Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery)

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ABSTRACT

Background

Nausea is a common symptom in advanced cancer, with a prevalence of up to 70%. While nausea and vomiting can be related to cancer treatments, such as chemotherapy, radiotherapy, or surgery, a significant number of people with advanced cancer also suffer from nausea unrelated to such therapies. Nausea and vomiting may also cause psychological distress, and have a negative impact on the quality of life of cancer patients; similarly to pain, nausea is often under-treated. The exact mechanism of action of corticosteroids on nausea is unclear, however, they are used to manage a number of cancer-specific complications, including spinal cord compression, raised intracranial pressure, and lymphangitis carcinomatosis. They are also commonly used in palliative care for a wide variety of non-specific indications, such as pain, nausea, anorexia, fatigue, and low mood. However, there is little objective evidence of their efficacy in symptom control, and corticosteroids have a wide range of adverse effects that are dose and time dependent. In view of their widespread use, it is important to seek evidence of their effects on nausea and vomiting not related to cancer treatment.

Objectives

To assess the effects of corticosteroids on nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in adult cancer patients.

Search methods

We searched CENTRAL, MEDLINE Ovid, Embase Ovid, CINAHL EBSCO, Science Citation Index Web of Science, Latin America and Caribbean Health Sciences (LILACS), Conference Proceedings Citation Index - Science Web of Science, and clinical trial registries, from inception to 23rd August 2016.

Selection criteria

Any double-blind randomised or prospective controlled trial that included adults aged 18 years and over with advanced cancer with nausea and vomiting not related to chemotherapy, radiotherapy, or surgery were eligible for the review, when using corticosteroids as antiemetic treatment.
Data collection and analysis

All review authors independently assessed trial quality and extracted data. We used arithmetic means and standard deviations for each outcome to report the mean difference (MD) with 95% confidence interval (CI). We assessed the quality of the evidence using GRADE and created a 'Summary of findings' table.

Main results

Three studies met the inclusion criteria, enrolling 451 participants. The trial size varied from 51 to 280 participants. Two studies compared dexamethasone to placebo, and the third study compared a number of additional interventions in various combinations, including metoclopramide, chlorpromazine, tropisetron, and dexamethasone. The duration of the studies ranged from seven to 14 days. We included two studies (127 participants) with data at eight days in the meta-analysis for nausea intensity; no data were available that incorporated the same outcome measures for the third study. Corticosteroid therapy with dexamethasone resulted in less nausea (measured on a scale of 0 to 10, with a lower score indicating less nausea) compared to placebo at eight days (MD 0.48 lower nausea, 95% CI 1.53 lower to 0.57 higher; very low-quality evidence), although this result was not statistically significant (P = 0.37). Frequency of adverse events was not significantly different between groups, and the interventions were well tolerated. Factors limiting statistical analysis included the lack of standardised measurements of nausea, and the use of different agents, dosages, and comparisons. Subgroup analysis according to type of cancer was not possible due to insufficient data. The quality of this evidence was downgraded by three levels, from high to very low due to imprecision, likely selection bias, attrition bias, and the small number of participants in the included studies.

Authors' conclusions

There are few studies assessing the effects of corticosteroids on nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in adult cancer patients. This review found very low-quality evidence which neither supported nor refuted corticosteroid use in this setting. Further high quality studies are needed to determine if corticosteroids are efficacious in this setting.

PLAIN LANGUAGE SUMMARY

Corticosteroids for the management of nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in adult cancer patients

Background

Nausea is a common symptom in advanced cancer. While nausea and vomiting can be related to cancer treatments, such as chemotherapy, radiotherapy, or surgery, a significant number of people with advanced cancer also suffer from nausea unrelated to such therapies. Nausea and vomiting may also cause psychological distress, and have a negative impact on the quality of life of cancer patients; it is often under-treated.

Study characteristics

In August 2016, we found three relevant studies with 451 participants. The trial size varied from 51 to 280 participants. The duration of the included studies ranged from seven to 14 days. Two studies compared dexamethasone to placebo. The third study compared a number of additional medicines in various combinations, including metoclopramide, chlorpromazine, tropisetron, and dexamethasone.

Key results and quality of the evidence

The current evidence is based on a small number of studies with a small number of participants. We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low quality evidence means that we are very uncertain about the results. High quality evidence means that we are very confident in the results. We made the following conclusions from the available evidence:

1) we found very low-quality evidence of the effects of steroids on nausea and vomiting in cancer patients;
2) there was no evidence about how steroids work in different types of cancer; and
3) there were few reported side effects, and the drugs were generally well tolerated. More high quality studies are needed to determine if steroids are effective anti-nausea agents.
**Summary of Findings for the Main Comparison**

Dexamethasone compared to placebo for adult patients with advanced cancer who have nausea and vomiting not related to chemotherapy, radiotherapy, or surgery

**Patient or population:** participants with advanced cancer who have nausea and vomiting not related to chemotherapy, radiotherapy, or surgery  
**Settings:** inpatients and outpatients  
**Intervention:** dexamethasone  
**Comparison:** placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk</th>
<th>Corresponding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td><strong>Nausea at 8 days</strong></td>
<td>The mean difference in the intensity of nausea at day 8 in the control groups ranged from -0.45 to 5.7</td>
<td>The mean difference in the intensity of nausea at day 8 in the intervention groups was, on average, -0.48 (from -1.53 lower to 0.57 higher)</td>
</tr>
<tr>
<td><strong>No of Participants</strong></td>
<td>127</td>
<td>(2 studies)</td>
</tr>
<tr>
<td><strong>Quality of the evidence</strong></td>
<td>⚫⚫⚫⚫</td>
<td>very low</td>
</tr>
</tbody>
</table>

**Number of vomiting episodes**  
No data  
No data

**Adverse events**  
No data  
No data

**Quality of life**  
No data  
No data

**Patient satisfaction**  
No data  
No data

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*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: Confidence interval
We downgraded the quality of evidence by three levels due to imprecision, likely selection bias, attrition bias, and the small number of participants in the included studies.
BACKGROUND

Description of the condition

Nausea is a subjective phenomenon of an unpleasant, wavelike sensation experienced in the back of the throat, the epigastrium, or both, which may culminate in vomiting (emesis) (National Cancer Institute 2010). Vomiting is defined as the forceful expulsion of the contents of the stomach, duodenum, or jejunum through the oral cavity. Nausea may be accompanied by autonomic symptoms, such as pallor, cold sweat, salivation, tachycardia, and diarrhoea (Davis 2000). Nausea is a common symptom in advanced cancer, with a prevalence of up to 70% (Davis 2000; Teunissen 2007; Walsh 2000). Nausea can be related to cancer treatments, e.g. chemotherapy, radiotherapy, or both (Feyer 1998; Foubert 2005), or surgery (Gan 2007), but a significant number of people with advanced cancer also suffer from nausea unrelated to such therapies (Fainsinger 1991). Common causes include medications (especially opioids), gastrointestinal complications, or progression of the underlying disease, metabolic abnormalities, brain metastases, or a combination of several of these factors. In addition to the physical effects, nausea and vomiting may cause psychological distress and have a negative impact on the quality of life of cancer patients (Ballatori 2007; Harris 2010; Pirri 2013; Portenoy 1994; Walsh 2000). As with pain, nausea is often under-treated (Reuben 1986). Uncontrolled nausea and vomiting can result in significant loss of appetite and weight (Pirri 2013).

Description of the intervention

Corticosteroids are effective antiemetics in the prevention of acute and delayed nausea and vomiting, induced by moderate to highly emetogenic chemotherapy (Ioannidis 2000). They are effective alone when compared to placebo, but provide even greater benefit when combined with other antiemetics (metoclopramide, serotonin (5HT-3) and neurokinin 1 (NK1) receptor antagonists) (Gralla 1999; Joss 1994; Latreille 1998; Roila 2006). Since 1998, corticosteroids have been included in the antiemetic guidelines for chemotherapy-induced nausea and vomiting of both the American Society of Clinical Oncology (ASCO) (Gralla 1999), and the Multinational Association of Supportive Care in Cancer (MASCC) (Perugia Consensus Conference 1998). The guidelines are based on the identification of the receptors supposedly involved in the generation of nausea, vomiting, or both, induced by chemotherapy and radiotherapy (Harris 2010; Smith 2005). Corticosteroids are also indicated in the prevention of post-operative nausea and vomiting (PONV) (De Oliveira 2013). As an extrapolation of these findings, corticosteroids are also widely used for nausea and vomiting not related to chemotherapy, radiotherapy, or surgery inpatients with cancer. The choice of an antiemetic in palliative care is based on either an empirical or a mechanistic approach (Hardy 2015). Most of the guidelines developed around the mechanistic approach recommend identifying the most likely cause of nausea and the underlying pathways and receptors involved. Clinicians then choose drugs known to inhibit those particular receptors (Glare 2004; Hardy 2015). In the empirical approach, a broad spectrum antiemetic is used, regardless of the presumed cause of nausea.

How the intervention might work

Nausea is promoted through the activation of neurotransmitters in three different centres. While these centres are anatomically clearly distinct in animal models, the pathways in humans are more diffuse and interactive (Hardy 2015). The vomiting centre within the blood-brain barrier receives inputs from the vestibular system, somatic sensation, emotion, and memory. The chemoreceptor trigger zone (CTZ), in the area postrema, lies outside the blood-brain barrier on the floor of the fourth ventricle, and is vulnerable to metabolic and chemical triggers. The solitary tractus nucleus (STN), in the medulla within the dorsal vagal complex, collects emetogenic inputs from the sympathetic and parasympathetic nervous systems. In the gastric tract, there are dopamine receptors that affect gastric motility (Grunberg 2007). Stretch mechanoreceptors also signal distention and organomegaly, through the vagal nerve (Chu 2014; Harris 2010). The exact mechanism of action of corticosteroids on nausea is unclear, but is probably related to their potent anti-inflammatory action, especially in nausea and vomiting related to raised intracranial pressure (Gralla 1999), and bowel obstruction (Laval 2000; Mercadante 2004). Furthermore, glucocorticoids inhibit the expression of serotonin, a potent emetogenic neurotransmitter (Mantovani 1997). Glucocorticoids maintain physiological functions of several organs and systems, particularly under stress, which may also cause nausea and vomiting (Chu 2014). A glucocorticoid deficiency has been shown to induce nausea and vomiting (Hursti 1993).

Why it is important to do this review

Corticosteroids are used to manage a number of cancer-specific complications, e.g. spinal cord compression, raised intracranial pressure, and lymphangitis carcinomatosis. They are also commonly used in palliative care for a wide variety of non-specific indications, such as pain, nausea, anorexia, fatigue, and low mood (Farr 1990; Hardy 2001; Riechelmann 2007). However, there is little objective evidence of their efficacy in symptom control (Haywood 2015). Moreover, corticosteroids are associated with significant side effects, especially in a long-term setting (Hanks 2009). Some authors have suggested greater vigilance in prescribing corticosteroids in the presence of limited clinical benefit (Gannon 2002).
In view of their widespread use, it is important to seek evidence of their effects on nausea and vomiting not related to cancer treatment.

OBJECTIVES

To assess the effects of corticosteroids on nausea and vomiting not related to chemotherapy, radiotherapy, or surgery in adult cancer patients.

METHODS

Criteria for considering studies for this review

Types of studies
Double-blind randomised controlled trials (RCTs). If no randomised trials were found, we had planned to include prospective controlled studies.

Types of participants
Participants with cancer suffering from nausea, vomiting or both not related to chemotherapy, radiotherapy, or surgery, aged 18 years and above.

Types of interventions
Interventions included any corticosteroid at any dose. We considered all routes of drug administration. Comparisons were:
- placebo;
- no intervention;
- other antiemetics;
- usual treatment or supportive care; or
- alternative treatments for nausea and vomiting.

Types of outcome measures

Primary outcomes
Patient-reported nausea intensity and relief using validated scales (visual analogue scales (VAS), numerical rating scales (NRS), verbal rating scales (VRS), or a combination), and the number of vomiting episodes in a predefined time interval.

Secondary outcomes
- Adverse events (e.g. psychiatric events, hyperglycemias or diabetic decompensation, fluid retention, and other);
- Quality of life;
- Patient satisfaction.

Search methods for identification of studies
We attempted to identify as many trials as possible that met the inclusion criteria, without limitation by language, publication type or status, or by date, with our search strategy.

Electronic searches
We searched the following electronic databases:
1. The Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8) in The Cochrane Library (accessed 23 August 2016);
2. MEDLINE Ovid (1966 to 23 August 2016);
3. MEDLINE PubMed in process (23 August 2016);
4. Embase.com (1970 to 23 August 2016);
5. CINAHL Ebsco (1982 to 23 August 2016);
6. Science Citation Index ISI Web of Science (1899 to 23 August 2016);
7. Conference Proceedings Citation Index - Science ISI Web of Science (1990 to 23 August 2016);
8. LILACS (Latin America and Caribbean Health Sciences; 1982 to 23 August 2016).
We used medical subject headings (MeSH) or equivalent and text word terms; searches were tailored to individual databases. The search strategies are shown in Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; and Appendix 7.

Searching other resources
We checked the bibliographic references and cited sources of any relevant identified studies, in order to find additional trials not identified by the electronic searches. We also searched www.clinicaltrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and the Clinical Trials database of the National Cancer Institute at the National Institute of Health (www.cancer.gov/clinicaltrials) to identify any ongoing trials. In order to identify any unpublished or grey literature, we searched the Internet, using the Google Scholar search engine (www.googlescholar.com), with selected terms from the above strategy. If only the abstract was published, we attempted to contact the authors for further details, or the unpublished paper. One of the review authors (KR), who is an Information Specialist, conducted the searches. All searches were current as of 23 August 2016.
Data collection and analysis

Selection of studies
Four of the review authors (JH, PG, PVB, KR) independently assessed the titles and abstracts of all the studies identified by the search, for potential inclusion. Each of these authors independently selected all potentially-relevant studies for inclusion by applying the selection criteria outlined in the 'Criteria for considering studies for this review' section. We then compared these lists, discussed any differences, and either included or excluded the papers based on a majority decision. A PRISMA study flow diagram is included in Figure 1 (Liberati 2009), which documents the screening process, as recommended in Part 2, Section 11.2.1 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Figure 1. PRISMA Study flow diagram

- Records identified through database searching (N = 8260)
- Number of records found by searching other sources (N = 0)
- Total records identified (N = 8260)
- Duplicates removed (N = 2031)
- Records screened (N = 6229)
- Records excluded (N = 6218)
- Full-text articles assessed for eligibility (N = 11)
- Full-text articles excluded, with reasons (N = 6)
- Studies included in qualitative synthesis (N = 3)
- Studies included in quantitative synthesis (meta-analysis; N = 2)
Data extraction and management

Two review authors (AH, SK) independently extracted data from the studies using a standard form, and checked for agreement before entry into Review Manager (RevMan 2014). They extracted data that included information about the year of study, study design, number of participants treated, participant demographic details, type of cancer, drug and dosing regimen, study design (placebo or active control) and methods, study duration and follow-up, outcome measures (measurement of nausea and other relevant outcomes), withdrawals, and adverse events. We resolved potential disagreements by discussion.

Assessment of risk of bias in included studies

Four of the authors (AH, SK, JH, PG) independently assessed the risk of bias of each of the included studies, by using the 'Risk of bias' assessment method outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We resolved potential disagreements by discussion. For each study, we assessed the risk of bias for the following domains:

1. Random sequence generation (checking for selection bias).
   We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); or unclear risk of bias (method used to generate sequence not clearly stated).

2. Allocation concealment (checking for selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); or unclear risk of bias (method not clearly stated).

3. Blinding of participants and personnel (checking for performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded, but did not provide an adequate description of how it was achieved). Studies that were not double-blind were considered to have high risk of bias.

4. Blinding of outcome assessment (checking for detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study stated that outcome assessors were blind to treatment allocation, but lacked a clear statement on how it was achieved). Studies where outcome assessment was not blinded were considered as having a high risk of bias.

5. Incomplete outcome data (checking for attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study); unclear risk of bias (investigators used 'last observation carried forward' analysis); or high risk of bias (investigators used 'complete' analysis).

6. Selective reporting (checking for reporting bias). We assessed whether primary and secondary outcome measures were prespecified, and whether they were consistent with those reported. We assessed the methods as: low risk of bias (study protocol was available and all of the study’s prespecified primary and secondary outcomes that were of interest were reported in the prespecified way, or if the study protocol was not available but it was clear that the published reports included all expected outcomes, including those that were prespecified); high risk of reporting bias (not all of the study’s prespecified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered into a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study).

7. Study size (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 or more participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); or high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

For dichotomous outcomes, we estimated and compared the risk ratio (RR) between groups using 95% confidence intervals (CIs). For continuous outcomes, we measured arithmetic mean and standard deviation (SD) and reported the mean difference (MD) be-
tween groups, with 95% CI. When an outcome was derived with different instruments measuring the same construct, we used standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

We only included studies in which individual participants were randomised. For trials containing multiple arms, we only included pair-wise comparisons of each intervention arm to the control arm.

Dealing with missing data

We ascertained how the investigators analysed the data from withdrawals, where possible. It was not possible to assess the impact of missing data in sensitivity analyses due to the low study numbers. In all cases, we aimed to perform intention-to-treat analyses. Where there were substantial numbers (more than 10%) of participants missing from analyses, we had planned to perform sensitivity analyses of best- and worst-case scenarios (Higgins 2011).

Assessment of heterogeneity

There may be an effect of differences between participants, environment (inpatient versus outpatient), and outcome measures. We assessed heterogeneity by using the $I^2$ statistic. We considered $I^2$ values above 50% to represent substantial heterogeneity, in line with Higgins 2011, and assessed the potential sources of heterogeneity through subgroup analyses.

Assessment of reporting biases

We had planned to interpret the results in light of a visual inspection of a funnel plot but were unable to due to the lack of studies.

Data synthesis

We entered the data extracted from the included studies into Review Manager 5 (RevMan 2014), which we used for data synthesis. Where appropriate, we pooled data for each continuous outcome, and calculated the MD as an estimate of effect size, using a random-effects model with 95% CIs.

Quality of the evidence and 'Summary of findings' table

Two review authors (AH, SK) independently rated the quality of the evidence for nausea, number of vomiting episodes, adverse events, quality of life, and patient satisfaction. We used the GRADE system to assess the quality of the evidence using GRADEpro GDT software (GRADEpro GDT 2014), and the guidelines provided in Chapter 12.2 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We presented the findings in a 'Summary of findings’ table, which is a transparent and simple tabular format. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system defines the quality of a body of evidence as the extent to which one can be confident of an estimate of effect:

- High: we are very confident that the true effect lies close to that of the estimate of the effect;
- Moderate: we are confident that the true effect lies close to that of the estimate of the effect;
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect.

We decreased the quality for:

- Serious (-1) or very serious (-2) limitations to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

Subgroup analysis and investigation of heterogeneity

There were not sufficient data to perform subgroup analyses based on type of corticosteroid, dose, type of cancer, and length of the trial.

Sensitivity analysis

We had planned to examine the robustness of the meta-analyses by conducting sensitivity analyses using different components of the 'Risk of bias' assessment, particularly those relating to selection bias, and trial size, to see if any of these factors influenced the results. We had also planned to investigate variation across studies (heterogeneity) by comparing a random-effects model with a fixed-effect model. We were unable to perform any sensitivity analyses due to the low number of studies included in the meta-analysis and the small number of participants in each comparison.

Results

Description of studies

See: 'Characteristics of included studies’ and 'Characteristics of excluded studies’ tables.
Results of the search

The PRISMA diagram (Figure 1) outlines the number of records identified in the search and the screening process for these papers. In the initial database search, we identified 8260 records; none were identified through other sources. Of these, 2031 were duplicates, and we rejected 6218 based on information given in the title and abstract. We identified 11 publications for full-text retrieval. We excluded eight of these studies during screening. The reasons for exclusion of each study are described in the 'Characteristics of excluded studies' table. Three studies met the inclusion criteria for this review. These included two placebo-controlled studies, and one parallel-arm trial where participants were randomised to seven groups. We evaluated the results of two trials relative to nausea intensity at eight days, since this was the only time that could be standardised across all trials (Bruera 2004; Yennurajalingam 2013). The third trial could not be included in the meta-analysis because nausea was measured incompletely (i.e. only the duration of nausea was evaluated and not the intensity).

Included studies

We identified three studies meeting inclusion criteria (Bruera 2004; Mystakidou 1998; Yennurajalingam 2013). These three studies enrolled 451 participants. The trial size varied from 51 to 280 participants. Two studies compared dexamethasone to placebo, and the third study compared a number of additional interventions in various combinations, including metoclopramide, chlorpromazine, tropisetron, and dexamethasone. The duration of the studies ranged from seven to 14 days. A detailed description of the included studies can be found in the 'Characteristics of included studies' table.

Primary disease sites

We have shown the primary disease sites in Table 1. Eligibility criteria in the included trials did not specify a particular cancer.

Types of studies

We included studies in which steroids were used as part of a treatment regimen; nausea and vomiting was assessed as an outcome.

Nausea and vomiting as a primary endpoint

Of the three included studies, only one study measured nausea and vomiting as a primary outcome (Mystakidou 1998). One study measured appetite, nausea, fatigue, and pain as primary endpoints (Bruera 2004), and the third study measured fatigue (a change in the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale) as the primary outcome (Yennurajalingam 2013).

Types of corticosteroids studied

Dexamethasone was used in all studies. One study had all participants on metoclopramide (60 mg/day), and compared dexamethasone (20 mg/day) to placebo (Bruera 2004). The second study compared dexamethasone (8 mg/day) to placebo (Yennurajalingam 2013). The third study also investigated metoclopramide, chlorpromazine, and tropisetron (Mystakidou 1998). All interventions were administered orally.

Nausea and vomiting measurement tools

Different measurement tools were used to measure nausea and vomiting.

- Numerical rating scale (NRS) 0 to 10 (Bruera 2004)
- Categorical scale 1 to 4 (Bruera 2004; Mystakidou 1998)
- Number of vomiting episodes per 24 hours (Bruera 2004)
- Vomiting control per 24 hours on a categorical scale of 1 to 4 (Mystakidou 1998)
- Functional Assessment of Cancer Therapy (FACT) instrument (Bruera 2004)
- Edmonton Symptom Assessment Scale (ESAS) (Yennurajalingam 2013)
- Functional Assessment of Cancer Therapy-Anorexia-Cachexia (FAACT) (Yennurajalingam 2013)

Excluded studies

We excluded eight studies. We have provided reasons for exclusion in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

We assessed each study using the Cochrane 'Risk of bias' tool. We have presented overall findings in the 'Risk of bias' graph (Figure 2), which presents the authors’ judgements about each risk of bias domain as percentages across all included studies. We have shown the authors’ judgements about each risk of bias domain for each included study in the 'Risk of bias' summary (Figure 3).
Figure 2. Risk of bias graph: review authors’ judgements about each ‘Risk of bias’ domain, presented as percentages across all included studies.
Figure 3. Risk of bias summary: review authors’ judgements about each ‘Risk of bias’ domain for each included study.
Allocation
All three included studies reported that they were randomised, however none of them properly described the method used to generate the random sequence. Therefore, we judged the studies to have an unclear risk of bias. For allocation concealment, one study used pharmacy randomisation, and therefore, was judged low risk for allocation concealment (Bruera 2004), however, the remaining two studies were of unclear risk, since not enough information was provided on the method of allocation concealment.

Blinding
Two studies were at low risk, with blinding of participants and personnel reported. In one study, blinding was not possible, since participants received different amounts of medication in each of the study arms, so we assessed it as having high risk for performance bias (Mystakidou 1998). The outcome assessment was reported to be blinded in two studies and these studies were judged as having low risk for detection bias. The outcome assessment was not blind in one study because physicians were provided with the participant’s assigned treatment, and there was no placebo given (Mystakidou 1998).

Incomplete outcome data
Two studies were judged as low risk of bias for attrition, with a low number of participants withdrawing from the study, and similar numbers across the intervention and control groups. One study was judged as high risk of bias, since a high number of participants receiving the intervention (19 of 62 participants) and control (17 of 58) could not be evaluated, thereby, leaving a gap in the evidence (Yennurajalingam 2013).

Selective reporting
No reporting gaps were identified in any of the studies. Therefore, we judged these studies to be at low risk for reporting bias.

Other potential sources of bias
Small studies are thought to be at increased risk of bias as they are unlikely to be adequately powered. No studies were large enough to be at low risk of bias (more than 200 participants per arm). We judged one study to have an unclear risk of bias due to sample size (50 to 199 participants per arm; Yennurajalingam 2013). We judged the remaining two studies to have a high risk of bias because of their small number of participants (less than 50 participants per treatment arm).

Effects of interventions
See: Summary of findings for the main comparison
Dexamethasone compared to placebo for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery)
See: Summary of findings for the main comparison.

Primary outcome
We judged the quality of evidence for the primary outcome of nausea intensity to be very low. We downgraded the quality of evidence by three levels due to imprecision, likely selection bias, attrition bias, and the small number of participants in the included studies.

Patient-reported nausea intensity and relief using validated scales
For the meta-analysis, two studies that provided mean nausea intensity (on a numerical rating scale from 0 to 10) and the standard deviation at eight days were included (Bruera 2004; Yennurajalingam 2013). A total of 183 participants at baseline and 127 participants after eight days of corticosteroid (dexamethasone) were involved in these two studies. After eight days, the dexamethasone group reported less nausea intensity than the control group (mean difference (MD) -0.48, 95% confidence interval (CI) -1.53 to 0.57; P = 0.37; Analysis 1.1; Figure 4), although this result was not statistically significant. No data were reported for nausea relief.

Figure 4. Forest plot of comparison: 1 Nausea, outcome: 1.1 Nausea at 8 days.
The other study could not be included in the meta-analysis because nausea was measured incompletely, and on a categorical scale; data were reported for change in nausea intensity from baseline to day eight (Mystakidou 1998).

**Number of vomiting episodes in a predefined time interval**

Only one study reported on the number of vomiting episodes in the preceding 24 hours (Bruera 2004). The median number of daily vomiting episodes was two at baseline, compared to zero at days three and eight in both the dexamethasone and placebo groups. Yennurajalingam 2013 did not report on vomiting, and Mystakidou 1998 measured vomiting control on a categorical scale, classified as total (no vomiting), major (one event/day), minor (two events/day), or no control (≥ three events/day).

**Secondary outcomes**

In all studies, the frequency of adverse events was not significantly different between groups, and the interventions were generally well tolerated. Two of the studies reported on quality of life (Bruera 2004; Yennurajalingam 2013). In Yennurajalingam 2013, mean improvement in FACT-F total quality of life scores was significantly better for participants receiving dexamethasone compared to placebo at day 15 (P = 0.03), with FACT physical well-being scores showing significantly better improvement at days eight (P = 0.007) and 15 (P = 0.002) in the dexamethasone group than in the control group. In Bruera 2004, there was a significant improvement by day eight in the physical well-being domain of the FACT quality of life score in both the dexamethasone and placebo groups, with no significant difference between groups in the level of improvement in the social and family, emotional, and functional well-being domains by day eight when compared to baseline. Patient satisfaction data were not available.

**DISCUSSION**

**Summary of main results**

The objective of this systematic review was to assess the effects of corticosteroids on nausea and vomiting in adult patients with advanced cancer. Three studies with 451 participants met the inclusion criteria. Included studies assessed dexamethasone (4 mg/day or 20 mg/day) compared to placebo, or a combination of interventions including chlorpromazine (25 mg/day or 50 mg/day), dexamethasone (2 mg/day), metoclopramide (20 mg/day or 40 mg/day), and tropisetron (5 mg/day). All interventions were administered per oral route.

Only two studies could be evaluated for nausea intensity in the meta-analysis. Data were reported after eight days of intervention, since this was the only time that could be standardised across all trials. The following conclusion regarding the effectiveness of corticosteroids for relief of nausea and vomiting not related to chemotherapy or radiotherapy or surgery in cancer patients should be interpreted with consideration of the small number of eligible studies with small numbers of participants in each treatment arm, and difference in comparators in the meta-analysis comparing dexamethasone to placebo or ‘standard care’ with metoclopramide. The quality of one of the three studies was generally poor with a high risk of bias identified.

- There was very low-quality evidence to suggest a benefit in favour of dexamethasone over placebo (mean difference (MD) -0.48, 95% confidence interval (CI) -1.53 to 0.57) for nausea for up to eight days of intervention. However, the result was not statistically significant (P = 0.37).
- There were insufficient data to evaluate different subgroups such as drug type, route of administration, dosage, and different primary disease types.

Further trials with increased numbers of participants are needed to evaluate the effectiveness of corticosteroids for the management of nausea and vomiting (not related to chemotherapy or radiotherapy or surgery) in adult patients with advanced cancer. Comparators should include placebo versus combinations of dexamethasone with other antiemetic agents acting at the different sites of action involved in emesis, since the mechanism of nausea is not well understood and involves multiple sites of action in the body.

**Overall completeness and applicability of evidence**

We identified three studies that met the inclusion criteria, but included only two studies in the meta-analysis for nausea intensity, with insufficient data available for the remaining study. There was a lack of studies for planned comparisons. There were insufficient data for subgroup analyses.

The results were also influenced by differences in dosages, comparators, and heterogeneity of study populations. Comparators included in the meta-analysis included dexamethasone compared to placebo. We also included trials where nausea was not the primary outcome.

**Quality of the evidence**

The quality of evidence was very low, downgraded by three levels due to imprecision, likely selection bias, attrition bias, and...
the small number of participants in the included studies. The primary outcome of nausea was incompletely measured in one study (Mystakidou 1998). The number of vomiting episodes in a predefined time interval was only available for the study by Bruera 2004. Yennurajalingam 2013 did not report on vomiting and Mystakidou 1998 measured vomiting control on a categorical scale of four categories. Therefore, the current body of evidence identified does not allow a robust conclusion. 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.

Potential biases in the review process
To minimise bias, four authors independently extracted data and assessed risk of bias. We were unable to create a funnel plot due to the lack of studies, so were unable to determine if there was evidence of small study effects.

AUTHORS’ CONCLUSIONS

Implications for practice

For people with nausea and vomiting
There is insufficient evidence to support or refute the suggestion that corticosteroids have any efficacy in nausea and vomiting.

For clinicians
There is insufficient evidence to support or refute the suggestion that corticosteroids have any efficacy in nausea and vomiting. This is particularly relevant when considering the toxicity of corticosteroids, especially following prolonged use.

For policy makers
There is insufficient evidence to support or refute the suggestion that corticosteroids have any efficacy in nausea and vomiting. In the absence of any supporting evidence, it should probably not be recommended, except at the discretion of a palliative care specialist with particular expertise in corticosteroid use.

For funders
There is insufficient evidence to support or refute the suggestion that corticosteroids have any efficacy in patients with advanced cancer suffering from nausea and vomiting not related to chemotherapy, radiotherapy and surgery.

Implications for research

General implications
This review has revealed a general lack of research in the subject area. Future robust, randomised trials with significant numbers of participants (e.g. over 200 per treatment arm) are needed to evaluate the safety and effectiveness of corticosteroids in the management of nausea and vomiting in adult patients with advanced cancer.

Design
There are a large number of RCTs assessing the benefit of antiemetics (including steroids) in chemotherapy-induced nausea and vomiting (CINV), especially in the acute phase following treatment, and well-established methodology. There are fewer high quality trials for delayed CINV. The emphasis in many of these studies has been in the control of vomiting. There is a need for further research into the benefit of corticosteroids for both delayed CINV and non-CINV with greater emphasis on the control of nausea.

Measurement (endpoints)
There is currently no standard outcome measure for the control of nausea. This must be determined prior to any future studies.

ACKNOWLEDGEMENTS

Cochrane Review Group funding acknowledgement: this project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.
Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery) (Review)

References to studies included in this review

Bruera 2004   [published data only]

Mystakidou 1998   [published data only]

Yennurajalingam 2013   [published data only]

References to studies excluded from this review

Arvieux 2005   [published data only]

Bruera 1996   [published data only]

Currow 2012   [published data only]

Currow 2015   [published data only]

Feuer 2000   [published data only]
Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database of Systematic Reviews* 2000, Issue 2. DOI: 10.1002/14651858.CD001219

Klein 2012   [published data only]

Laval 2006   [published data only]

Yennurajalingam 2012   [published data only]

Additional references

Ballatori 2007

Chu 2014

Davis 2000

De Oliveira 2013

Fainsinger 1991

Farr 1990

Feyer 1998

Foumbert 2005
Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery) (Review)

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Gan 2007
Gan TJ. Mechanisms underlying postoperative nausea and vomiting and neurotransmitter receptor antagonist-based pharmacotherapy. *CNS Drugs* 2001;21(10):813–33.

Gannon 2002

Glare 2004

GRADEpro GDT 2014 [Computer program]

Gralla 1999

Grunberg 2007

Hanks 2009

Hardy 2001

Hardy 2015

Harris 2010
Harris DG. Nausea and vomiting in advanced cancer. *British Medical Bulletin* 2010;96:175–85.

Haywood 2015

Higgins 2011

Hursti 1993

Ioannidis 2000

Joss 1994

Latreille 1998

Laval 2000

Liberati 2009

Mantovani 1997

Mercadante 2004

National Cancer Institute 2010
Perugia Consensus Conference 1998

Pirri 2013

Portenoy 1994

Reuben 1986

RevMan 2014 [Computer program]

Riegelmann 2007

Roila 2006

Smith 2005

Teunissen 2007

Walsh 2000

* Indicates the major publication for the study
Characteristics of included studies  [ordered by study ID]

Bruera 2004

| Methods | Randomised, double-blind, parallel-arm trial  
Five international centres  
Study duration: seven days |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Fifty-one participants (25 intervention, 26 control) with advanced cancer and chronic nausea (&gt; two weeks) resulting from advanced cancer, despite treatment with metoclopramide at a minimal daily dose of 40 to 60 mg for two days</td>
</tr>
<tr>
<td>Interventions</td>
<td>Participants randomised into two groups to receive dexamethasone (20 mg/day) + metoclopramide (60 mg/day), or placebo + metoclopramide (60 mg/day). All interventions administered per oral route</td>
</tr>
</tbody>
</table>
| Outcomes | Appetite, nausea, fatigue, and pain, measured on both a 0 to 10 numerical rating scale (NRS; 0 = symptom absent, 10 = worst possible symptom) and a categorical scale of four categories for appetite, nausea, and fatigue (1 = best appetite or no nausea or fatigue, 4 = worst). The number of vomiting episodes in the preceding 24 hours was recorded. Wellbeing was estimated on a 0 to 10 numerical scale (0 = best possible well-being, 10 = worst possible well-being). Quality of life (physical, social and family, emotional, and functional well-being) measured by the Functional Assessment of Cancer Therapy (FACT) instrument  
Toxicity assessment: presence or absence of ankle oedema, insomnia, restlessness, or other symptoms (patient-rated) |
| Notes | Dexamethasone was not significantly better than placebo in the management of chronic nausea, appetite, or fatigue. Dexamethasone did improve appetite sooner (day 3), however, no significant difference in improvement in appetite by day eight compared to placebo. No significant difference between the dexamethasone and placebo groups for wellbeing, quality of life, medium number of daily vomiting episodes, or adverse effects. Study funded by The Brown Foundation, Houston, Texas. Author FS was supported by a grant from Swiss Cancer Research |

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not specified</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Pharmacy-controlled randomisation</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Double-blind</td>
</tr>
</tbody>
</table>

Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery) (Review)  
Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Blinding of outcome assessment (detection bias)
All outcomes | Low risk | Double-blind, capsules containing either drug or placebo were identical in appearance

Incomplete outcome data (attrition bias)
All outcomes | Low risk | Three of 25 participants receiving dexamethasone dropped out, compared to five of 26 participants receiving placebo

Selective reporting (reporting bias)
Low risk | None detected

Other bias | High risk | Sample size: 51 participants; < 50 participants per treatment arm

**Mystakidou 1998**

**Methods**
Randomised, parallel-arm trial
Single-institution
Study duration: 14 days

**Participants**
Two hundred and eighty participants (40 metoclopramide + dexamethasone, 40 metoclopramide + tropisetron, 40 metoclopramide + tropisetron + dexamethasone) with advanced cancer who, though well controlled on antiemetic medication (metoclopramide 10 mg twice daily), suddenly presented with nausea and vomiting (≥ three vomiting or retching events/day)

**Interventions**
Participants randomised into seven groups to receive either: (i) metoclopramide (40 mg/day) + dexamethasone (2 mg/day), (ii) tropisetron (5 mg/day), (iii) tropisetron (5 mg/day) + metoclopramide (20 mg/day), (iv) tropisetron (5 mg/day) + metoclopramide (20 mg/day) + dexamethasone (2 mg/day), (v) chlorpromazine (50 mg/day) + dexamethasone (2 mg/day), (vi) tropisetron (5 mg/day) + chlorpromazine (25 mg/day), or (vii) tropisetron (5 mg/day) + chlorpromazine (25 mg/day) + dexamethasone (2 mg/day) for 14 days. All interventions administered per oral route

**Outcomes**
Nausea and vomiting measured on patient diary cards at 24 hours, days three, seven, and 15. Outcomes measured on a categorical scale of four categories. Nausea control was classified as total (no nausea), major (< 4 hrs), minor (> 4 hrs to < 8 hrs), or no control (> 8 hrs). Vomiting control was classified as total (no vomiting), major (one event), minor (two events), or no control (≥ three events)

Tolerability assessment: occurrence of adverse reactions (constipation, dizziness, weakness, extrapyramidal symptoms or other upsetting symptoms) (patient-recorded)

**Notes**
Only duration of nausea evaluated, not intensity. All antiemetic drugs well tolerated with no significant difference between intervention groups. Study was supported by Santoz Pharma Ltd, Athens, Greece

**Risk of bias**
### Mystakidou 1998
(Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not specified</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method of concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>High risk</td>
<td>Participants received different amounts of medication, therefore blinding not possible</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) All outcomes</td>
<td>High risk</td>
<td>Quote: “…lack of blinded experimentation” and nausea was measured incompletely</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Participants withdrawing from the study due to minor emesis control was low, with similar numbers across the intervention groups</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>None detected</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Sample size: 280 participants; &lt; 50 participants per treatment arm</td>
</tr>
</tbody>
</table>

### Yennurajalingam 2013

**Methods**
Randomised, double-blind, placebo-controlled
Three study centres
Study duration: 14 days

**Participants**
One hundred and twenty participants (62 intervention, 58 control) with advanced cancer who had ≥ three cancer-related fatigue symptoms (fatigue, pain, nausea, loss of appetite, depression, anxiety, or sleep disturbance), ≥ 4 of 10 on the Edmonton Symptom Assessment Scale (ESAS)

**Interventions**
Participants randomised into two groups to receive dexamethasone 4 mg or placebo orally twice per day for 14 days

**Outcomes**
The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) subscale, ESAS, Hospital Anxiety and Depression Scale (HADS), and Functional Assessment of Cancer Therapy-Anorexia-Cachexia (FAACT) instruments were used. Participants were monitored for adverse events, and a research nurse supervised their completion of the rating scales

**Notes**
Primary endpoint was fatigue (change in the FACIT-F subscale from baseline to day 15). Secondary outcomes included anorexia, anxiety, depression, and symptom distress
Yennurajalingam 2013  *(Continued)*

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
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<td></td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Randomisation method not specified</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Method of concealment not described</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Double-blind</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>All members of the research team except the investigational pharmacist and statistician were blinded to treatment assignment throughout the study</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Nineteen of 62 participants receiving dexamethasone were not evaluable Seventeen of 58 participants receiving placebo were not evaluable</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>None detected</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Sample size: 120 participants; 50 to 199 participants per treatment arm</td>
</tr>
</tbody>
</table>

Characteristics of excluded studies  *ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arvieux 2005</td>
<td>Wrong study design and symptoms measured did not include nausea</td>
</tr>
<tr>
<td>Bruera 1996</td>
<td>Wrong study design</td>
</tr>
<tr>
<td>Currow 2012</td>
<td>Wrong study design - dexamethasone was used in both arms</td>
</tr>
<tr>
<td>Currow 2015</td>
<td>Wrong study design - dexamethasone was used in both arms</td>
</tr>
<tr>
<td>Feuer 2000</td>
<td>Wrong outcomes - did not measure nausea</td>
</tr>
</tbody>
</table>
Klein 2012 | Wrong study design
---|---
Laval 2006 | Wrong study design
Yennurajalingam 2012 | Wrong outcomes - nausea not reported as part of symptom distress
DATA AND ANALYSES

Comparison 1. Nausea

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Nausea at 8 days</td>
<td>2</td>
<td>127</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>-0.48 [-1.53, 0.57]</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison 1 Nausea, Outcome 1 Nausea at 8 days.

Review: Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery)

Comparison: 1 Nausea

Outcome: 1 Nausea at 8 days

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
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</thead>
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<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Yennurajalingam 2013</td>
<td>43</td>
<td>-1.18 (2.91)</td>
<td>41</td>
<td>-0.45 (2.81)</td>
<td>73.4%</td>
</tr>
<tr>
<td>Bruera 2004</td>
<td>22</td>
<td>5.9 (3.6)</td>
<td>21</td>
<td>5.7 (3.2)</td>
<td>26.6%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>65</td>
<td></td>
<td>62</td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.59$, df = 1 ($P = 0.44$); $I^2 = 0.0$

Test for overall effect: $Z = 0.90$ ($P = 0.37$)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Primary sites of disease

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Head, and neck</th>
<th>Gastrointestinal</th>
<th>Gynaecological</th>
<th>Genitourinary</th>
<th>Sarcoma</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruera 2004</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
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</tbody>
</table>
Table 1. Primary sites of disease  (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Lungs</th>
<th>Bronchi</th>
<th>Pleura</th>
<th>Pericardium</th>
<th>Mediastinum</th>
<th>Abdominal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mystakidou 1998</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yennurajalingam 2013</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

**APPENDICES**

**Appendix 1. CENTRAL search strategy**

#1 (corticosteroid* OR glucocorticoid* OR corticoid* OR betamethasone OR fludrocortisone OR cortisone OR deflazacort OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR triamcinolone):TI,AB,KY
#2 (adrenal cortex hormones):MH 1534
#3 #1 OR #2
#4 (nause* OR vomit* OR emesis ):TI,AB,KY
#5 anti*eme*:TI,AB,KY
#6 MESH DESCRIPTOR Vomiting, Anticipatory
#7 MESH DESCRIPTOR Vomiting
#8 MESH DESCRIPTOR Nausea
#10 MESH DESCRIPTOR neoplasms EXPLODE ALL TREES
#11 (malignant* OR malignancy OR tumor* OR tumour* OR cancer* OR carcinoma* OR sarcoma* OR melanoma* OR glioma* OR glioblastoma* OR medulloblastoma*):TI,AB,KY
#12 #10 OR #11
#13 #3 AND #9 AND #12

**Appendix 2. MEDLINE Ovid search strategy**

1 exp Adrenal Cortex Hormones/
2 (corticoid* or corticosteroid* or glucocorticoid*).tw.
3 (adrenal adj2 hormone*).tw.
4 Betamethasone/
5 betamethasone.tw.
6 Fludrocortisone/
7 fludrocortisone.tw.
8 Cortisone/
9 cortisone.tw.
10 deflazacort.tw.
11 Dexamethasone/
12 dexamethasone.tw.
13 Hydrocortisone/
14 hydrocortisone.tw.
15 Methylprednisolone/
16 methylprednisolone.tw.
Appendix 3. MEDLINE PubMed in Process search strategy

Search (nause* OR vomit* OR emesis) AND (betamethasone OR fludrocortisone OR cortison* OR corticosteroid* OR methylpred* OR dexamethasone OR prednisone OR prednisolone OR hydrocortisone) AND (neoplas* OR tumour* OR tumor OR tumors OR cancer OR malignan* OR oncol* OR carcinoma*)
Appendix 4. Embase Ovid search strategy

#35 #5 AND #23 AND #26 AND #34
#34 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #14 OR #16
#26 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (doubl* NEAR/1 blind*):de,ab,ti OR (singl* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#23 #17 OR #19
#19 cancer*:ab,ti OR malignan*:ab,ti OR tumo*r*:ab,ti OR carcinoma*:ab,ti OR adenocarcinoma*:ab,ti OR melanoma*:ab,ti OR glioma*:ab,ti OR glioblastoma*:ab,ti OR medulloblastoma*:ab,ti OR sarcoma*:ab,ti
#17 'neoplasm'/exp
#16 'antiemetic agent'/de
#14 nause*:ab,ti OR vomit*:ab,ti OR anti*eme*:ab,ti OR emesis:ab,ti
#11 'vomiting'/exp
#10 'serotonin syndrome'/de
#9 'opioid induced emesis'/de
#8 'nausea'/de
#7 'anticipatory nausea and vomiting'/de
#6 'nausea and vomiting'/de
#5 #1 OR #3
#3 corticoid*:ab,ti OR corticosteroid*:ab,ti OR glucocorticoid*:ab,ti OR betamethasone:ab,ti OR fludrocortisone:ab,ti OR cortisol:ab,ti OR deflazacort:ab,ti OR dexamethasone:ab,ti OR hydrocortisone:ab,ti OR methylprednisolone:ab,ti OR prednisolone:ab,ti OR triamcinolone:ab,ti
#1 'corticosteroid'/exp

Appendix 5. CINAHL EBSCO search strategy

S49 S36 AND S48
S48 S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S46 OR S47
S47 TX allocat* random*
S46 (MH "Quantitative Studies")
S45 (MH "Placebos")
S44 TX placebo*
S43 TX random* allocat*
S42 (MH "Random Assignment")
S41 TX random* control* trial*
S40 TX (singl* OR doubl* OR tripl* OR trebl*) N1 (blind* OR mask*)
S39 TX clinic* n1 trial*
S38 PT Clinical Trial
S37 (MH "Clinical Trials+")
S36 S15 AND S23 AND S35
S35 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
S34 TX medulloblastoma
S33 TX glioblastoma
S32 TX glioma*
S31 TX melanoma*
S30 TX sarcoma*
S29 TX adenocarcinoma*
S28 TX carcinoma*
S27 TX tumo*r*
S26 TX malignant*
S25 TX cancer*
S24 (MH "Neoplasms+")
Appendix 6. Web of Science search strategy (Science Citation Index AND Conference Proceedings Citation Index - Science)

TOPIC: (corticosteroid* OR betamethasone OR fludrocortisone OR corticoid* OR glucocorticoid* OR cortisone OR deflazacort OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR triamcinolone) AND

TOPIC: (nause* OR vomit* OR emesis OR emet* OR anti*emetic)

TOPIC: (cancer* OR neoplas* OR carcinoma* OR tumour* OR tumor* OR adenocarcinoma* OR malignan* OR sarcoma* OR melanoma* OR glioma* OR glioblastoma* OR medulloblastoma*) AND

TOPIC: (clinical* OR trial* OR random* OR mask* OR blind* OR allocate* OR assign* OR cross*over* OR control* OR single* OR double* OR treble* OR triple*)

Appendix 7. LILACS search strategy

tw:(betamethasone OR cortisone OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone)) AND (tw: (cancer* OR malignan* OR tumour* OR tumor* OR adenocarcinoma* OR carcinoma*)) AND (tw:(nause* OR vomit* OR emesis OR anti*emetic)
WHAT'S NEW

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 February 2019</td>
<td>Review declared as stable</td>
<td>See Published notes.</td>
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CONTRIBUTIONS OF AUTHORS

All authors initiated and designed the study and drafted the protocol. KR developed the search strategy in collaboration with the Cochrane PaPaS Group. PVB, JH, PG, and KR assessed the titles and abstracts of the studies identified by the search for potential inclusion. AH, SK, JH, and PG extracted the data and conducted the 'Risk of bias' assessment. AH and SK conducted the statistical analyses and GRADE assessment. JH and PG commented on and revised the review, checked the data extraction, and arbitrated in the event of disagreement between other authors.

DECLARATIONS OF INTEREST

JH: none known; JH is a specialist palliative medicine physician and manages patients with nausea and vomiting due to advanced cancer. JH has authored a book "Opioids in cancer pain".

PVB: none known; PVB is a specialist palliative medicine physician and manages patients with nausea and vomiting due to advanced cancer.

PG: none known; PG is a specialist palliative medicine physician and manages patients with nausea and vomiting due to advanced cancer.

AH: none known.

SK: none known.


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Internal sources

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External sources

- Travel fellowship for Petra Vayne-Bossert, Switzerland. Sponsored by the University Hospital of Geneva

Differences between protocol and review

We expanded the description of our approach to GRADE and moved it to the data synthesis section in line with current PaPaS guidance. Blinding of participants and personnel and selective reporting have been added to the assessment of risk of bias in included studies. Four of the review authors (JH, PG, PVB, KR) independently assessed the titles and abstracts due to the large number of results obtained in the literature search.

Notes

An updated search in January 2019 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. The review will be re-assessed for updating in 2020. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

Index terms

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects; “therapeutic use”]; Chlorpromazine [adverse effects; therapeutic use]; Dexamethasone [adverse effects; therapeutic use]; Indoles [adverse effects; therapeutic use]; Metoclopramide [adverse effects; therapeutic use]; Nausea [*drug therapy; etiology]; Neoplasms [*complications]; Time Factors; Tropisetron; Vomiting [*drug therapy; etiology]

MeSH check words

Adult; Humans