Corticosteroids for the management of cancer-related pain in adults (Review)

Haywood A, Good P, Khan S, Leupp A, Jenkins-Marsh S, Rickett K, Hardy JR

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[Intervention Review]

Corticosteroids for the management of cancer-related pain in adults

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ABSTRACT

Background

One of the most feared symptoms associated with cancer is pain. Opioids remain the mainstay of pain treatment but corticosteroids are often used concurrently as co- or adjuvant analgesics. Due to their anti-inflammatory mechanism of action, corticosteroids are said to provide effective analgesia for pain associated with inflammation and in the management of cancer-related complications such as brain metastasis and spinal cord compression. However, corticosteroids have a wide range of adverse effects that are dose and time dependent.

Objectives

To evaluate the efficacy of corticosteroids in treating cancer-related pain in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 4), MEDLINE (OVID) (1966 to 29 September 2014), EMBASE (OVID) (1970 to 29 September 2014), CINAHL (1982 to 29 September 2014), Science Citation Index (Web of Science) (1899 to 29 September 2014) and Conference Proceedings Citation Index - Science (Web of Science) (1990 to 29 September 2014).

Selection criteria

Any randomised or prospective controlled trial that included patients over 18 years with cancer-related pain were eligible for the review. Corticosteroids were compared to placebo or usual treatment and/or supportive care.

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).

Main results

Fifteen studies met the inclusion criteria, enrolling 1926 participants. The trial size varied from 20 to 598 patients. Most studies compared corticosteroids, particularly dexamethasone, to standard therapy. We included six studies with data at one week in the meta-analysis for pain intensity; no data were available at that time point for the remaining studies. Corticosteroid therapy resulted in less pain (measured on a scale of 0 to 10 with a lower score indicating less pain) compared to control at one week (MD 0.84 lower pain, 95% CI 1.38 to 0.30 lower; low quality evidence). Adverse events were poorly documented. Factors limiting statistical analysis included the lack of standardised measurements of pain and the use of different agents, dosages, comparisons and routes of drug delivery. Subgroup analysis according to type of cancer was not possible. The quality of this evidence was limited by the risk of bias of the studies and small sample size. The results were also compromised by attrition, with data missing for the enrolled patients.

Authors' conclusions

The evidence for the efficacy of corticosteroids for pain control in cancer patients is weak. Significant pain relief was noted in some studies, albeit only for a short period of time. This could be important for patients with poor clinical status. Further trials, with increased numbers of participants, are needed to evaluate the safety and effectiveness of corticosteroids for the management cancer pain in adults, and to establish an ideal dose, duration of therapy and route of administration.

PLAIN LANGUAGE SUMMARY

Corticosteroids for the management of cancer pain in adults

Background: One of the most feared symptoms associated with cancer is pain. Opioids remain the mainstay of pain treatment but corticosteroids are often used at the same time, along with standard pain relievers. This review evaluates the clinical trial evidence up to 29 September 2014 to determine how effective corticosteroids are in treating cancer-related pain in adults and how well tolerated this treatment is for these patients.

Study characteristics: We found 15 relevant studies with 1926 participants. The trial size varied from 20 to 598 patients and the duration of the included studies ranged from seven days to 42 weeks. Most studies compared corticosteroids, particularly dexamethasone, to standard therapy.

Key results and quality of the evidence: Overall, we found that the current evidence is based on studies that contain only a small number of patients. The following conclusions can be made from the available evidence: 1) the evidence for the efficacy of corticosteroids for pain control in cancer patients is weak (GRADE quality of evidence for pain outcome was low); 2) significant pain relief was noted in some studies, albeit only for a short period of time; this could be important for patients who have only a short time to live; 3) overall, more studies found corticosteroids not to be of benefit; 4) it was not possible to determine whether steroids are more effective for pain in specific cancers; and 5) the side effect profile of steroids, especially in the longer term, is not well described.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Corticosteroids for cancer-related pain in adults

Patient or population: adult patients with cancer-related pain
Settings: in- and out-patients
Intervention: corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Corticosteroids				
Pain at 1 week Scale from: 0 to 10	The mean pain at 1 week in the control group was **3.77**	The mean pain at 1 week in the intervention groups was **0.84 lower** (1.38 to 0.3 lower)		315 (6 studies)	⊕⊕◯◯ **low**[1]	Pain (1 to 10) with lower score indicating less pain Quality of evidence low due to the small number of participants in each arm for the included studies

*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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded the quality of evidence by two levels from high to low because of likely selection bias and the small number of patients in the included studies.

BACKGROUND

Description of the condition

Cancer remains the leading cause of death worldwide. Over 12 million new cases are diagnosed each year (Foley 2011). The disease carries significant morbidity. Pain resulting directly or indirectly from the abnormal growth of malignant cells in normal tissue is the most common and most feared symptom associated with cancer (Van den Beuken-van Everdingen 2007). It is estimated that one-third of cancer patients on active therapy, and two-thirds of those with advanced disease, experience pain that requires treatment with analgesic drugs (Foley 2011). Of concern, there is also considerable evidence that cancer pain is often under treated (Foley 2011). While opioids remain the mainstay of treatment for cancer pain, co-analgesics or adjuvants are often used concurrently to optimise pain control. Corticosteroids (steroids) are commonly used in this context.

Description of the intervention

Steroids are essential for maintaining homeostasis and regulating a wide variety of physiological processes in the human body (Busillo 2013). Therapeutically, they are widely prescribed for the treatment of inflammation, auto-immune disorders and malignancies (Busillo 2013). They are commonly used in the management of cancer pain.

How the intervention might work

Corticosteroids are used for relief of pain associated with space-occupying lesions, not only in the brain, spinal cord and nerves, but also in the liver and soft tissues (eTG Complete 2014). They are used where there may be inflammation and oedema in confined spaces, including intracerebral, pelvic, retroperitoneal and spinal malignant disease, and are often used as an interim measure while awaiting more definitive therapies such as radiotherapy (eTG Complete 2014).

Corticosteroids have been proposed to have effects on all four stages of pain nociception including transduction, transmission, modulation and pain perception, although the exact mechanisms remain unclear (Leppert 2012). The anti-inflammatory effect of corticosteroids may be due to (i) inhibition of the expression of collagenase, an enzyme involved in tissue degeneration during inflammatory mechanisms, (ii) inhibition of pro-inflammatory cytokines, which have been implicated in a number of pain states, or (iii) by stimulating the synthesis of lipocortin, which in turn blocks the production of eicosanoids (Leppert 2012; Paulsen 2013).

It is proposed that the mechanism of pain relief for cancer-related neuropathic pain is by the inhibition of prostaglandin production, reduction of inflammation thus decreasing capillary permeability and reducing oedema (Pharo 2005)

In summary, the mechanism of action of corticosteroids in the reduction of cancer pain remains unclear.

Why it is important to do this review

Corticosteroids are prescribed frequently in oncology practice to reduce swelling and pain caused by cancer and may also be used to control and prevent nausea and vomiting caused by chemotherapy. In addition, it is common in palliative care practice, especially for patients with advanced malignant disease, for a variety of symptom control indications including pain, nausea, mood elevation, anorexia and fatigue (Farr 1990; Hardy 2001; Riechelmann 2007). This is despite the fact that steroids are associated with significant side effects, especially following long-term use (Hanks 2009). There is little objective evidence in the literature to support the use of corticosteroids for symptom control, and concerns have been raised about the 'uncontrolled' use of steroids in cancer patients (Gannon 2002; Twycross 1985). Patients who are started on steroids in the palliative care setting are often not closely monitored, allowing for the development of debilitating side effects, often in the context of limited clinical benefit. Some of these side effects include: proximal myopathy, oral candidiasis, symptomatic hyperglycaemia, psychological disturbances, gastrointestinal irritation, increased susceptibility to infections and the development of osteoporosis. For example, although steroids are frequently administered to assist with mood elevation, some studies have shown that corticosteroid therapy may result in more disturbing side effects such as insomnia, delirium, depression, anxiety and psychosis (Vyvey 2010). There is a relevant gap in the body of knowledge, in that most patients with cancer will be prescribed steroids at some stage during their disease course with very little evidence of effectiveness.

OBJECTIVES

To evaluate the efficacy of corticosteroids in treating cancer-related pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Any randomised controlled or prospective controlled trial.

Types of participants

Participants with cancer-related pain, aged 18 years and above.

Types of interventions

Types of interventions included any corticosteroid used to treat cancer-related pain.
We considered all routes of drug administration.
Comparisons were:

- placebo;
- no intervention;
- usual treatment or supportive care; or
- non-pharmacological treatment for pain.

Types of outcome measures

Primary outcomes

- Patient-reported pain intensity and pain relief using validated scales (visual analogue scale (VAS), verbal rating scale (VRS), numerical rating scale (NRS)).

Secondary outcomes

- Adverse events
- Quality of life
- Patient satisfaction
- Other relevant outcome measures, e.g. cost-effectiveness data

Search methods for identification of studies

The search strategy attempted to identify as many trials as possible that met the inclusion criteria without limitation by language, publication type or status or by date.

Electronic searches

We searched the following electronic databases:

1. the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 4);
2. MEDLINE (OVID) (1966 to 29 September 2014);
3. EMBASE (OVID) (1970 to 29 September 2014);
4. CINAHL (1982 to 29/ September 2014);
5. Science Citation Index (Web of Science) (1899 to 29 September 2014);
6. Conference Proceedings Citation Index - Science (Web of Science) (1990 to 29 September 2014).

The MEDLINE search strategy was adapted by a Librarian (KR) from one originally devised by the Trials Search Co-ordinator of the Cochrane Pain, Palliative and Supportive Care Review Group. The Cochrane Highly Sensitive Search Strategy (CHSS) filter for identifying randomised trials in MEDLINE via OVID was also modified and applied. This search was adapted and modified across the other databases. The search strategies are shown in Appendices 1 to 4 (Appendix 1; Appendix 2; Appendix 3; Appendix 4).

Searching other resources

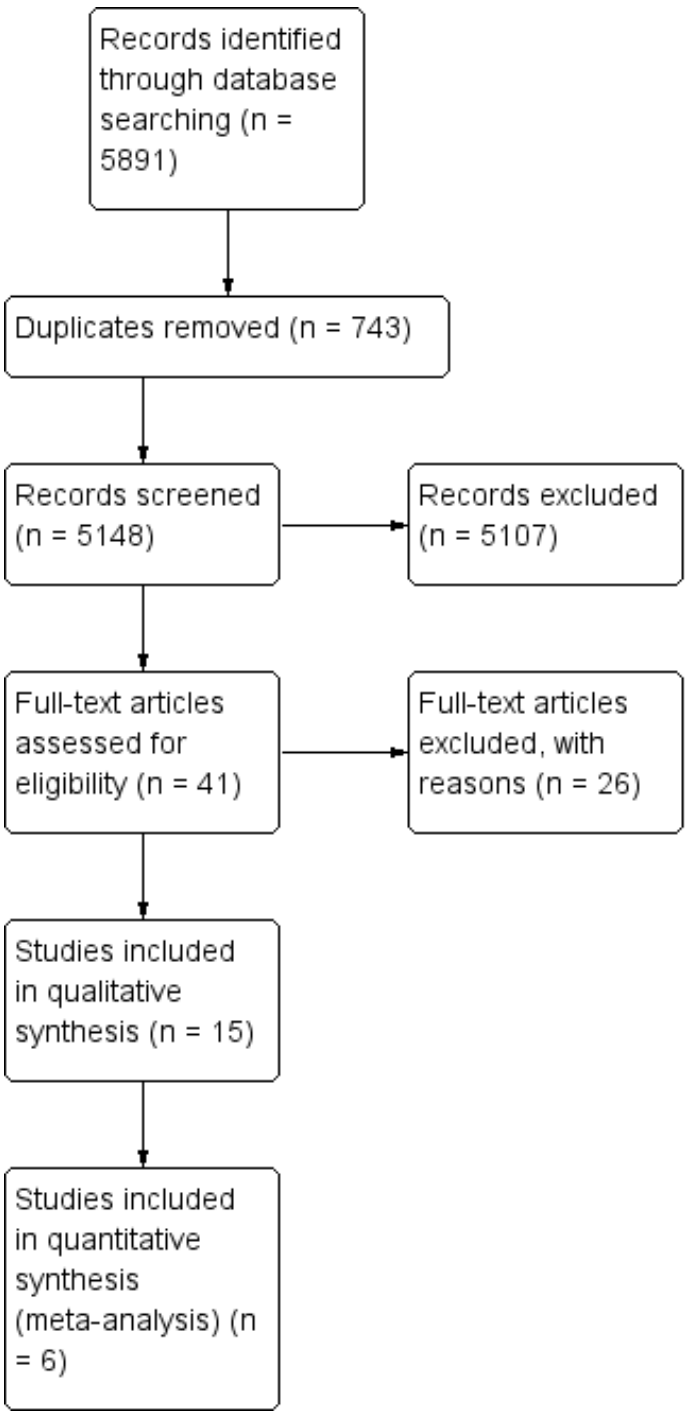
We checked the bibliographic references of any relevant identified studies in order to find additional trials not identified by the electronic searches. We also searched www.ClinicalTrials.gov, the *meta*Register of Controlled Trials (*m*RCT www.controlled-trials.com/mrct/), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) 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 for the unpublished paper. The searches were conducted by one of the review authors (KR) who is a Librarian. All searches were current as of 29 September 2014.

Data collection and analysis

Selection of studies

Four of the review authors (JH, PG, SJ-M, 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 four lists, discussed any differences and either included or excluded the papers based on a majority decision.
A PRISMA study flow diagram (Liberati 2009) is included in Figure 1 to document 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.



Data extraction and management

Four review authors (AL, AH, SK, SJ-M) independently extracted data from the studies, using a piloted data extraction form. Data extracted 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 pain, pain scale), withdrawals and adverse events. We resolved potential disagreements by discussion.

Assessment of risk of bias in included studies

Six of the authors (AL, AH, JH, PG, SK, KR) 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).
2. Allocation concealment (checking for selection bias).
3. Blinding of participants and personnel (checking for performance bias).
4. Blinding of outcome assessment (checking for detection bias).
5. Incomplete outcome data (checking for attrition bias).
6. Selective reporting (checking for reporting bias).
7. Size of study (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).

We used the GRADE approach to assess the overall quality of the evidence for the primary outcome, with downgrading of the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias (Langendam 2013). The outcome included in the 'Summary of findings' table was pain at week one (Summary of findings for the main comparison).

Measures of treatment effect

For continuous outcomes between groups, we measured arithmetic means and standard deviations (SD) and reported the mean difference (MD) with 95% CI. When an outcome was derived with different instruments measuring the same construct, we used the standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

We only included studies in which randomisation was by the individual patient; this included cross-over or n = 1 studies.

Dealing with missing data

In cases where data were missing, we attempted to contact the authors to request the missing data. This strategy did not result in any additional data. We ascertained the method of assessing data processed 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.

Assessment of heterogeneity

There may be an effect of differences between patients, 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 potential sources of heterogeneity through subgroup analyses.

Assessment of reporting biases

We interpreted the results of tests in the light of visual inspection of the funnel plot. If there was evidence of small study effects, we considered publication bias as only one of a number of possible explanations (Higgins 2011).

Data synthesis

We entered the data extracted from the included studies into Review Manager (RevMan 2014), which we used for data synthesis. Where appropriate, we pooled data for each dichotomous outcome and calculated RRs with 95% CIs using a random-effects model.

Sensitivity analysis

When sufficient data were available, we examined the robustness of the meta-analyses by conducting sensitivity analyses using different components of the 'Risk of bias' assessment, particularly those relating to whether allocation concealment and patient/assessor blinding were adequate. We conducted further sensitivity analyses to examine the impact of missing data on the results as a large proportion of the studies are at an 'unknown' or 'high' risk of attrition bias and, finally, sensitivity analyses to examine whether

publication status and trial size influenced the results. Unfortunately, due to the low number of studies within each comparison, we were unable to perform any sensitivity analyses.

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 5891 records. Of these, 743 were duplicates and we rejected 5107 based on information given in the title and abstract.

We identified 41 publications for full-text retrieval. We excluded 26 of these studies during screening. In three studies, only the abstract had been published and, as further detail was unavailable, we excluded them. Seven studies did not satisfy the inclusion criteria and we excluded 16 because pain was not an endpoint. The reasons for exclusion of each study are described in the 'Characteristics of excluded studies' table. A total of 15 studies met the inclusion criteria for this review. These included six placebo-controlled studies, one placebo-controlled cross-over study, five studies with active controls, one open-label and two low-dose versus high-dose studies (Table 1). We evaluated the results of six trials relative to pain intensity at one week (Basile 2012; Bruera 1985; Bruera 2004; Mercadante 2007; Paulsen 2014; Yennurajalingam 2013). The other trials could not be included in the meta-analysis due to missing data at this time point.

Included studies

We identified 15 studies meeting the inclusion criteria (Basile 2012; Bruera 1985; Bruera 2004; Della 1989; Fossa 2001; Graham 2006; Lauretti 2013; Lee 2008; Mercadante 2007; Paulsen 2014; Popiela 1989; Teshima 1996; Twycross 1985; Vecht 1989; Yennurajalingam 2013). The 15 studies included 1926 enrolled participants. Trial size varied from 20 to 598 participants.

A detailed description of the included studies can be found in the 'Characteristics of included studies' table.

Primary disease sites

The primary disease sites addressed are tabulated in Table 2.

Most of the trials did not include patients with a specific cancer type, with the exception of Fossa 2001, Lee 2008 and Teshima 1996.

Types of studies

Studies were included in which steroids were used as part of a treatment regimen and pain was assessed as an outcome (Fossa 2001; Lee 2008). Two studies tested high-dose versus low-dose steroids (Graham 2006; Vecht 1989).

Pain requirement as an entry criteria

Eight of the 15 studies required that participants had pain at study entry (Basile 2012; Della 1989; Lauretti 2013; Mercadante 2007; Paulsen 2014; Popiela 1989; Teshima 1996; Yennurajalingam 2013).

Pain as primary endpoint

Of the 15 included studies, only nine trials were designed with pain relief as a primary outcome measure (Basile 2012; Bruera 1985; Graham 2006; Lauretti 2013; Mercadante 2007; Paulsen 2014; Teshima 1996; Twycross 1985; Vecht 1989). Of the remainder, six studies were designed to describe differences in chronic nausea, cancer-related fatigue and quality of life (Bruera 2004; Della 1989; Fossa 2001; Lee 2008; Popiela 1989; Yennurajalingam 2013).

Types of corticosteroids studied

Dexamethasone was used in eight studies (Basile 2012; Bruera 2004; Graham 2006; Lauretti 2013; Lee 2008; Mercadante 2007; Vecht 1989; Yennurajalingam 2013), methylprednisolone in five studies (Bruera 1985; Della 1989; Paulsen 2014; Popiela 1989; Teshima 1996), and prednisone (Fossa 2001) and prednisolone (Twycross 1985) in one study each (Table 1).

Dexamethasone was administered orally in three studies (Bruera 2004; Mercadante 2007; Yennurajalingam 2013), and intravenously in five studies (Basile 2012; Graham 2006; Lauretti 2013; Lee 2008; Vecht 1989). Methylprednisolone was used in five trials, administered orally in two studies (Bruera 1985; Paulsen 2014), and intravenously in three studies (Della 1989; Popiela 1989; Teshima 1996). Prednisone (Fossa 2001) and prednisolone (Twycross 1985) were administered orally in both studies.

Additional details of dosage are provided in Table 3.

Pain and analgesic measurement tools

Different measurement tools were used to measure pain intensity.

- Visual analogue scale 0 to 10 (four studies) (Basile 2012; Graham 2006; Lauretti 2013; Vecht 1989)
- Visual analogue scale 0 to 100 (two studies) (Bruera 1985; Twycross 1985)
- Numerical scale 0 to 10 (six studies) (Bruera 2004; Della 1989; Mercadante 2007; Paulsen 2014; Popiela 1989; Yennurajalingam 2013)
- Quality of life questionnaire including pain (two studies) (Fossa 2001; Lee 2008)

- Radiation Therapy Oncology Group (RTOG) pain scale (one study) (Teshima 1996)

Excluded studies

We excluded 26 studies (Campio 1983; Chanan-Khan 2011; Coloma 2001; Datta 1997; Dutta 2012; Friedenberg 1991; Fuccio 2011; Gomez-Hernandez 2010; Hird 2009; Laval 2000; North 2003; Richardson 2009; Richardson 2010; Richardson 2011; Richardson 2012; Rinehart 2010; Rizzo 2009; Sanguineti 2003; Schmuth 2002; Tantawy 2008; Tong 1982; Vecht 1994; Vij 2012; Yennurajalingam 2010; Yennurajalingam 2012; Yoshioka 2011). Reasons for exclusion are provided in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

We assessed each study using the Cochrane 'Risk of bias' tool. Overall findings are presented in the 'Risk of bias' graph (Figure 2), which reviews the authors' judgements about each risk of bias item presented as percentages across all included studies. Authors' judgements about each risk of bias for each included study is shown in 'Risk of bias' summary (Figure 3).

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

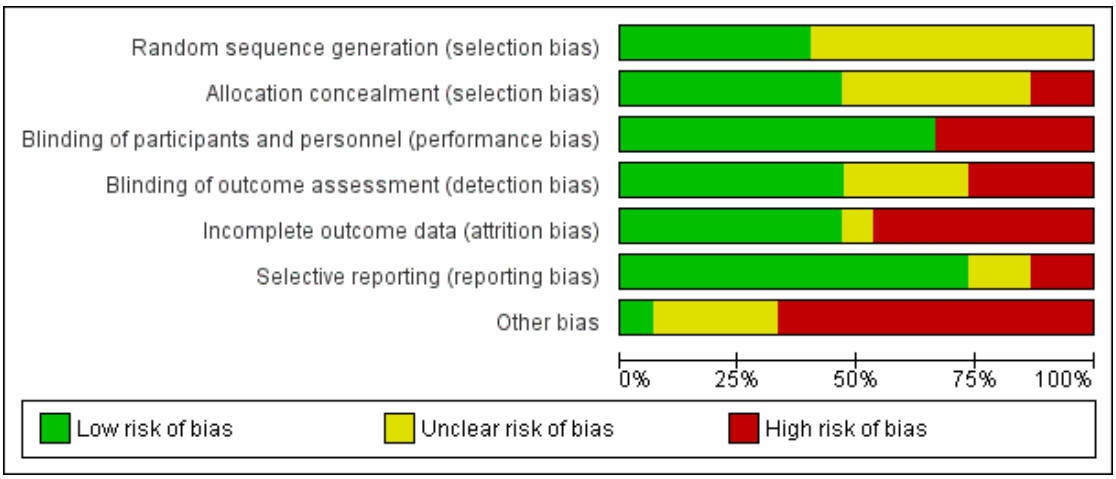
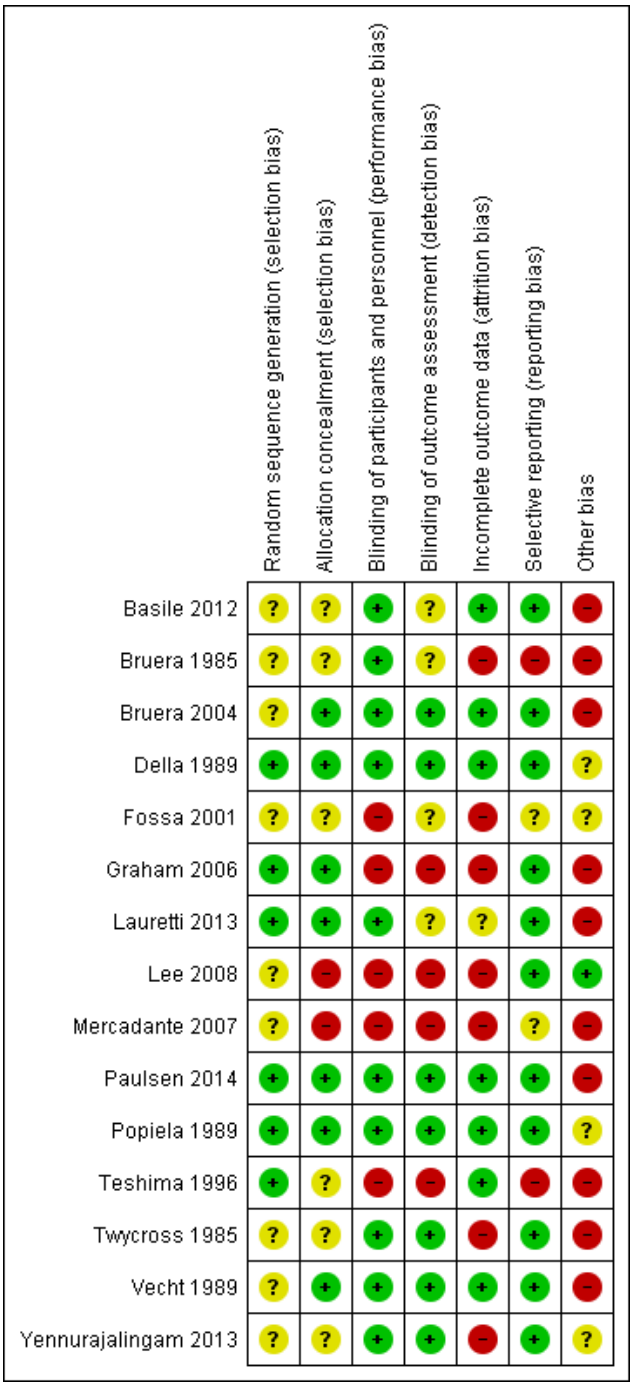


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies reported that they were randomised, but only six out of 15 properly described the method used to generate the random sequence. Four studies were randomised using a computer program (Della 1989; Lauretti 2013; Paulsen 2014; Popiela 1989). The participants from Graham 2006 were randomised using the Superdex website. Those from Teshima 1996 were randomly allocated according to Peto's balanced randomised list. We judged the six studies describing randomisation to have low risk and the other nine to have unclear risk of bias.

We judged seven studies to be low risk for allocation concealment; the trial medications were of identical appearance (Bruera 2004; Paulsen 2014), the packages were blinded (Della 1989; Lauretti 2013; Popiela 1989; Vecht 1989), or they used a password protected website to maintain blinding (Graham 2006). Two trials were at high risk, being open-label or not placebo-controlled (Lee 2008; Mercadante 2007). The remaining six trials were of unclear risk as not enough information was provided on the method of allocation concealment.

Blinding

Ten trials were at low risk, reporting blinding of patients and personnel (Basile 2012; Bruera 1985; Bruera 2004; Della 1989; Paulsen 2014; Popiela 1989; Twycross 1985; Vecht 1989; Yennurajalingam 2013). In five studies blinding was not possible due to different dosage intervals, because physicians were provided with patient's assigned treatment or because it was an open-label trial, so we assessed them as having high risk (Fossa 2001; Graham 2006; Lee 2008; Mercadante 2007; Teshima 1996).

The outcome assessment was blind in eight trials, judged to have low risk (Bruera 1985; Bruera 2004; Della 1989; Paulsen 2014; Popiela 1989; Twycross 1985; Vecht 1989; Yennurajalingam 2013). In the other three trials it was unclear whether the outcome assessor was blinded or not (Basile 2012; Fossa 2001; Lauretti 2013). In four studies the outcome assessment was not blind because physicians were provided with the patient's assigned treatment, it was an open-label study or there was no placebo given (Graham 2006; Lee 2008; Mercadante 2007; Teshima 1996). These studies are at high risk of bias.

Incomplete outcome data

It was not certain whether Lauretti 2013 reported all the outcomes that had been assessed, but in seven trials it appeared that additional pertinent outcomes should have been reported and their omission left a gap in the evidence (Bruera 1985; Fossa 2001; Graham 2006; Lee 2008; Mercadante 2007; Twycross 1985; Yennurajalingam 2013). We assessed these seven studies to have a high risk of bias. The remaining seven trials appear to have reported all relevant outcomes related to the subject matter (Basile 2012; Bruera 2004; Della 1989; Paulsen 2014; Popiela 1989; Teshima 1996; Vecht 1989).

Selective reporting

In two studies it was unclear if there was a reporting bias (Fossa 2001; Mercadante 2007). We found a high risk in Bruera 1985 and Teshima 1996, as some data evaluating pain and adverse events were not mentioned. In 11 trials, judged to be low risk, no reporting gaps were detected (Basile 2012; Bruera 2004; Della 1989; Graham 2006; Lauretti 2013; Lee 2008; Paulsen 2014; Popiela 1989; Twycross 1985; Vecht 1989; Yennurajalingam 2013).

Other potential sources of bias

Sample size was an issue. Small studies are thought to be at increased risk of bias as they are unlikely to be adequately powered. We considered only one of the studies large enough to give a low risk of bias (more than 200 patients per arm) (Lee 2008). We judged four studies to have an unclear risk of bias due to sample size (50 to 199 participants per arm) (Della 1989; Fossa 2001; Popiela 1989; Yennurajalingam 2013). We judged the remaining 10 trials to have a high risk of bias because of their small number of participants (Basile 2012; Bruera 1985; Bruera 2004; Graham 2006; Lauretti 2013; Mercadante 2007; Paulsen 2014; Teshima 1996; Twycross 1985; Vecht 1989).

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroids for cancer-related pain in adults

Primary outcome

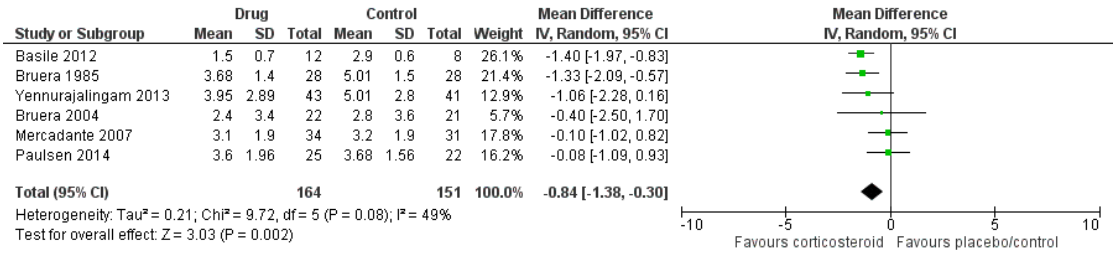
Patient-reported pain intensity and pain relief using validated scales

For the meta-analysis, only those studies that provided mean pain intensity and the standard deviation at one week could be included. In this case, we evaluated six studies relative to pain intensity (Basile 2012; Bruera 1985; Bruera 2004; Mercadante 2007; Paulsen 2014; Yennurajalingam 2013). The other trials could not be included in the meta-analysis due to missing data. Data were reported for baseline and after one week of intervention.

A total of 372 patients at baseline and 315 patients after one week of intervention were involved in these six studies. After one week of intervention, the intervention arm was favoured in all trials (Figure

4). The total mean difference is -0.84 with a 95% confidence interval of -1.38 to -0.30 (Analysis 1.1). While the study by Bruera 1985 was a cross-over trial, inclusion in the meta-analysis did not affect the overall review findings.

Figure 4. Forest plot of pain at 1 week.



Secondary outcomes

A meta-analysis for secondary outcomes could not be undertaken as the data were heterogeneous with no consistency of measurement tools or outcome measures. Patient satisfaction and cost-effectiveness data was not available.

Adverse events

Not all studies included information on adverse events and several reported no or only minimal adverse events compared to controls or placebo (Bruera 2004; Graham 2006; Lauretti 2013; Mercadante 2007; Yennurajalingam 2013). The most common adverse events attributed to steroids were restlessness and sleeplessness (Paulsen 2014), gastrointestinal and cardiovascular events (Popiela 1989), Cushingoid facies, anxiety, fluid retention (Bruera 1985), hypocalcaemia and hyperglycaemia (Della 1989). In the latter study, more patients randomised to steroids dropped out because of toxicity.

Quality of life/patient well-being

Four studies reported on quality of life (Bruera 1985; Bruera 2004; Mercadante 2007; Yennurajalingam 2013). Quality of life or patient well-being improved in three of four studies (Bruera 1985; Mercadante 2007; Yennurajalingam 2013).

DISCUSSION

Summary of main results

The objective of this systematic review was to assess whether corticosteroids are effective in reducing cancer-related pain. Fifteen randomised controlled trials with 1926 enrolled participants were included; six placebo-controlled studies, one placebo-controlled cross-over study, five studies with active controls, one open-label study and two low-dose versus high-dose studies. Included studies assessed either dexamethasone (at doses of 8 mg and 20 mg in an oral tablet or 4 mg/ml, 10 mg, 16 mg, 40 mg, 96 mg and 100 mg intravenously), methylprednisolone (16 mg and 32 mg orally or 125 mg and 500 mg intravenously) or prednisone 15 mg or prednisolone 20 mg orally.

For the meta-analysis only six studies could be evaluated for pain intensity. Data were reported after one week of intervention, since this was the only time that could be standardised across all six trials. The following conclusion regarding the effectiveness of corticosteroids for pain relief in cancer patients should be interpreted with consideration of the small number of eligible studies. The quality of studies was generally poor with a high risk of bias identified.

- There is some evidence to suggest that there is a benefit in favour of the use of corticosteroids (mean difference (MD) -0.84, 95% confidence interval (CI) -1.38 to -0.30) for cancer pain for up to one week of intervention. However, it is debatable if the reduction of a mean pain score of 0.8 with wide confidence intervals is clinically meaningful.
- 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 safety and effectiveness of corticosteroids for the

management cancer pain in adults, and to establish an ideal dose, duration of therapy and route of administration.

Overall completeness and applicability of evidence

We identified 15 studies that met the inclusion criteria, but included only six studies in the meta-analysis for pain intensity with insufficient data available for the remaining studies.

We did not attempt to classify specific pain syndromes. There were insufficient data for subgroup analyses.

Statistical analysis in relation to pain intensity in this review was limited by a number of factors. There is a lack of standardised measurement of pain. Several different tools have been used for pain measurement. In the meta-analysis, visual analogue scale scores (0 to 10) and numerical scale scores (0 to 10) were compared.

The results are also influenced by differences in steroid type, dosage, comparators, routes of administration, primary disease type, aetiology of pain and heterogeneity of study populations. One of the studies had a single dose of intravenous dexamethasone as an intervention compared to multiple oral doses of dexamethasone or methylprednisolone. Comparators included in the meta-analysis included both "standard treatment" (two studies) and placebo (four studies). Trials where dexamethasone was used primarily as an anticancer treatment rather than as a co-analgesic were also included.

Reporting of data

Basile 2012 reported clear data for pain outcomes at baseline and after one week of intervention. Adverse events were not reported.

Bruera 1985 tabulated the intensity of pain (VAS), adverse events and quality of life in each group at baseline and after one week of intervention.

Bruera 2004 presented mean pain scores, intensity of nausea and fatigue, as well as quality of life scores for both patient groups.

Della 1989 presented graphical representation of mean change from baseline in Nurses' Observation Scale for Inpatient Evaluation (NOSIE) and linear analogue scale assessment (LASA) total score. No standard deviation was provided.

Fossa 2001 presented data in the form of graphs. No original data were presented and it was therefore not possible to include this trial in the meta-analysis.

Graham 2006 published graphical representation of pain scores. Standard deviations were missing and therefore the trial could not be included in the meta-analysis.

Lauretti 2013 was not included in the meta-analysis as data on measured pain scores were not presented.

Lee 2008 had missing data on mean pain intensity and standard deviation. The study was not included in the meta-analysis.

Mercadante 2007 tabulated the mean scores and 95% CI for pain intensity, intensity of nausea, fatigue, drowsiness and also quality of life scores.

Paulsen 2014 reported clear data for pain outcomes, fatigue and appetite at baseline and after one week of intervention.

Popiela 1989 published a graphical representation of adverse events and quality of life. No data were presented on pain intensity scores, therefore the study could not be included in the meta-analysis.

Teshima 1996 presented pain scores and quality of life in a graphical field, but no standard deviation was provided. The trial was not included in the meta-analysis.

Twycross 1985 tabulated pain intensity scores. These could not be included in the meta-analysis as only the difference in outcome was reported at day eight with no baseline data available.

Vecht 1989 presented average pain scores and standard deviation assessed by a numerical rating scale in graphical form. No original data were presented and therefore it was not possible to include it in the meta-analysis.

Yennurajalingam 2013 presented the mean and standard deviation of pain intensity, nausea, depression, fatigue, drowsiness and quality of life.

Quality of the evidence

The quality of the evidence was low. This is due to imprecision (likely selection bias and the small number of patients) in the included studies. Nine studies did not adequately describe sequence generation and one study did not provide information about allocation concealment. In five studies the blinding of participants and personnel was not provided and in four studies the outcome assessment was not blinded. In a number of studies it appeared that additional pertinent outcomes should have been reported and in two studies a risk of bias in selective reporting was identified. Sample size was of concern. Only one study had more than 200 participants in each arm. Ten studies had fewer than 50 participants in each arm.

Potential biases in the review process

Data extraction, including 'Risk of bias' assessment, was done independently by all authors to minimise bias. The conclusion that can be drawn is limited by the number and the quality of the included studies. Several trials were susceptible to bias and hampered by incomplete outcome data and small sample size.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence of the efficacy of corticosteroids for pain control in cancer patients is weak. Our meta-analysis of studies with data

at one week suggests that corticosteroids may relieve cancer pain, even if only for a short period of time. However, it is debatable if the reduction of a mean pain score of 0.8 with wide confidence intervals is clinically meaningful. In addition, any evidence of the efficacy of corticosteroids in the reduction of cancer pain must be weighed up against the associated significant side effects. Furthermore, we can make no recommendation regarding type of steroid, dose, route of delivery, side effect profile or treatment period.

In light of the above, we recommend that clinicians are cautious in their prescribing of steroids for pain management, that they assess benefit carefully, treat for the shortest possible time and discontinue early in the absence of symptom relief.

Implications for research

Further trials with increased numbers of participants are needed to evaluate the safety and effectiveness of corticosteroids for the management cancer pain in adults, and to establish an ideal dose, duration of therapy and route of administration. Further adequately powered randomised controlled trials with pain as a primary outcome, measured with universally accepted standardised tools, using a single agent (dexamethasone), at a pre-specified dose and route over a short time period are indicated. Longer-term toxicity should be documented during a follow-up period.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Basile 2012

Methods	Randomised controlled trial Study duration: 3 months
Participants	20 consecutive patients (12 intervention, 8 control) with single-level vertebral neoplasm or pathological fractures totally or partially refractory to analgesic treatment, with indication for vertebroplasty Inclusion criteria: • visual analogue scale (VAS, 0 to 10) pain score ≥ 5 • life expectancy ≥ 3 months
Interventions	Intervention: intrasomatic injection of 4 mg/ml of dexamethasone phosphate through vertebroplasty needle followed by cement injection (group A) Control: standard vertebroplasty (group B)
Outcomes	Pain intensity using VAS at various time intervals: 6 hours to 3 months
Notes	Baseline VAS 8/10 in both groups. Greater reduction in VAS in group A at early time points (including day 7), but no significant difference at last follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly divided into 2 groups Not specified how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	Randomisation was obtained by blind extraction of letters A or B in a closed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	3 interventional radiologists (all blinded to treatment allocation)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 patients died in group A, 3 patients died in group B during follow-up
Selective reporting (reporting bias)	Low risk	No problem detected

Basile 2012 (*Continued*)

Other bias	High risk	Sample size: 20 participants; < 50 participants per treatment arm

Bruera 1985

Methods	Prospective, randomised, double-blind, cross-over trial Study duration: 14 days
Participants	40 terminally ill patients (in- and out-patients) with malignant disease No specific anticancer treatment within 1 month Oral analgesia according to individual requirements
Interventions	32 mg methylprednisolone (MP) daily (16 mg twice a day orally) or placebo for 5 days Days 5 to 7: treatment-free Days 8 to 12: cross-over to other arm then open label MP
Outcomes	Pain intensity using VAS (0 to 100) assessed at days 0, 5, 13 and 33 (response defined as > 30% improvement over placebo) Anxiety Daily oral analgesic consumption appetite Food consumption (% of each meal) Performance status Activity score
Notes	Pain one of several endpoints Intensity of pain and daily consumption of analgesics was significantly lower after MP compared with baseline or placebo Depression, appetite and food consumption also improved on MP

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly divided into 2 groups Not specified how the random sequence was generated
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified, same investigator did all evaluations

Bruera 1985 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	9 patients did not complete the trial and were not included in evaluation 3 patients reported no pain at baseline
Selective reporting (reporting bias)	High risk	Only 28 patients were evaluated for pain
Other bias	High risk	Sample size: 40 participants; < 50 participants per treatment arm

Bruera 2004

Methods	Double-blind, parallel-arm trial 5 international centres Study duration: 7 days
Participants	51 participants (25 intervention, 26 control) with advanced cancer and chronic nausea (> 2 weeks) resulting from advanced cancer despite treatment with metoclopramide at a minimal daily dose of 40 to 60 mg for 2 days
Interventions	Intervention: 20 mg/day dexamethasone orally in addition to metoclopramide (60 mg/day orally) Control: placebo in addition to metoclopramide (60 mg/day)
Outcomes	Pain, appetite, fatigue and nausea, measured on a 0 to 10 numerical rating scale (NRS) (0 = symptom absent, 10 = worst possible symptom) Quality of life: physical well-being, social well-being, functional well-being, emotional well-being Toxicity assessment: presence or absence of ankle oedema, insomnia, restlessness or other symptoms (patient-rated)
Notes	Pain secondary outcome measure. Nausea as primary endpoint Pain intensity at baseline low in both arms. Authors therefore query meaningfulness of pain as outcome measure

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, method not specified
Allocation concealment (selection bias)	Low risk	Capsules containing both drugs identical in appearance, randomisation in pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Bruera 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 of 25 patients receiving dexamethasone dropped out 5 of 26 patients receiving placebo dropped out
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Sample size: 51 participants; < 50 participants per treatment arm

Della 1989

Methods	Double-blind, placebo-controlled, multi-centre study Study duration: 8 weeks
Participants	403 participants (207 intervention, 196 control) with "pre-terminal" cancer Inclusion criteria: • pain, debility, cachexia, anorexia or other signs of advanced disseminated disease • no longer candidates for aggressive anticancer therapy • expected to survive ≥ 2 months • no steroids within 1 month of study
Interventions	Intervention: 125 mg/day IV methylprednisolone sodium succinate (MPSS) daily Control: placebo (88.8 mg mannitol) daily IV for maximum of 8 weeks
Outcomes	Linear Analogue Self-Assessment scale (LASA), 10 questions on pain, appetite, well-being, nausea, sleepiness, weakness (10-point scale ranging from 'worst' to 'best') Nurses Observation Scale for Inpatient Evaluation (NOSIE), 21 questions, 5-point scale ranging from 'never' to 'always' (total score= 50 + social competence + social interest - irritability - retardation - depression)
Notes	Pain not primary outcome measure. Comparable LASA scores at baseline. MPSS produced significantly more improvement than placebo in LASA score for pain, appetite, vomiting and well-being. Pain one of several endpoints

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation scheme

Della 1989 (*Continued*)

Allocation concealment (selection bias)	Low risk	Double-blind Study medication was provided in blinded packages that contained vials of either MPSS or placebo
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Identity of the investigational therapy was not known by the investigator, his staff or the patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	30 MPSS-treated and 33-placebo treated patients dropped out, 83 MPSS-treated and 59-placebo treated patients died prior to completing 8 weeks of treatment
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Sample size: 403 participants; 50 to 199 participants per treatment arm

Fossa 2001

Methods	Randomised controlled trial Study duration: 24 weeks
Participants	201 participants (101 prednisone, 100 flutamide) with castrate resistant prostate cancer (CRPC) and symptomatic metastatic disease Inclusion criteria: • WHO performance status of 0 to 3 no previous use of prednisone • flutamide or any other oral antiandrogen • no previous systemic anticancer treatment, except the above primary hormonal manipulation
Interventions	Group F: 250 mg flutamide orally 3 times a day Group P: 5 mg prednisone orally 4 times a day Patients receiving LHRH analogues continued with this treatment
Outcomes	Quality of life (QoL): QLQ C-30, a 30-item questionnaire assessing a range of physical, emotional and social health issues • all scales and single-item measures were linearly transformed to a 0 to 100 scale • for function scale: higher score represents a higher level of function • for symptom measures: a higher score corresponds to a worsening of symptoms. Main endpoints were time to progression (TTP) and duration of survival

Fossa 2001 (*Continued*)

Notes	Pain not primary endpoint Prednisone used as treatment of prostate cancer Statistically significant treatment effects following prednisone were noted for pain, nausea, vomiting and diarrhoea

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Flutamide 3 times a day, prednisone 4 times a day, therefore no blinding possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat Patients had to remain in the trial for at least 6 weeks to be assessable for response. They were otherwise included in the analysis as 'non-assessable'
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	Unclear risk	Sample size: 201 participants; 50 to 199 participants per treatment arm

Graham 2006

Methods	Pilot randomised controlled trial 8 recruiting centres Study duration: 14 days
Participants	20 participants with malignant spinal cord compression (MSCC) Inclusion criteria: • malignant disease • at least one of: pain, weakness, sensory symptoms, sphincter problems • ECOG performance status $\geq$ 4 before the MSCC event • minimum limb power 1/5 • estimated minimum survival of 2 months

Graham 2006 (*Continued*)

Interventions	High-dose: 96 mg dexamethasone intravenously day 0, continued to day 2 then weaned to 0 by day 15 or Low-dose: 16 mg dexamethasone intravenously day 0, continued to day 2 then weaned to 0 by day 15 Radiotherapy in both arms
Outcomes	Visual analogue pain score (0 to 10) Toxicity (method not specified) Survival Ambulation and functional outcome (method not specified)
Notes	High-dose versus low-dose dexamethasone study terminated because of inadequate recruitment No significant difference in pain in the first week Analgesic use tended to be lower in high dose arm Pilot study, not powered for outcome, descriptive analysis Pain one of several endpoints

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients randomised via the Superdex website
Allocation concealment (selection bias)	Low risk	Website protected with password unique to each investigator
Blinding of participants and personnel (performance bias) All outcomes	High risk	Physicians were provided with patient's assigned treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Physicians were provided with patient's assigned treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	4 out of 20 patients not evaluable
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Sample size: 20 participants (pilot study); < 50 participants per treatment arm

Lauretti 2013

Methods	Randomised, prospective, placebo-controlled trial Study duration: 21 days
Participants	72 participants (6 groups of n = 12) with moderate/severe chronic cancer pain Inclusion criteria: • requiring around-the-clock opioid therapy • all participants on amitriptyline 25 g daily and oral morphine • VAS scale > 4/10 despite opioid therapy
Interventions	Control group (CG): epidural 40 mg lidocaine diluted to 10 ml volume with N/saline Dexamethasone group (DG): 40 mg lidocaine plus 10 mg dexamethasone 2.5 Met group: 2.5 mg epidural methadone with 40 mg lidocaine 5 Met group: 5 mg epidural methadone plus 40 mg lidocaine 7.5 Met group: 7.5 mg epidural methadone plus 40 mg lidocaine 7.5 Met-Dex group: 7.5 mg methadone with 40 mg lidocaine and 10 mg dexamethasone All delivered as sacral block with free access to oral morphine to maintain VAS < 4/10
Outcomes	Analgesic use, pain score (VAS), adverse effects Assessed by patient daily diary
Notes	Very small numbers in each group Significantly less oral morphine consumption with dexamethasone

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation using a randomised number generator in a computer program
Allocation concealment (selection bias)	Low risk	Drugs were diluted in a 10 ml covered syringe in order to maintain blindness
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Same anaesthetist, unaware of the study drug prepared by a second anaesthetist Patients blind to treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 patients from GC, 3 from DG, 2 from 2.5 MetG, 2 from 5 MetG, 2 from 7.5 MetG and 1 from 7.5 MetDG were excluded due to incomplete data collection Minimum of 8 patients per group maintained for statistical purposes
Selective reporting (reporting bias)	Low risk	None detected

Other bias	High risk	Sample size: 72 participants; < 50 participants per treatment arm

Lee 2008

Methods	Prospective, randomised, open-label study Multi-site, international Study duration: 42 weeks
Participants	598 participants (bortezomib 296, or dexamethasone 302) with relapsed multiple myeloma
Interventions	Bortezomib (B): 1.3 mg/m^2, days 1, 4, 8 and 11 for eight 3-week cycles, then days 1, 8, 15 and 22 for three 5-week cycles IV bolus Dexamethasone (D): 40 mg/day, days 1 to 4, 9 to 12 and 17 to 20 for four 5-week cycles, then days 1 to 4 only for five 4-week cycles, oral
Outcomes	Health-related quality of life (HRQL) (EORTC QLQ-C30), score range from 0 to 100; higher scores reflect better quality of life, for symptom scale, higher scores reflect worse symptoms Functional Assessment of Cancer Therapy Neurotoxicity questionnaire (FACT/GOG-NTX), 11 individual items evaluating symptoms of neurotoxicity on a scale of 0 (not at all) to 4 (very much), items were reversed (reversed score = 4 - row score) therefore total scores ranged from 0 to 44 with higher values indicating a lower burden of neurotoxicity Questionnaires administered at baseline and 6-weekly to 42 weeks
Notes	Health related QoL and toxicity assessed in patients participating in an efficacy study of bortezomib versus dexamethasone in multiple myeloma Pain not primary outcome measure Benefit in pain scores in favour of B using available data but not when using imputed data sets Corticosteroids used as an anticancer treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised (1:1) Method not specified
Allocation concealment (selection bias)	High risk	Open-label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label

Lee 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	Amount of missing data increased over time due to attrition related to adverse events, disease progression, the premature termination of the dexamethasone arm of the study and death. Only 9% in the B and 5% in the D arm completed protocol-specified treatment. Significant missing data with time
Selective reporting (reporting bias)	Low risk	None detected since pain not primary outcome
Other bias	Low risk	Sample size: 598 participants; ≥ 200 participants per treatment arm

Mercadante 2007

Methods	Prospective, randomised, controlled study of steroids as adjuvant drugs to opioids Study duration: 9 weeks
Participants	76 patients with advanced cancer (31 opioid, 35 dexamethasone) with pain requiring strong opioids Other co-analgesics allowed
Interventions	Group O: conventional opioid treatment Group OS: 8 mg dexamethasone orally along with conventional treatment
Outcomes	Average daily pain intensity measured using the patient's self report on NRS from 0 (absent) to 10 (maximum) Well-being sensation, rated by means of a NRS from 0 to 10 Symptoms associated with opioid therapy or commonly present in advanced cancer patients (nausea and vomiting, weakness, drowsiness, constipation, confusion), scale from 0 to 3 (not at all, slight, a lot, awful) Opioid escalation index percentage (OEI%) and absolute dose (OEI mg)
Notes	No difference between groups in OEI Other co-analgesics allowed, not standardised Difference in OEI between arms at baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mercadante 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Patients randomly divided into 2 groups Method not described
Allocation concealment (selection bias)	High risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Half of the patients died before the third week making the interpretation of any long-term corticosteroid benefit difficult
Selective reporting (reporting bias)	Unclear risk	Authors did not specify the adverse drug reactions where they claimed symptomatic improvement except for nausea, vomiting and constipation
Other bias	High risk	Sample size: 76 participants; < 50 participants per treatment arm

Paulsen 2014

Methods	Randomised, placebo-controlled, double-blind, parallel-group, multi-centre, phase III trial
Participants	Patients with cancer experiencing pain > 4/10 receiving opioids
Interventions	Methylprednisolone 16 mg or placebo 16 mg twice daily for 7 days
Outcomes	Primary outcome: average pain intensity measured by BPI (0 to 10) Secondary outcome: • daily pain intensity at rest (ESAS 0 to 10) • change in fatigue and appetite baseline to day 7 (EORTC-C30) • adverse events
Notes	592 patients screened, 50 recruited over 3 to 4-year time period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation conducted independently

Paulsen 2014 (*Continued*)

Allocation concealment (selection bias)	Low risk	Methylprednisolone and placebo capsules were identical in appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All parties blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation was blinded for all parties until the completion of data collection
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient died in the placebo group and 1 patient withdrew from the intervention group as a result of malignant bowel obstruction; none lost to follow-up ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Sample size: 50 participants; < 50 participants per treatment arm

Popiela 1989

Methods	Randomised, prospective, double-blind, placebo-controlled, multi-site clinical trial Study duration: 8 weeks	
Participants	173 female participants (85 intervention, 88 control) with advanced, terminal cancer and symptoms (pain, debility, nausea, cachexia etc)	
Interventions	Intervention: 125 mg infusion of methylprednisolone sodium succinate (MPSS) IV Control: matching placebo (P) Both for 56 consecutive days	
Outcomes	Linear Analogue Self-Assessment scale (LASA), patient ratings for pain, appetite, sense of well-being completed weekly x 8 weeks Mortality Concomitant medications Adverse events	
Notes	No significant changes with time for pain or sleep No significant changes in opioid use Better overall LASA score for patients on MPSS	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Popiela 1989 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomisation specified by a computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Double-blind Study medication was provided in blinded packages containing vials of either placebo or MPSS
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, data from 2 sites removed ("significant investigator interaction")
Incomplete outcome data (attrition bias) All outcomes	Low risk	38% MPSS and 30% P died before study completion ITT analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Sample size: 173 participants; 50 to 199 participants per treatment arm

Teshima 1996

Methods	Multi-site, prospective randomised controlled trial of RT alone or RT and methylprednisolone for bone metastases Study duration: 14 days
Participants	38 participants (20 intervention, 18 control) with bone metastases and clinical symptoms such as pain, loss of appetite, general fatigue, sleep disturbance, anxiety, depression and nausea and/or vomiting
Interventions	Intervention: radiation combined with methylprednisolone 500 g IV daily x 3 days Control: radiation alone
Outcomes	RTOG pain score plus QoL (1 to 10), patient scored Performance status Urinary hydroxyproline/creatinine ratio Serum tartrate-resistance acid phosphatase (tumour marker)
Notes	Pain not only endpoint No difference between groups with respect to pain
Risk of bias	

Teshima 1996 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated to 1 of the 2 treatments according to Peto's balanced randomised list
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo, no blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo, no blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts declared
Selective reporting (reporting bias)	High risk	Graphical presentation of pain scores and no mention of adverse events
Other bias	High risk	Sample size: 38 participants; < 50 participants per treatment arm

Twycross 1985

Methods	Double-blind, randomised, placebo-controlled trial Study duration: 7 days
Participants	27 participants (16 intervention, 11 control) with cancer of the breast or lung
Interventions	Intervention: 5 mg prednisolone by mouth 3 times a day Control: placebo of identical appearance
Outcomes	Visual analogue scales (VAS), 100 mm, relating to pain, nausea, mood, sleep, alertness and strength
Notes	Poor quality RCT, no standard background dosing, changes in adjunct medication "kept to a minimum" Analgesics adjusted as required Difference in pain scales at baseline No significant difference at day 8

Risk of bias

Bias	Authors' judgement	Support for judgement

Twycross 1985 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomised Method not specified
Allocation concealment (selection bias)	Unclear risk	266 potentially eligible, only 56 randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	266 screened, 56 entered Double-blind Placebo of identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 27/56 completed outcome assessments
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Sample size: 27 participants; < 50 participants per treatment arm

Vecht 1989

Methods	Randomised, multi-centre controlled trial Study duration: 1 week
Participants	37 participants (22 high-dose, 15 low-dose) with metastatic spinal cord compression (SCC)
Interventions	High-dose: 100 mg dexamethasone dissolved in glycerol and water Low-dose: 10 mg dexamethasone dissolved in glycerol and water, both delivered immediately following diagnosis of SCC by myelography
Outcomes	NRS for pain (0 to 10) Ambulatory status (grade 1, walking independently - grade 5, no power in legs) Bladder function
Notes	High-dose versus low-dose dexamethasone plus radiotherapy for SCC No difference seen in pain, ambulation or bladder function

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised Not specified how the random sequence was generated

Vecht 1989 (*Continued*)

		22 patients received high-dose and 15 low-dose (no explanation given)
Allocation concealment (selection bias)	Low risk	Coded ampoules blindly administered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Code broken by statistician at final analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Code broken by statistician at final analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients randomised, 3 had insufficient data for analysis
Selective reporting (reporting bias)	Low risk	None detected
Other bias	High risk	Sample size: 37 participants; < 50 participants per treatment arm

Yennurajalingam 2013

Methods	Randomised, double-blind, placebo-controlled trial Study duration: 14 days
Participants	120 participants (62 intervention, 58 control) with advanced cancer and ≥ 3 symptoms during the previous 24 hours (e.g. pain, fatigue, chronic nausea cluster) with average intensity of ≥ 4 on the Edmonton Symptom Assessment Scale (ESAS)
Interventions	Intervention: 4 mg dexamethasone orally twice per day for 14 days Control: placebo orally twice per day for 14 days
Outcomes	ESAS to assess severity of common symptoms (e.g. pain, fatigue, nausea, depression, anxiety) rated on a NRS of 0 to 10 (0 = no symptoms, 10 = worst possible severity) Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), 27 questions, scale 0 to 4 (0 = not at all, 4 = very much) Functional Assessment of Cancer Therapy-Anorexia-Cachexia (FAACT), 12-item symptom-specific subscale, scale 0 to 4 Hospital Anxiety and Depression Scale (HADS), 14-item questionnaire
Notes	Fatigue was primary outcome measure Pain as measured by ESAS significantly better on dexamethasone at day 8, but not day 15

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Yennurajalingam 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All members of the research team except the investigational pharmacist and statistician were blinded to treatment assignment throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All members of the research team except the investigational pharmacist and statistician were blinded to treatment assignment throughout the study
Incomplete outcome data (attrition bias) All outcomes	High risk	19 of 62 patients receiving dexamethasone were not evaluable 17 of 58 patients receiving placebo were not evaluable
Selective reporting (reporting bias)	Low risk	None detected
Other bias	Unclear risk	Sample size: 120 participants; 50 to 199 participants per treatment arm

BPI: Brief Pain Inventory
ECOG: Eastern Cooperative Oncology Group
ESAS: Edmonton Symptom Assessment Scale
ITT: intention-to-treat
IV: intravenous
LASA: Linear Analogue Self-Assessment scale
LHRH: Luteinizing Hormone Releasing Hormone
MP: methylprednisolone
MPSS: methylprednisolone sodium succinate
MSCC: malignant spinal cord compression
NRS: numerical rating scale
OEI: opioid escalation index
P: placebo
QoL: quality of life
RCT: randomised controlled trial
RT: radiation
RTOG: Radiation Therapy Oncology Group
SCC: spinal cord compression
VAS: visual analogue scale

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

Study	Reason for exclusion
Campio 1983	Abstract only; pain not an outcome measure
Chanan-Khan 2011	2 arms not identical; measuring tumour flare reaction (TFR) of which pain is primary feature, more a measure of TFR
Coloma 2001	Postoperative pain rather than cancer pain
Datta 1997	Not all patients had pain at baseline
Dutta 2012	Prophylactic steroids; primary endpoint was skin toxicity, not pain
Friedenberg 1991	Not randomised; toxicity assessments included
Fuccio 2011	Prophylactic steroids; pain not specifically measured
Gomez-Hernandez 2010	Prevention of postoperative pain
Hird 2009	Non-randomised; no toxicity assessment
Laval 2000	Trial underpowered; focus on resolution of bowel obstruction and symptoms
North 2003	Quality of life not pain as an outcome measure
Richardson 2009	Pain not assessed
Richardson 2010	Phase 1/2 trial; pain not an endpoint
Richardson 2011	Pain not an endpoint
Richardson 2012	Pain not assessed
Rinehart 2010	Pain not an endpoint
Rizzo 2009	No detailed results
Sanguineti 2003	Assessed post-radiation toxicity, not pain
Schmuth 2002	Pain not assessed
Tantawy 2008	Postoperative pain after oncologic pelvic surgery
Tong 1982	Patients not treated with corticosteroids
Vecht 1994	Pain not an endpoint

(*Continued*)

Vij 2012	Pain not an endpoint
Yennurajalingam 2010	Abstract only
Yennurajalingam 2012	Abstract only
Yoshioka 2011	Pain not an endpoint

DATA AND ANALYSES

Comparison 1. Pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain at 1 week	6	315	Mean Difference (IV, Random, 95% CI)	-0.84 [-1.38, -0.30]

Analysis 1.1. Comparison 1 Pain, Outcome 1 Pain at 1 week.

Review: Corticosteroids for the management of cancer-related pain in adults

Comparison: 1 Pain

Outcome: 1 Pain at 1 week

Study or subgroup	Drug N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Basile 2012	12	1.5 (0.7)	8	2.9 (0.6)		26.1 %	-1.40 [-1.97, -0.83]
Bruera 1985	28	3.68 (1.4)	28	5.01 (1.5)		21.4 %	-1.33 [-2.09, -0.57]
Yennurajalingam 2013	43	3.95 (2.89)	41	5.01 (2.8)		12.9 %	-1.06 [-2.28, 0.16]
Bruera 2004	22	2.4 (3.4)	21	2.8 (3.6)		5.7 %	-0.40 [-2.50, 1.70]
Mercadante 2007	34	3.1 (1.9)	31	3.2 (1.9)		17.8 %	-0.10 [-1.02, 0.82]
Paulsen 2014	25	3.6 (1.96)	22	3.68 (1.56)		16.2 %	-0.08 [-1.09, 0.93]
Total (95% CI)	**164**		**151**			**100.0 %**	**-0.84 [-1.38, -0.30]**

Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 9.72$, df = 5 (P = 0.08); $I^2 = 49\%$

Test for overall effect: Z = 3.03 (P = 0.0024)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Comparison of included studies

Comparison	Number of studies	References
Dexamethasone - standard therapy	5	Basile 2012; Lauretti 2013; Lee 2008; Mercadante 2007; Teshima 1996
(Methyl-)prednisolone - placebo	5	Bruera 1985; Della 1989; Paulsen 2014; Popiela 1989; Twycross 1985
Dexamethasone - placebo	2	Bruera 2004; Yennurajalingam 2013
High-dose versus low-dose dexamethasone	2	Graham 2006; Vecht 1989
Prednisone - flutamide	1	Fossa 2001

Table 2. Primary sites of disease

	Breast	Lung	Prostate	Ovary	Gastrointestinal	Genitourinary	Uterus	Other	Not specified
Basile 2012					x			x	
Bruera 1985	x	x	x	x				x	
Bruera 2004	x	x		x	x	x			
Della 1989	x	x	x		x		x	x	
Fossa 2001			x						
Graham 2006	x	x	x		x	x			
Lauretti 2013	x	x	x				x	x	
Lee 2008								x	
Mercadante 2007									x
Paulsen 2014	x	x	x	x	x				

Table 2. Primary sites of disease (*Continued*)

Popiela 1989									x
Teshima 1996								x	
Twycross 1985	x	x							
Vecht 1989									x
Yennurajalingam 2013	x	x			x	x	x	x	

Table 3. Target population, drug and dose of the 15 included studies

Study	Target population	Drug	Dose
Basile 2012	Bone neoplasm	Dexamethasone	4 mg/mL
Bruera 1985	Advanced cancer	Methylprednisolone	32 mg
Bruera 2004	Advanced cancer	Dexamethasone	20 mg
Della 1989	Advanced cancer	Methylprednisolone	125 mg
Fossa 2001	Prostate cancer	Prednisone	20 mg
Graham 2006	Malignant spinal cord compression	Dexamethasone	16 mg
Graham 2006	Malignant spinal cord compression	Dexamethasone	96 mg
Lauretti 2013	Advanced cancer	Dexamethasone	10 mg
Lee 2008	Multiple myeloma	Dexamethasone	40 mg
Mercadante 2007	Adjuvant drug in advanced cancer patients	Dexamethasone	8 mg
Paulsen 2014	Advanced cancer	Methylprednisolone	16 mg
Popiela 1989	Advanced cancer	Methylprednisolone	125 mg

Table 3. Target population, drug and dose of the 15 included studies (*Continued*)

Teshima 1996	Bone metastases	Methylprednisolone	500 mg
Twycross 1985	Breast or bronchus cancer	Prednisolone	15 mg
Vecht 1989	Advanced cancer	Dexamethasone	10 mg
Vecht 1989	Advanced cancer	Dexamethasone	100 mg
Yennurajalingam 2013	Advanced cancer	Dexamethasone	8 mg

APPENDICES

Appendix 1. MEDLINE 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 acetate or cortisone).tw.
10. deflazacort.tw.
11. Dexamethasone/
12. dexamethasone.tw.
13. Hydrocortisone/
14. hydrocortisone.tw.
15. Methylprednisolone/
16. methylprednisolone.tw.
17. Prednisolone/
18. prednisolone.tw.
19. Triamcinolone/
20. triamcinolone.tw.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp Pain/
23. pain.tw.
24. Pain Measurement/
25. exp Analgesics/
26. exp Analgesia/
27. "analges*".tw.
28. (quality adj2 life).tw.
29. quality of life/
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31. malignant.tw.
32. malignancy.tw.
33. "tumor*".tw.
34. "tumour*".tw.
35. "cancer*".tw.
36. "carcinoma*".tw.
37. exp Neoplasms/
38. 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 21 and 30 and 38
40. randomized controlled trial.pt.
41. controlled clinical trial.pt.
42. randomized.ab.
43. randomised.ab.
44. placebo.ab.
45. drug therapy.fs.
46. randomly.ab.
47. trial.ab.
48. groups.ab.
49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
50. exp animals/ not humans.sh.
51. 49 not 50
52. 39 and 51

Appendix 2. MEDLINE (in-process & other non-indexed citations)

1. (corticoid* or corticosteroid* or cortisone or betamethasone or deflazacort or dexamethasone or hydrocortisone or methylprednisolone or prednisolone or triamcinolone or fludrocortisone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. (pain or analges* or "quality of life").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. (malignan* or cancer* or carcinoma* or neoplas*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. 1 and 2 and 3
5. 1 and 3
6. ((pain or analges* or quality adj3 life).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. 5 and 6

Appendix 3. EMBASE search strategy

1. exp corticosteroid/
2. betamethasone.ti,ab.
3. cortisone.ti,ab.
4. deflazacort.ti,ab.
5. dexamethasone.ti,ab.
6. fludrocortisone.ti,ab.
7. hydrocortisone.ti,ab.
8. methylprednisolone.ti,ab.
9. prednisolone.ti,ab.
10. triamcinolone.ti,ab.
11. (corticoid* OR corticosteroid* OR glucocorticoid*).ti,ab.
12. 1 or 2 or 3 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. exp pain/
14. pain assessment/
15. exp analgesic agent/
16. exp analgesia/
17. pain.ti,ab.
18. "analges*".ti,ab.
19. (quality adj2 life).ti,ab.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. malignant.ti,ab.
22. malignancy.ti,ab.
23. "carcinoma$".ti,ab.
24. "cancer$".ti,ab.
25. "tumo*r$".ti,ab.
26. exp neoplasm/
27. 21 or 22 or 23 or 24 or 25 or 26
28. 12 and 20 and 27
29. Clinical trial/
30. Randomized controlled trial/
31. Randomization/
32. Single blind procedure/
33. Double blind procedure/
34. Crossover procedure/
35. Placebo/
36. (randomised or randomized or placebo or randomly or trial or groups).ti,ab.
37. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. animal/
39. human/
40. 37 not (37 and 38)
41. 37 not 40
42. 28 not 41

Appendix 4. CENTRAL search strategy

#1 MeSH descriptor [Adrenal Cortex Hormones] explode all trees
#2 (corticoid* or corticosteroid* or glucocorticoid*):ti,ab,kw
#3 (betamethasone or fludrocortisone or cortisone or deflazacort or dexamethasone or hydrocortisone or methylprednisolone or prednisolone or triamcinolone):ti,ab,kw
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor [Pain] explode all trees
#6 MeSH descriptor [Pain Measurement] this term only
#7 MeSH descriptor [Analgeia] explode all trees
#8 MeSH descriptor [Analgesics] explode all trees
#9 MeSH descriptor [Quality of Life] this term only
#10 (pain or analges* or Quality near/3 Life):ti,ab,kw
#11 (#5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 (malignan* OR malignancy OR tumor* OR tumour* OR cancer* OR carcinoma*):ti,ab,kw
#13 MeSH descriptor [Neoplasms] explode all trees
#14 (#12 OR #1)
#15 (#4 AND #11 AND #14)

WHAT'S NEW

Last assessed as up-to-date: 29 September 2014.

Date	Event	Description
28 April 2015	Amended	Corrections made to author affiliations.

CONTRIBUTIONS OF AUTHORS

All authors initiated and designed the study and drafted the protocol. All authors extracted the data and/or conducted the 'Risk of bias' assessment.

AH, SK, AL and PG supervised the statistical analysis. 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

AH, PG, SK, AL, S-JM, KR and JH all have no relevant conflicts of interest to declare.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the methods of the review to include the GRADE approach to assess the overall quality of the evidence for the primary outcome. There were insufficient data to evaluate different subgroups for this review, however we will perform subgroup analysis in any updated versions of this review. We will perform intention-to-treat analysis where possible in future updates.