3 .

Metoclopramide versus cannabinoids in people receiving chemotherapy:

See option on cannabinoids, p 14 .

Metoclopramide versus $5HT_3$ antagonists in people receiving chemotherapy:

See option on $5HT_3$ antagonists, p 8 .

Further information on studies

[16] **Metoclopramide versus placebo or versus prochlorperazine in people receiving chemotherapy — adverse effects:** There was no evidence of a difference in the number of bowel movements (which might be expected with a prokinetic) among groups (significance of difference among groups not reported). One person receiving metoclopramide had an extrapyramidal reaction (trismus), which settled within 5 minutes of an injection of diphenhydramine.

Comment: **Clinical guide:**
Metoclopramide is unlikely to be given in such large doses in clinical practice. [16]

OPTION PHENOTHIAZINES

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- There is consensus that phenothiazines are effective for controlling nausea and vomiting in people with cancer.
- We found no direct information from RCTs about whether phenothiazines are more effective than no active treatment.

Benefits and harms

Phenothiazines versus prokinetics in people receiving chemotherapy:

See option on prokinetics, p 10 .

Further information on studies

Comment: **Clinical guide:**
Despite the lack of robust RCT evidence, phenothiazines (chlorpromazine, levomepromazine, prochlorperazine) are almost universally used for nausea from various causes, and there is consensus that they are likely to be beneficial. [17]

OPTION VENTING GASTROSTOMY

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- There is consensus that venting gastrostomy is effective for controlling nausea and vomiting in people with cancer.
- We found no direct information from RCTs about the effects of venting gastrostomy in people with nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer.

Benefits and harms

Venting gastrostomy:

We found no systematic reviews or RCTs.

Further information on studies

Comment: **Clinical guide:**
RCTs into the effects of venting gastrostomy are unlikely to be undertaken. On the basis of observational evidence [18] [19] and clinical experience, there is consensus that it is effective.

OPTION CANNABINOIDS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- Cannabinoids are effective for nausea and vomiting in people receiving chemotherapy, but may be associated with a high and often unacceptable burden of adverse effects.

Benefits and harms

Cannabinoids versus placebo in people receiving chemotherapy:

We found one systematic review (search date 2000) comparing cannabinoids versus placebo in people receiving a variety of cytotoxic chemotherapy regimens for various types of cancer, some early and some advanced. [20] The cannabinoids assessed were oral nabilone, oral dronabinol (tetrahydrocannabinol), and intramuscular levonantradol.

Vomiting

Cannabinoids compared with placebo Cannabinoids are more effective at controlling nausea and vomiting associated with chemotherapy (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 4 RCTs in this analysis	**Complete control of nausea** 81/116 (70%) with cannabinoids 66/115 (57%) with placebo 4 RCTs in analysis	RR 1.21 95% CI 1.03 to 1.42 NNT 8 95% CI 4 to 775	●○○	cannabinoids
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 4 RCTs in this analysis	**Complete control of vomiting** 76/116 (66%) with cannabinoids 41/115 (36%) with placebo 4 RCTs in analysis	RR 1.84 95% CI 1.42 to 2.38 NNT 4 95% CI 3 to 6	●○○	cannabinoids

Ability to remove nasogastric tube

No data from the following reference on this outcome. [20]

Quality of life

No data from the following reference on this outcome. [20]

Adverse effects

Cannabinoids compared with placebo Cannabinoids seem to be associated with an increase of adverse effects (including "high" sensation, drowsiness, euphoria, dizziness, dysphoria or depression, hallucination, paranoia, arterial hypertension, withdrawal due to adverse effects) compared with placebo or other antiemetics (results for both groups combined in analysis) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 8 RCTs in this analysis	**"High" sensation** 162/470 (35%) with cannabinoids 17/562 (3%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 8 RCTs in analysis	RR 10.6 95% CI 6.86 to 16.50 NNT 3 95% CI 2 to 3	●●●	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 15 RCTs in this analysis	**Drowsiness, sedation, somnolence** 320/636 (50%) with cannabinoids 224/737 (30%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 15 RCTs in analysis	RR 1.66 95% CI 1.46 to 1.89 NNT 5 95% CI 4 to 6	●○○	control (placebo or other antiemetics)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 3 RCTs in this analysis	**Euphoria** 24/168 (14%) with cannabinoids 1/168 (1%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 3 RCTs in analysis	RR 12.50 95% 3.00 to 52.10 NNT 7 95% CI 5 to 12	●●●	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 9 RCTs in this analysis	**Dizziness** 173/357 (49%) with cannabinoids 57/334 (17%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 9 RCTs in analysis	RR 2.97 95% CI 2.31 to 3.83 NNT 3 95% CI 2 to 4	●●○	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 10 RCTs in this analysis	**Dysphoria or depression** 39/312 (13%) with cannabinoids 1/378 (1%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 10 RCTs in analysis	RR 8.06 95% CI 3.38 to 19.20 NNT 8 95% CI 6 to 12	●●●	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 10 RCTs in this analysis	**Hallucination** 26/435 (6%) with cannabinoids 0/424 (0%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 10 RCTs in analysis	RR 6.10 95% CI 2.41 to 15.40 NNT 17 95% CI 12 to 27	●●●	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 6 RCTs in this analysis	**Paranoia** 14/285 (5%) with cannabinoids 0/286 (0%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 6 RCTs in analysis	RR 8.58 95% CI 6.38 to 15.40 NNT 20 95% CI 13 to 42	●●●	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 13 RCTs in this analysis	**Arterial hypertension** 124/497 (25%) with cannabinoids 53/485 (11%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 13 RCTs in analysis	RR 2.23 95% CI 1.75 to 2.83 NNT 7 95% CI 5 to 11	●●○	control (placebo or other antiemetics)
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced	**Withdrawal because of adverse effects** 108/1003 (11%) with cannabinoids	RR 4.67 95% CI 3.07 to 7.09 NNT 11 95% CI 9 to 14	●●○	control (placebo or other antiemetics)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	19 RCTs in this analysis	18/1108 (2%) with placebo or other antiemetics Control group included placebo and other antiemetics; not analysed separately 19 RCTs in analysis			

Cannabinoids versus other antiemetics in people receiving chemotherapy:

We found one systematic review (search date 2000) comparing cannabinoids versus other antiemetics in people receiving chemotherapy for various types of cancer, some early and some advanced. [20] The cannabinoids assessed were oral nabilone, oral dronabinol (tetrahydrocannabinol), and intramuscular levonantradol. The other antiemetics assessed were prochlorperazine, metoclopramide, chlorpromazine, haloperidol, domperidone, and alizapride.

Vomiting

Cannabinoids compared with other antiemetics Cannabinoids are more effective at controlling vomiting associated with chemotherapy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 7 RCTs in this analysis	**Complete control of nausea** 122/207 (59%) with cannabinoids 93/215 (43%) with other antiemetics 7 RCTs in analysis	RR 1.38 95% CI 1.18 to 1.62 NNT 7 95% CI 4 to 16	●○○	cannabinoids
[20] Systematic review	People receiving variety of cytotoxic chemotherapy regimens for cancer: some early, some advanced 7 RCTs in this analysis	**Complete control of vomiting** 111/194 (57%) with cannabinoids 90/201 (45%) with other antiemetics 7 RCTs in analysis	RR 1.28 95% CI 1.08 to 1.51 NNT 8 95% CI 5 to 38	●○○	cannabinoids

Ability to remove nasogastric tube

No data from the following reference on this outcome. [20]

Quality of life

No data from the following reference on this outcome. [20]

Further information on studies

[20] **Cannabinoids versus other antiemetics in people receiving chemotherapy — adverse effects**: The review did not analyse adverse effects of cannabinoids versus other antiemetics separately, but undertook a combined analysis using a control group of placebo or other antiemetics (for reporting of this analysis see adverse effects in cannabinoids versus placebo).

Comment: None.

OPTION ANTIHISTAMINES

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether antihistamines are effective in people with cancer-related nausea and vomiting.
- We found no direct information from RCTs about the effects of antihistamines in people with nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer.

Benefits and harms

Antihistamines:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although antihistaminics (cyclizine, prochlorperazine) are sometimes used for the control of nausea and vomiting in people with cancer, there is no evidence from well-conducted trials that they are beneficial.

OPTION ANTIMUSCARINICS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether antimuscarinics are effective in people with cancer-related nausea and vomiting.
- We found no direct information from RCTs about the effects of antimuscarinics in people with nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer.

Benefits and harms

ANTIMUSCARINICS:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although there are no RCTs of antimuscarinics, observational evidence suggests that hyoscine butylbromide may be effective in people with malignant bowel obstruction. [21]

OPTION ANTIPSYCHOTICS (ATYPICAL)

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether antipsychotics are effective in people with cancer-related nausea and vomiting.
- We found no direct information from RCTs about the effects of atypical antipsychotics in people with nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer.

Benefits and harms

Antipsychotics:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether benzodiazepines are effective in people with cancer-related nausea and vomiting.
- Lorazepam is associated with sedation and amnesia.

Benefits and harms

Lorazepam versus placebo in people receiving chemotherapy:

We found one RCT. [22] Participants received lorazepam 2.5 mg or placebo before chemotherapy and again after 12 hours.

Vomiting

Lorazepam compared with placebo Lorazepam may be no more effective at controlling vomiting when given before chemotherapy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[22] RCT	53 people with early breast cancer receiving adjuvant fluorouracil plus epirubicin plus cyclophosphamide (FEC) or cyclophosphamide plus methotrexate plus fluorouracil (CMF) All participants also received methylprednisolone	**Mild nausea** 60% with lorazepam plus methylprednisolone 68% with placebo plus methylprednisolone Absolute results not reported	Reported as no significant difference between groups P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT	53 people with early breast cancer receiving adjuvant fluorouracil plus epirubicin plus cyclophosphamide (FEC) or cyclophosphamide plus methotrexate plus fluorouracil (CMF) All participants also received methylprednisolone	**Complete control of vomiting** 33% with lorazepam plus methylprednisolone 35% with placebo plus methylprednisolone Absolute results not reported	Reported as no significant difference between groups P value not reported	⟷	Not significant
[22] RCT	53 people with early breast cancer receiving adjuvant fluorouracil plus epirubicin plus cyclophosphamide (FEC) or cyclophosphamide plus methotrexate plus fluorouracil (CMF) All participants also received methylprednisolone	**Proportion of people who had more than five episodes of vomiting** 52% with lorazepam plus methylprednisolone 55% with placebo plus methylprednisolone Absolute results not reported	Reported as no significant difference between groups P value not reported	⟷	Not significant

Ability to remove nasogastric tube

No data from the following reference on this outcome. [22]

Quality of life

No data from the following reference on this outcome. [22]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[22] RCT	53 people with early breast cancer receiving adjuvant fluorouracil plus epirubicin plus cyclophosphamide (FEC) or cyclophosphamide plus methotrexate plus fluorouracil (CMF)	**Sedation** 86%–92% with lorazepam (depending on what chemotherapy regimen given) 8%–10% with placebo (depending on what chemotherapy regimen given) Absolute results not reported	Reported as significant difference between groups P value not reported	○○○	placebo
[22] RCT	53 people with early breast cancer receiving adjuvant fluorouracil plus epirubicin plus cyclophosphamide	**Amnesia** 48%–50% with lorazepam (depending on what chemotherapy regimen given) 0% with placebo	P value and statistical analysis between groups not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	(FEC) or cyclophosphamide plus methotrexate plus fluorouracil (CMF)	Absolute results not reported			

Further information on studies

Comment: None.

OPTION NK1 ANTAGONISTS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether NK1 antagonists are effective in people with cancer-related nausea and vomiting.
- We found no direct information from RCTs about whether aprepitant is more effective when used alone than no active treatment, or about NK1 antagonists other than aprepitant.

Benefits and harms

Aprepitant versus placebo in people receiving a standard antiemetic regimen for chemotherapy-related nausea:

We found two RCTs, both comparing aprepitant versus placebo in people receiving a standard antiemetic regimen (5HT3 receptor antagonist plus dexamethasone). [23] [24]

Vomiting

Aprepitant compared with placebo Adding aprepitant to a conventional antiemetic regimen of a $5HT_3$ antagonist plus a corticosteroid reduces treatment-related nausea and vomiting in people receiving highly emetogenic chemotherapy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[23] RCT	569 people receiving highly emetogenic, high-dose cisplatin-based chemotherapy, disease stage unclear All people in RCT were also receiving a standard antiemetic regimen ($5HT_3$ receptor antagonist plus dexamethasone)	**Proportion of people with complete response at 5 days, defined as no vomiting and no use of rescue drug treatment for established nausea or vomiting** 163/260 (63%) with aprepitant 114/263 (43%) with placebo	P <0.001 Results based on 523/569 (92%) of people in RCT	○○○	aprepitant
[24] RCT	530 people receiving highly emetogenic, high-dose cisplatin-based chemotherapy, Karnofsky score at least 70	**Proportion of people with complete response (defined as no vomiting and no use of rescue drug treatment for established nausea or vomiting) at day 1 (acute phase), days 2–5, and overall**	P <0.01 for all comparisons Results based on 420/530 (86%) of people in RCT	○○○	aprepitant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	All people in RCT were also receiving a standard antiemetic regimen ($5HT_3$ receptor antagonist plus dexamethasone)	85%, 66%, and 63% with aprepitant 75%, 51%, and 49% with placebo Absolute results not reported			

Ability to remove nasogastric tube

No data from the following reference on this outcome. [23] [24]

Quality of life

No data from the following reference on this outcome. [23] [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT	569 people receiving highly emetogenic, high-dose cisplatin-based chemotherapy, disease stage unclear All people in RCT were also receiving a standard antiemetic regimen ($5HT_3$ receptor antagonist plus dexamethasone)	**Adverse effects** with aprepitant with placebo The RCT found similar rates of adverse effects between groups, but did not assess the significance of difference between groups (for full details see further information on studies)	Significance not assessed		
[24] RCT	530 people receiving highly emetogenic, high-dose cisplatin-based chemotherapy, Karnofsky score at least 70 All people in RCT were also receiving a standard antiemetic regimen ($5HT_3$ receptor antagonist plus dexamethasone)	**Asthenia/fatigue** 17% with aprepitant 10% with placebo Absolute results not reported	P >0.1	⟷	Not significant
[24] RCT	530 people receiving highly emetogenic, high-dose cisplatin-based chemotherapy, Karnofsky score at least 70	**Constipation** 8% with aprepitant 12% with placebo Absolute results not reported	P >0.1	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	All people in RCT were also receiving a standard antiemetic regimen ($5HT_3$ receptor antagonist plus dexamethasone)				
[24] RCT	530 people receiving highly emetogenic, high-dose cisplatin-based chemotherapy, Karnofsky score at least 70 All people in RCT were also receiving a standard antiemetic regimen ($5HT_3$ receptor antagonist plus dexamethasone)	**Hiccups** 14% with aprepitant 7% with placebo Absolute results not reported	P >0.1	⟷	Not significant

Other NK1 antagonists:

We found no systematic review or RCTs.

Further information on studies

[23] The RCT assessed adverse effects in almost all participants in the first RCT (567/569 [99.6%]). [23] The RCT found similar rates of adverse effects between groups, including neutropenia, dehydration, anorexia, asthenia/fatigue, constipation, diarrhoea, and headache (neutropenia: 1.8% with aprepitant *v* 2.1% with placebo; dehydration: 1.8% with aprepitant *v* 0.7% with placebo; anorexia: 15.2% with aprepitant *v* 14.0% with placebo; asthenia/fatigue: 18.4% with aprepitant *v* 14.0% with placebo; constipation: 12.4% with aprepitant *v* 12.3% with placebo; diarrhoea: 12.1% with aprepitant *v* 10.5% with placebo; headache: 9.9% with aprepitant *v* 11.6% with placebo). The RCT did not assess the significance of the difference between groups.

[24] In the RCT, the investigators concluded that other serious adverse effects were caused by the cisplatin-based chemotherapy (dehydration, febrile neutropenia, neutropenia, and thrombocytopenia), but the RCT did not assess the significance of the difference between groups for these outcomes.

Comment: Further RCTs are required to fully assess the effects of aprepitant alone.

OPTION 5HT3 ANTAGONISTS IN PEOPLE WITH RADIOTHERAPY-RELATED NAUSEA AND VOMITING

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether $5HT_3$ antagonists alone reduce nausea and vomiting in people receiving radiotherapy.

Benefits and harms

$5HT_3$ antagonists versus metoclopramide in people receiving radiotherapy:

We found one systematic review (search date 1997). [25] Excluding small-scale, poor-quality RCTs, it identified one RCT comparing ondansetron versus metoclopramide in people receiving radiotherapy to the upper abdomen.

Vomiting

5HT$_3$ antagonists compared with metoclopramide The 5HT$_3$ antagonist ondansetron seems to be more effective than metoclopramide at reducing acute vomiting (within 24 hours) in people undergoing radiotherapy, but has no demonstrable benefit in delayed emesis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[25] RCT	105 people with early or advanced cancer receiving radiotherapy to the upper abdomen	**Reduction in vomiting over 24 hours** with ondansetron with metoclopramide	NNT 3 95% CI 2 to 4	○○○	ondansetron
[25] RCT	105 people with early or advanced cancer receiving radiotherapy to the upper abdomen	**Reduction in nausea over 24 hours** with ondansetron with metoclopramide	NNT 4 95% CI 2 to 10	○○○	ondansetron
[25] RCT	105 people with early or advanced cancer receiving radiotherapy to the upper abdomen	**Proportion of people with control of vomiting at 5 days** 48/49 (98%) with ondansetron 54/56 (96%) with metoclopramide	Significance not assessed P value not reported		

Ability to remove nasogastric tube

No data from the following reference on this outcome. [25]

Quality of life

No data from the following reference on this outcome. [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] RCT	105 people with early or advanced cancer receiving radiotherapy to the upper abdomen	**Constipation** 16% with ondansetron 0% with metoclopramide	NNT 6 95% CI 4 to 14	○○○	metoclopramide
[25] RCT	105 people with early or advanced cancer receiving radiotherapy to the upper abdomen	**Headache** 7% with ondansetron 2% with metoclopramide	NNT 17 95% CI 9 to 80	○○○	metoclopramide

5HT$_3$ antagonists in people receiving chemotherapy:

See option on 5HT$_3$ antagonists in people receiving chemotherapy, p 8 .

Further information on studies

Comment: None.

OPTION 5HT3 ANTAGONISTS PLUS CORTICOSTEROIDS IN PEOPLE WITH RADIOTHERAPY-RELATED NAUSEA AND VOMITING New

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- Adding dexamethasone to $5HT_3$ antagonists seems more effective than $5HT_3$ antagonists alone in people with radiotherapy-related nausea and vomiting.

Benefits and harms

Adding corticosteroids versus adding placebo in people receiving $5HT_3$ antagonists:

We found one RCT (211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields) comparing dexthamethasone versus placebo during fractions 1–5. [26]

Vomiting

Adding corticosteroids versus adding placebo in people receiving $5HT_3$ antagonists Dexamethasone is more effective than placebo at reducing vomiting in people receiving $5HT_3$ antagonists to prevent radiotherapy-induced emesis (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Vomiting					
[26] RCT	211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields	**Proportion of people with complete control of emesis , after 15 fractions of radiotherapy** 22/95 (23%) with dexamethasone plus ondansetron 11/96 (12%) with placebo plus ondansetron	P = 0.02	○○○	dexamethasone
[26] RCT	211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields	**Average nausea scores after 15 fractions of radiotherapy (maximum score 4)** 0.28 with dexamethasone plus ondansetron 0.39 with placebo plus ondansetron	P <0.03	○○○	dexamethasone
[26] RCT	211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields	**Proportion of people not using rescue antiemetics** 10/101 (30%) with dexamethasone plus ondansetron 21/103 (20%) with placebo plus ondansetron	P = 0.09	⟷	Not significant
[26] RCT	211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields	**Proportion of people with complete control of nausea** 14/95 (15%) with dexamethasone plus ondansetron 9/96 (9%) with placebo plus ondansetron	P = 0.14	⟷	Not significant

Ability to remove nasogastric tube

No data from the following reference on this outcome. [26]

Quality of life

No data from the following reference on this outcome. [26]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] RCT	211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields	**Sleep quality over the course of 15 fractions of radiotherapy** with dexamethasone plus ondansetron with placebo plus ondansetron Absolute results reported graphically	P <0.002	○○○	placebo
[26] RCT	211 people with cancer receiving radiotherapy of at least 15 fractions to a variety of fields	**Constipation over the course of 15 fractions of radiotherapy** with dexamethasone plus ondansetron with placebo plus ondansetron Absolute results reported graphically	P <0.003	○○○	placebo

Further information on studies

[26] One person taking dexamethasone developed a grade 3 gastric ulcer.

Comment: None.

QUESTION **What are the effects of treatments for nausea and vomiting occurring as a result of either the disease or its treatment in adults with chronic diseases other than cancer?**

OPTION **ANTIHISTAMINES**

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- Despite the lack of robust RCT evidence, there is a consensus based on clinical experience that antihistamines have a place in the management of nausea and vomiting, especially that related to motion sickness, mechanical bowel obstruction, and raised intracranial pressure.

- We found no direct evidence from RCTs on the effects of antihistamines in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Antihistamines:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although antihistamines (cyclizine, prochlorperazine) are used for the control of nausea and vomiting in some clinical situations (e.g., malignant bowel obstruction), there is no evidence from well-conducted trials that they are beneficial. Despite the lack of robust RCT evidence, there is a consensus, based on clinical experience with these drugs, that they have a place in the management of nausea and vomiting, especially that related to motion sickness, mechanical bowel obstruction, and raised intracranial pressure.

OPTION ANTIMUSCARINICS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether antimuscarinics are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of antimuscarinics in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Antimuscarinics:

We found no systematic reviews or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although antimuscarinics, in particular hyoscine, are commonly used for the control of vomiting in people with malignant bowel obstruction, there is no evidence from well-conducted trials that they are beneficial.

OPTION ANTIPSYCHOTICS (ATYPICAL)

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether atypical antipsychotics are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of atypical antipsychotics in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Antipsychotics (atypical):

We found no systematic reviews or RCTs.

Further information on studies

Comment: None.

OPTION BENZODIAZEPINES

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether benzodiazepines are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of benzodiazepines in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Benzodiazepines:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION BUTYROPHENONES

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether butyrophenones are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of butyrophenones in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Butyrophenones:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although haloperidol is almost universally used for nausea, especially where the cause is chemical or metabolic, there is no evidence from well-conducted trials that it is beneficial.

OPTION CANNABINOIDS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether cannabinoids are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of cannabinoids in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Cannabinoids:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION CORTICOSTEROIDS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether corticosteroids are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of corticosteroids in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Corticosteroids:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION 5HT3 ANTAGONISTS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .

- We don't know whether $5HT_3$ antagonists are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of $5HT_3$ antagonists in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

$5HT_3$ antagonists:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION **NK1 ANTAGONISTS**

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether NK1 antagonists are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of NK1 antagonists in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

NK1 antagonists:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION **PHENOTHIAZINES**

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether phenothiazines are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of phenothiazines in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Phenothiazines:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Although phenothiazines (chlorpromazine, levomepromazine, prochlorperazine) are almost universally used for nausea from a variety of causes, there is no evidence from well-conducted trials that they are beneficial. Open label studies of levomepromazine have already been undertaken; further large, blinded RCTs are needed. [17]

OPTION PROKINETICS

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether prokinetics are effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of prokinetics in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Prokinetics:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION VENTING GASTROSTOMY

- For GRADE evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases, see table, p 34 .
- We don't know whether venting gastrostomy is effective for controlling nausea and vomiting in people with chronic conditions other than cancer.
- We found no direct evidence from RCTs on the effects of venting gastrostomy in people with nausea and vomiting caused by either the disease or its treatment in adults with chronic diseases other than cancer.

Benefits and harms

Venting gastrostomy:

We found no systematic review or RCTs.

Further information on studies

Comment: None.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Karnofsky score Is a measure of performance status based on physical ability (scale 0–100). 100: normal, no complaints or evidence of disease; 90: able to perform normal activity, minor signs and symptoms of disease; 80: able to perform normal activity with effort, some signs and symptoms of disease; 70: cares for self, unable to perform normal activity or to do active work; 60: requires occasional assistance but is able to care for most of own needs; 50: requires considerable assistance and frequent medical care; 40: requires special care and assistance, disabled; 30: hospital admission indicated, although death not imminent, severely disabled; 20: hospital admission necessary, active supportive treatment required, very sick; 10: fatal processes progressing rapidly, moribund; 0: death.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

$5HT_3$ antagonists plus corticosteroids in people with radiotherapy-related nausea and vomiting New option for which we identified one large RCT, [26] which found that dexamethasone was more effective than placebo at reducing nausea and vomiting in people receiving $5HT_3$ antagonists to prevent radiotherapy-induced emesis. Combination categorised as Likely to be beneficial.

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GRADE **Evaluation of interventions for Nausea and vomiting in people with cancer and other chronic diseases.**

Important outcomes	Ability to remove nasogastric tube, Adverse effects, Quality of life, Vomiting								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for nausea and vomiting occurring as a result of either the disease or its treatment in adults with cancer?									
41 (7891) [12]	Vomiting	Dexamethasone versus placebo or no treatment in people receiving chemotherapy	4	0	0	–1	+1	High	Effect-size point added for OR >2. Directness point deducted for inclusion of other antiemetics
3 (189) [12]	Vomiting	Dexamethasone versus metoclopramide in people receiving chemotherapy	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for heterogeneity between RCTs. Directness point deducted for inclusion of 5HT3 antagonist in one study
1 (51) [13]	Vomiting	Dexamethasone plus metoclopromide versus metoclopramide alone in people with nausea owing to disease, chemotherapy, or radiotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (51) [13]	Quality of life	Dexamethasone plus metoclopromide versus metoclopramide alone in people with nausea owing to disease, chemotherapy, or radiotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
11 (2119) [14]	Vomiting	Dexamethasone plus $5HT_3$ antagonists versus $5HT_3$ antagonists alone in people receiving chemotherapy	4	0	0	0	1	High	Effect-size point added for OR of 0.42
15 (2634) [14]	Vomiting	$5HT_3$ antagonists versus metoclopramide-based regimens in people receiving chemotherapy	4	0	0	0	0	High	
1 (41) [16]	Vomiting	Metoclopramide versus placebo or versus prochlorperazine (a phenothiazine) in people receiving chemotherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unusually high dose of metoclopramide used in the RCT
4 (231) [20]	Vomiting	Cannabinoids versus placebo in people receiving chemotherapy	4	0	0	0	0	High	
at least 19 (at least 2012) [20]	Adverse effects	Cannabinoids versus placebo in people receiving chemotherapy	4	0	0	–1	0	Moderate	Directness point deducted for inclusion of both placebo and antiemetics in control group in analysis
7 (422) [20]	Vomiting	Cannabinoids versus other antiemetics in people receiving chemotherapy	4	0	0	–1	0	Moderate	Directness point deducted for range of antiemetics included in the comparison
1 (53) [22]	Vomiting	Lorazepam versus placebo in people receiving chemotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

Important outcomes	Ability to remove nasogastric tube, Adverse effects, Quality of life, Vomiting								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (989) [23] [24]	Vomiting	Aprepitant versus placebo in people receiving a standard antiemetic regimen for chemotherapy-related nausea	4	0	0	–1	0	Moderate	Directness point deducted for narrowness of population in RCT
1 (105) [25]	Vomiting	$5HT_3$ antagonists versus metoclopramide in people receiving radiotherapy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (191) [26]	Vomiting	Adding corticosteroids versus adding placebo in people receiving $5HT_3$ antagonists	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.