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Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults (Review)

Haywood A, Duc J, Good P, Khan S, Rickett K, Vayne-Bossert P, Hardy JR

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[Intervention Review]

Systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults

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ABSTRACT

Background

Dyspnoea is a common symptom in advanced cancer, with a prevalence of up to 70% among patients at end of life. The cause of dyspnoea is often multifactorial, and may cause considerable psychological distress and suffering. Dyspnoea is often undertreated and good symptom control is less frequently achieved in people with dyspnoea than in people with other symptoms of advanced cancer, such as pain and nausea. The exact mechanism of action of corticosteroids in managing dyspnoea is unclear, yet corticosteroids are commonly used in palliative care for a variety of non-specific indications, including pain, nausea, anorexia, fatigue and low mood, despite being associated with a wide range of adverse effects. In view of their widespread use, it is important to seek evidence of the effects of corticosteroids for the management of cancer-related dyspnoea.

Objectives

To assess the effects of systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, Science Citation Index Web of Science, Latin America and Caribbean Health Sciences (LILACS) and clinical trial registries, from inception to 25 January 2018.

Selection criteria

We included randomised controlled trials that included adults aged 18 years and above. We included participants with cancer-related dyspnoea when randomised to systemic corticosteroids (at any dose) administered for the relief of cancer-related dyspnoea or any other indication, compared to placebo, standard or alternative treatment.

Data collection and analysis

Five review authors independently assessed trial quality and three extracted data. We used means and standard deviations for each outcome to report the mean difference (MD) with 95% confidence interval (CI). We assessed the risk of bias and quality of evidence using GRADE. We extracted primary outcomes of sensory-perceptual experience of dyspnoea (intensity of dyspnoea), affective distress (quality

of dyspnoea) and symptom impact (burden of dyspnoea or impact on function) and secondary outcomes of serious adverse events, participant satisfaction with treatment and participant withdrawal from trial.

Main results

Two studies met the inclusion criteria, enrolling 157 participants (37 participants in one study and 120 in the other study), of whom 114 were included in the analyses. The studies compared oral dexamethasone to placebo, followed by an open-label phase in one study. One study lasted seven days, and the duration of the other study was 15 days.

We were unable to conduct many of our predetermined analyses due to different agents, dosages, comparators and outcome measures, routes of drug delivery, measurement scales and time points. Subgroup analysis according to type of cancer was not possible.

Primary outcomes

We included two studies (114 participants) with data at one week in the meta-analysis for change in dyspnoea intensity/dyspnoea relief from baseline. Corticosteroid therapy with dexamethasone resulted in an MD of lower dyspnoea intensity compared to placebo at one week (MD –0.85 lower dyspnoea (scale 0–10; lower score = less breathlessness), 95% CI -1.73 to 0.03; very low-quality evidence), although we were uncertain as to whether corticosteroids had an important effect on dyspnoea as results were imprecise. We downgraded the quality of evidence by three levels from high to very low due to very serious study limitations and imprecision.

One study measured affective distress (quality of dyspnoea) and results were similar between groups (29 participants; very low-quality evidence). We downgraded the quality of the evidence three times for imprecision, inconsistency, and serious study limitations.

Both studies assessed symptom impact (burden of dyspnoea or impact on function) (113 participants; very low-quality evidence). In one study, it was unclear whether dexamethasone had an effect on dyspnoea as results were imprecise. The second study showed more improvement for physical well-being scores at days eight and 15 in the dexamethasone group compared with the control group, but there was no evidence of a difference for FACIT social/family, emotional or functional scales. We downgraded the quality of the evidence three times for imprecision, inconsistency, and serious study limitations.

Secondary outcomes

Due to the lack of homogenous outcome measures and inconsistency in reporting, we could not perform quantitative analysis for any secondary outcomes. In both studies, the frequency of adverse events was similar between groups, and corticosteroids were generally well tolerated. The withdrawal rates for the two studies were 15% and 36%. Reasons for withdrawal included lost to follow-up, participant or carer (or both) refusal, and death due to disease progression. We downgraded the quality of evidence for these secondary outcomes by three levels from high to very low due to serious study limitations, inconsistency and imprecision.

Neither study examined participant satisfaction with treatment.

Authors' conclusions

There are few studies assessing the effects of systemic corticosteroids on cancer-related dyspnoea in adults with cancer. We judged the evidence to be of very low quality that neither supported nor refuted corticosteroid use in this population. Further high-quality studies are needed to determine if corticosteroids are efficacious in this setting.

PLAIN LANGUAGE SUMMARY

Corticosteroids for the management of cancer-related breathlessness in adults with cancer

Background

Breathlessness (dyspnoea) is a common symptom in advanced cancer. Breathlessness may be due to a combination of different causes including lung cancer, metastatic disease elsewhere in the body (for example, cancer in the abdomen pushing up the diaphragm), or cancer-related conditions affecting the nerves or muscles associated with breathing. Pain and psychological conditions (such as fear and anxiety) or pre-existing lung disease may make symptoms worse. People with cancer report breathlessness is associated with higher psychological distress and poorer quality of life. Medicines can be used to treat breathlessness in this population, and one common medicine used is corticosteroids. In this review, we evaluated how effective systemic corticosteroids are in treating cancer-related breathlessness in adults, compared to any control.

Study characteristics

We searched the literature in January 2018. We found two studies, enrolling 157 participants in total, that tested the effect of systemic corticosteroids on breathlessness in adults with cancer, compared to a dummy medicine (placebo). One study lasted seven days, and the other study lasted 15 days. Both studies compared a corticosteroid (oral (by mouth) dexamethasone) to a dummy medicine with no properties to reduce breathlessness, which we included in our analyses.

We were interested in the primary outcomes of participant-reported breathlessness intensity, quality and burden. We were also interested in the secondary outcomes of serious side effects, participant satisfaction with treatment and participant withdrawal from trial.

Key results

We could not complete many of our planned analyses due to the small number of studies, the different medicines and comparisons, and outcomes that the studies reported. We did conduct one analysis of 114 participants to assess change in breathlessness intensity/relief from baseline. We found that corticosteroids had no beneficial effect compared to a dummy medicine on reducing breathlessness intensity in people with cancer.

We found that the frequency of side effects was similar between groups, and corticosteroids were generally well tolerated. None of the studies measured participant satisfaction with treatment. Participant withdrawals were 15% and 36% in the two studies.

Quality of evidence

The current evidence was based on only two studies with a small number of participants. We rated the quality of the evidence from these 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 judged the quality of the evidence in this review to be very low, downgraded due to problems with study quality and too few data. We are very uncertain of the results. More high-quality studies are needed to determine if corticosteroids are effective for dyspnoea in people with cancer.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Systemic corticosteroids compared with placebo for the management of cancer-related breathlessness (dyspnoea)

Systemic corticosteroids compared with placebo for the management of cancer-related breathlessness (dyspnoea)

Patient or population: adults with cancer-related breathlessness (dyspnoea)

Settings: inpatients and outpatients

Intervention: dexamethasone

Comparison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Dexamethasone				
Breathlessness (dyspnoea) at 1 week (intensity) Scale 0–10; lower score = less breathlessness	The mean score for intensity of breathlessness at baseline was 4.7 and 3 for the control groups. The mean difference in the intensity of breathlessness at 1 week was −1.3 and −0.58 for the control groups.	The mean score for intensity of breathlessness at baseline was 5.0 and 4.09 for the intervention groups. The mean difference in the intensity of breathlessness at 1 week was −1.8 and −1.56 for the intervention groups.	—	114 (2 studies)	⊕⊖⊖⊖ **Very low**[a]	—
Breathlessness (dyspnoea) at 1 week (quality) Cancer Dyspnea Scale	Small reduction in effort, discomfort and anxiety.	Small reduction in effort and anxiety, with a slight increase in discomfort.	—	29 (1 study)	⊕⊖⊖⊖ **Very low**[b]	
Breathlessness (dyspnoea) at 1 week (burden)	Different measurement tools used in each study. Significant reduction in burden at 1 week for dexamethasone group compared to control group observed only for the FACIT physical subscale in one study.		—	113 (2 studies)	⊕⊖⊖⊖ **Very low**[c]	

EORTC QLQ-C30, FACIT, ESAS						
Adverse events	Severity of adverse events was not properly defined making it difficult to assess this outcome. The frequency of adverse events was similar between groups. The intervention was well tolerated in corticosteroid group.		—	157 (2 studies)	⊕⊖⊖⊖ **Very low**[c]	
Patient satisfaction with treatment	No data	No data	No data	No data	No data	Not possible to GRADE this outcome due to a lack of data
Participant withdrawal from trial	54 withdrawals out of 173 participants (31%) for the two studies. Rate of withdrawal was similar between placebo and dexamethasone groups.		—	173 (2 studies)	⊕⊖⊖⊖ **Very low**[c]	

CI: confidence interval.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect;

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded the quality of the evidence once for imprecision due to the small number of participants in the included studies, and twice for very serious study limitations (likely selection and attrition bias).

[b]Downgraded the quality of the evidence three times: once for imprecision due to the small number of participants in the included study, once for inconsistency, and once for serious study limitations (likely attrition bias).

[c]Downgraded the quality of the evidence three times: once for imprecision due to the small number of participants in the included studies, once for inconsistency, and once for serious study limitations (likely selection and attrition bias).

BACKGROUND

Description of the condition

Dyspnoea (breathlessness) is a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (American Thoracic Society 1999). It is "one of the most common and most feared symptoms amongst cancer patients" (Hui 2013), increases with disease progression (Solano 2006), and occurs in up to 70% of people with advanced cancer at end of life (Bruera 2000; Dudgeon 2001; Hui 2015; Kutner 2001; Mercadante 2017; Tishelman 2007; Viola 2008). Dyspnoea has a negative impact on a patient's quality of life. It interferes with daily life activities (ERS Monograph 2016; Mercadante 2017; Tanaka 2002a), and has been associated with fatigue, anxiety and depression, and decreased function and quality of life, since it may precipitate both physical and psychological distress (Ben-Aharon 2012; ERS Monograph 2016; Mularski 2010; Seow 2011; Tanaka 2002b; Williams 2006). It may cause significant suffering for patients and their families (Bernhard 1991; Booth 2008), and be a source of substantial healthcare expenditure (Booth 2003; Booth 2015; ERS Monograph 2016; Johnson 2014; Seamark 2004; Skaug 2009). It is frightening for many patients who report feeling that they are suffocating, choking (Skevington 1997), short of breath, unable to get a breath or drowning (eTG 2016; Kloke 2015; Parshall 2012; Wilcock 2002).

Good symptom control is less frequently achieved in people with dyspnoea than in people with other symptoms of advanced cancer, such as pain and nausea (Yennurajalingam 2015). When disease is advanced, patients may experience episodes of acute breathlessness (Mercadante 2017), "superimposed on a background level of continuous breathlessness" (Johnson 2016). Episodes of breathlessness may be predictable (generally caused by physical exertion) or unpredictable (Johnson 2016; Simon 1990).

The pathophysiology of dyspnoea is complex and is not fully understood (Booth 2008; Burki 2010; ERS Monograph 2016; Hui 2013; Manning 1995; Parshall 2012). A constellation of sensory inputs may contribute to the multiple sensations of dyspnoea, which may include the "sensations of work or effort, tightness, and air hunger/unsatisfied inspiration" (Parshall 2012). Tightness is relatively specific to stimulation of airway receptors in conjunction with bronchoconstriction, while intensity of air hunger/unsatisfied inspiration is magnified by imbalances among inspiratory drive, efferent activation (outgoing motor command from the brain), and feedback from afferent receptors throughout the respiratory system (Parshall 2012). In the palliative care setting, the cause of dyspnoea is often multifactorial (ERS Monograph 2016), with an unpredictable response to treatment (Lin 2012). Indeed, the subjective experience of dyspnoea is influenced by "multiple physical, psychological, social and spiritual factors, and may induce secondary physiological and behavioral responses" (Lok 2016). The concept of 'total dyspnoea' – similar to that of 'total pain' – may provide a framework in the multidimensional assessment and management of breathlessness (Abernethy 2008; ERS Monograph 2016), as each of these factors may contribute to the perceived severity of a person's dyspnoea (Banzett 2008; Chin 2016; De Peuter 2004; Evans 2002; Parshall 2012).

Common pulmonary causes of dyspnoea in cancer may include progressive metastatic disease, lymphangitis carcinomatosa, pleuritis carcinomatosa, pleural effusion, interstitial lung disease, parenchymal lung involvement, pulmonary embolism, infection, atelectasis, airway obstruction and pre-existing pulmonary disease (Booth 2014; Chan 2004; eTG 2016; Kvale 2007; Manning 1995). Systemic causes of dyspnoea may include anaemia, hypoxaemia, uraemia or acidaemia, congestive cardiac failure, pericarditis or pericardial effusion, pulmonary hypertension, sepsis, cardiovascular/physical deconditioning, muscle weakness or neuromuscular conditions (Booth 2014; Parshall 2012). Other common causes include pain, ascites, hepatomegaly, obesity, lymphadenopathy, superior vena cava obstruction, treatment-related adverse effects (e.g. pneumonitis or fibrosis following chemotherapy or radiotherapy) and pre-existing lung disease (e.g. asthma or chronic obstructive pulmonary disease (COPD)). Psychological drivers or psychogenic causes, such as panic disorder, anxiety and distress, may also contribute to the genesis of breathlessness or further compound symptoms, or both (Giardino 2010; Kunik 2005; Moore 1999; Nardi 2009; Parshall 2012; Perna 2004; Rassovsky 2006; Smoller 1996; Williams 2010). The symptoms of dyspnoea are usually managed following careful assessment of the potential cause and impact on the person's experience, and treatment of any reversible causes (Chin 2016; Manning 1995). Dyspnoea that appears suddenly is more likely to be reversible than progressive longstanding dyspnoea that is related to disease progression as it is likely to be related to a treatable acute event such as infection or pulmonary embolism (eTG 2016). Therefore, it is important to consider assessment for potentially reversible causes of dyspnoea (eTG 2016). As the sensation of dyspnoea is mediated by the central nervous system (Herigstad 2011), strategies that address psychosocial stressors or psychological triggers are also key, to "reduce the impact of the sensation of breathlessness, even when it cannot be removed" (Booth 2015). Therefore, non-pharmacological techniques are of central importance in the management of breathlessness (Booth 2015; Farquhar 2014), and active management of psychosocial issues such as anxiety, depression, carer stress and distress, and the implementation of non-pharmacological self-management strategies such as physical and mental activity, relaxation techniques, breathing exercises, education and information should be a priority (Booth 2015). Modification of the patient's environment, activity pacing and energy conservation (Sackley 2009), and anxiety reduction training (Lai 2010), may also maximise comfort, improve respiratory efficiency, and reduce fear and anxiety (De Peuter 2004; eTG 2016; Farquhar 2014; Higginson 2014; Kamal 2012). For example, the use of a fan is one of the most important and effective non-pharmacological interventions in the management and relief of breathlessness (Bausewein 2008; Galbraith 2010). Johnson and colleagues postulated that "as skeletal muscle (not limited to the muscles of respiration) is intimately involved in the genesis of breathlessness, reduced activity leads to reduced muscle bulk so that over time, breathlessness will be triggered by less and less exertion breathlessness" (Johnson 2014). Exercise-based rehabilitation, a complex intervention that incorporates cognitive and behavioural management strategies (Parshall 2012), pulmonary rehabilitation, and other integrated, complex intervention services for breathlessness may thus be of use or benefit for people with dyspnoea (Booth 2006; Booth 2011; Farquhar 2010; Farquhar 2014). From an anxiety reduction training point of view, cognitive behavioural therapy, simple relaxation therapy, distraction methods, music or mindfulness may also help people feel more control (Lok 2016), and 'gain mastery' over their breathlessness (Booth 2014). For severe,

chronic, refractory or intractable dyspnoea, non-pharmacological methods may be supplemented by pharmacological treatments. These may include oral or parenteral opioids (Ben-Aharon 2012; Johnson 2014; Parshall 2012; Viola 2008), benzodiazepines (if the person is experiencing significant anxiety), alongside other non-pharmacological strategies (ERS Monograph 2016), oxygen (if a person is hypoxic) (Parshall 2012), and steroids (eTG 2016; Kamal 2012). Systemic corticosteroids are also commonly used for specific antitumour effect in conditions such as lymphangitis carcinomatosa or airway obstruction by tumour (Elsayem 2007).

Description of the intervention

Systemic corticosteroids are commonly used in palliative care practice for symptom control of fatigue (Yennurajalingam 2013), nausea and vomiting (Vayne-Bossert 2017), anorexia, cachexia and pain, relief of spinal cord compression, reduction of vasogenic oedema from brain metastasis and resolution from malignant bowel obstruction (Hardy 2001; Lin 2012; Mercadante 2001; Paulsen 2014; Shih 2007). The corticosteroid used most commonly in palliative care is dexamethasone, due to its potency, long duration of action allowing once-daily dosing and the ability to administer it subcutaneously (eTG 2016). The balance of benefit versus risk of harm must be carefully considered. Adverse effects are usually dose and duration related, and include insomnia, mental disturbances (including depression, mania, psychosis or delirium), hyperglycaemia, increased susceptibility to infection, gastric irritation, Cushingoid features and proximal myopathy (eTG 2016).

How the intervention might work

Dyspnoea, or the sensation of breathlessness, is closely related to the sensation of respiratory effort experienced via the activation of proprioceptive pathways during respiration (Dorman 2009). While the respiratory centre in the medulla controls breathing, dyspnoea is the result of cortical stimulation (Dorman 2009; Hui 2013). Both lung and central chemoreceptors detect abnormalities in blood gases (hypoxia, increased partial pressure of carbon dioxide), and together with lung and respiratory muscle mechanoreceptors (responding to stretching and pulmonary irritants), stimulate the medullary respiratory centre. The activity of the chemoreceptors, mechanoreceptors and respiratory centre can also stimulate the cerebral cortex, thus directly contributing to the sensation of dyspnoea (Dorman 2009; Hui 2013). Cancer, in a similar manner to COPD, is characterised by a significant inflammatory component that includes airway wall infiltration of macrophages and T lymphocytes, increased lung tumour necrosis factor-alpha and interleukin (IL)-8, elevated serum IL-6, C-reactive protein, increased peripheral neutrophil activation (Hui 2016), and inflammatory cytokines (Wang 2010). Corticosteroids have potent anti-inflammatory activity that may explain their ability to alleviate dyspnoea, as people with advanced cancer often have an elevated inflammatory response that can contribute to dyspnoea both peripherally and centrally (Hui 2016). The usefulness of the anti-inflammatory activity of corticosteroids in managing acute exacerbations of COPD is well established (Barczyk 2004; Brightling 2000; Culpitt 2003; Falk 2008; Wood-Baker 2005). However, as dyspnoea is likely to be multifactorial in the context of cancer, corticosteroids may work more effectively in some instances (e.g. where there is a process of inflammation), but not as well in other instances.

Why it is important to do this review

Dyspnoea is a common and devastating symptom in people with cancer that often worsens in the last months of life and may be difficult to treat (Dudgeon 2001; Hui 2015; Hui 2016; Mercadante 2017; Tishelman 2007). Systemic corticosteroids are commonly used in palliative care, particularly for people with advanced malignant disease, for a variety of symptom control indications including pain, nausea, vomiting, anorexia, fatigue and dyspnoea (Lin 2012; Shih 2007), despite the fact that steroids may be associated with significant adverse effects (Matsuo 2011), especially following long-term use. However, there is little objective evidence in the literature to support the use of systemic corticosteroids for symptom control (ERS Monograph 2016; Viola 2008), and concerns have been raised about the 'uncontrolled' use of steroids in people with cancer (Haywood 2015; Levy 2016; Vayne-Bossert 2017).

OBJECTIVES

To assess the effects of systemic corticosteroids for the management of cancer-related breathlessness (dyspnoea) in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised double-blind controlled trials (RCTs) with full journal publication, as well as online clinical trial results and summaries of otherwise unpublished clinical trials or abstracts with sufficient data for analysis. We excluded studies that were non-randomised, case reports and clinical observations, and short abstracts (usually meeting reports).

Types of participants

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

Types of interventions

Systemic corticosteroids at any dose, administered for the relief of cancer-related dyspnoea or other cancer-related symptoms (where dyspnoea was also measured), compared to placebo or any active comparator including supportive care or alternate non-pharmacological treatment. We excluded studies assessing inhaled corticosteroids.

Types of outcome measures

Primary outcomes

- Our primary outcome was the effect of systemic corticosteroids on breathlessness (dyspnoea), as assessed by the American Thoracic Society 'Domains of Dyspnoea Measurement' (Parshall 2012).

Domain 1: Sensory-perceptual experience – intensity of dyspnoea

Definition: measures of what breathing feels like to the patient or research subject. Examples include:

- single-item ratings of intensity such as the Borg scale (Borg 1982), Visual Analogue Scale (VAS) (Gift 1989).

Domain 2: Affective distress – quality of dyspnoea

Definition: measures of how distressing breathing feels. Focus can be either immediate (e.g. unpleasantness) or evaluative (e.g. judgements of meaning or consequence). Examples include:

- single-item ratings of severity of distress or unpleasantness; and
- multi-item scales of emotional responses such as anxiety such as the Hospital Anxiety and Depression Scale (HADS), or State-Trait Anxiety Inventory (STAI).

Domain 3: Symptom impact-burden of dyspnoea/impact on function

Definition: measures of how dyspnoea affects functional ability, employment (disability), quality of life or health status. Examples include:

- unidimensional rating of disability or activity limitation such as the Medical Research Council (MRC) Dyspnoea Scale (Mahler 1988);
- unidimensional or multidimensional ratings of functional ability (Pulmonary Functional Status and Dyspnoea Questionnaire (PFSDQ) (Lareau 1998); and
- multidimensional scales of quality of life/health status.

We aimed to use both standardised, mean pre–post change in breathlessness scores after the intervention (comparator), as well as post-intervention standardised mean difference (SMD) in breathlessness scores between intervention and comparator groups. We aimed to also summarise breathlessness outcomes separately, to delineate between breathlessness measured 'now' versus 'on average over the past 24 hours' or as described by the validated outcome measure.

We aimed to obtain standardised means when seeking to summarise and compare studies that use different breathlessness measures (regardless of the scoring system).

Secondary outcomes

- Serious adverse events – any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect (ICH 1994).
- Participant satisfaction with treatment.
- Participant withdrawal.

Search methods for identification of studies

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

Electronic searches

We searched the following databases without language restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) 2018, Issue 1 in the Cochrane Library (Appendix 1);
- MEDLINE (Ovid) 1966 to 25 January 2018 (Appendix 2);
- Embase.com 1970 to 25 January 2018 (Appendix 3);
- CINAHL (EBSCO) 1982 to 25 January 2018 (Appendix 4);
- Science Citation Index (ISI Web of Science) 1899 to 25 January 2018 (Appendix 5);
- Latin America and Caribbean Health Sciences (LILACS) 1982 to 25 January 2018 (Appendix 6).

Medical subject headings (MeSH) or equivalent and text word terms were used. Where appropriate, MeSH terms and other subject headings were exploded. We applied a modified version of the Cochrane filter for the identification of RCTs, as published in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Searches were tailored to individual databases.

Searching other resources

We searched ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we checked the bibliographic references and cited sources of any relevant identified studies to find additional trials not identified by the electronic searches. 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 source the unpublished paper. One of the review authors (KR), who is an Information Specialist, conducted the searches. All searches are current as of 25 January 2018.

Data collection and analysis

Selection of studies

Four review authors (JH, PG, PVB, JD) independently assessed the titles and abstracts of all 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 (Moher 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.

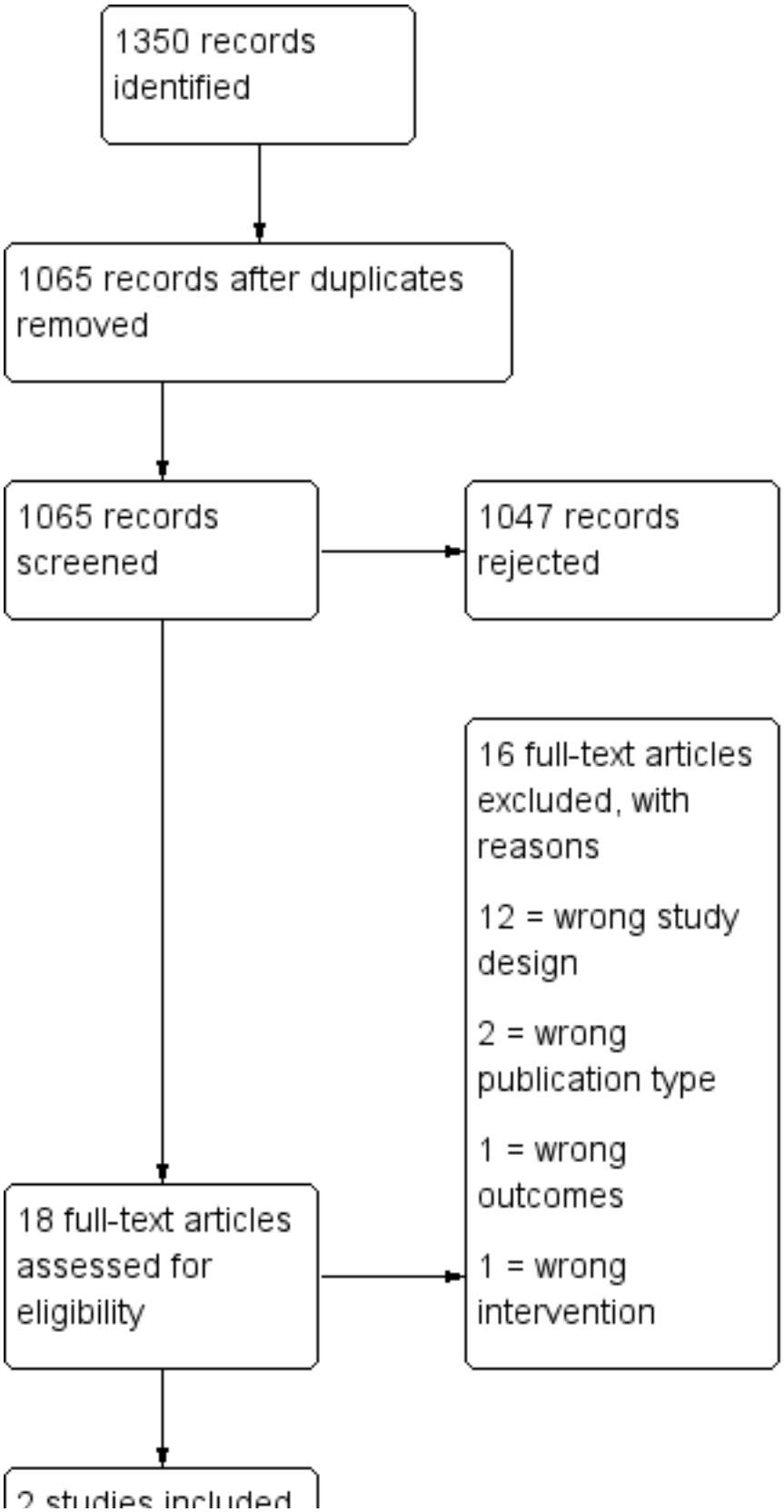
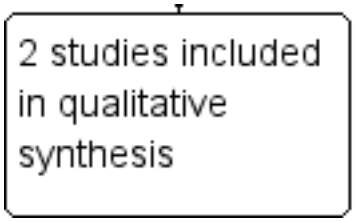


Figure 1. (Continued)



Data extraction and management

Three review authors (AH, SK, JD) independently extracted data using a standard form, and checked for agreement before entry into Review Manager 5 (Review Manager 2014). The authors extracted data that included information about the year of the 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 dyspnoea and other relevant outcomes), withdrawals and adverse events. We resolved potential disagreements by discussion.

Assessment of risk of bias in included studies

Five review authors (AH, SK, JH, PG, JD) independently assessed the risk of bias of each included study 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.

- 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). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- 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); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- 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-blinded were considered to have high risk of bias.
- 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.
- 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 or investigators used 'baseline observation carried forward' analysis, or both); unclear risk of bias (investigators used 'last observation carried forward' analysis); or high risk of bias (investigators used 'completer' analysis).
- 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 were 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 prespecified (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.
- Size of study (checking for bias 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 between groups, we estimated and compared the risk ratio (RR) and 95% confidence intervals (CIs). For continuous outcomes, we measured arithmetic mean and standard deviation (SD) and reported the mean difference (MD) between groups, with 95% CI. When an outcome was derived with different instruments measuring the same construct, we used the SMD with 95% CIs.

Unit of analysis issues

We only included studies that randomised individual participants. 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 (ITT) analyses.

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 attempted to assess 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 do so due to the lack of studies.

Data synthesis

We entered the data extracted from the included studies into Review Manager 5, which we used for data synthesis (Review Manager 2014). We had planned to pool data for each continuous outcome and calculate the MD as an estimate of effect size, using a random-effects model with 95% CIs, but were unable to do so due to the lack of studies.

Quality of the evidence

Two review authors (AH, SK) planned to independently rate the quality of evidence for dyspnoea relief using the three 'Domains of Dyspnoea Measurement' of dyspnoea, serious adverse events, participant satisfaction with treatment, and participant withdrawal from trial. We used the GRADE system to assess the quality of the available evidence using the GRADEpro Guideline Development Tool software (GRADEpro GDT 2015), 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.

The GRADE approach employs 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, namely:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately 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 effect.

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Higgins 2011).

- High: randomised trials or double-upgraded observational studies.
- Moderate: downgraded randomised trials or upgraded observational studies.
- Low: double-downgraded randomised trials or observational studies.
- Very low: triple-downgraded randomised trials, downgraded observational studies or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide CIs);
- high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

- large magnitude of effect;
- all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
- dose–response gradient.

We decreased the grade rating by one (–1) or two (–2) (up to a maximum of –3 to 'very low') for:

- serious (–1) or very serious (–2) limitation to study quality;
- important inconsistency (–1);
- some (–1) or major (–2) uncertainty about directness;
- imprecise or sparse data (–1); or
- high probability of reporting bias (–1).

'Summary of findings' table

We included a ‘Summary of findings’ table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on dyspnoea relief, as measured by the three domains of dyspnoea, i.e. intensity of dyspnoea (sensory-perceptual experience, as measured by ratings of breathlessness intensity), quality of dyspnoea (affective distress, as measured by ratings of severity of distress), and burden of breathlessness/ impact on function (as measured by ratings of functional ability, quality of life or health status), adverse events, patient satisfaction with treatment, and participant withdrawal from trial.

Subgroup analysis and investigation of heterogeneity

There were insufficient data available to perform subgroup analyses based on type of systemic 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 outlines the number of records identified in the search and screening process for these papers (Figure 1). In the initial database search, we identified 1350 records. None were identified through other sources. Of these, 285 were duplicates and we rejected 1047 based on information given in the title and abstract. We identified 18 publications for full-text retrieval, and excluded 16 of these records during screening. The reasons for exclusion of each study are described in the Characteristics of excluded studies table. Two placebo-controlled studies met the inclusion criteria for this review (Hui 2016; Yennurajalingam 2013). We evaluated the results relative to dyspnoea intensity/dyspnoea relief at one week from baseline (day seven and eight), since this was the only time that could be standardised across both trials.

Included studies

We identified two studies meeting the inclusion criteria (Hui 2016; Yennurajalingam 2013). These two studies enrolled 157 participants (37 and 120 participants per study), of whom 114 were included in the analyses. The studies compared oral dexamethasone to placebo. One study lasted seven days, and the duration of the other study was 15 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 corticosteroids were used for cancer-related dyspnoea, or any other indication. The studies assessed dyspnoea relief intensity, quality and burden/impact on function.

Dyspnoea as a primary endpoint

Of the two included studies, one measured change in dyspnoea intensity as a primary endpoint (Hui 2016). The other 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

Both studies used oral dexamethasone. One study compared dexamethasone (8 mg twice a day for four days, then 4 mg twice a day for three days) to placebo (Hui 2016). The other study compared dexamethasone (8 mg/day) to placebo (Yennurajalingam 2013).

Dyspnoea measurement tools

The studies used different measurement tools to measure dyspnoea relief intensity, quality, burden/impact on function and quality of life.

- Dyspnea Numeric Rating Scale 'now' (NRS) 0 to 10 (0 = no shortness of breath) (Hui 2016).
- Edmonton Symptom Assessment Scale (ESAS) 0 to 10 (0 = no shortness of breath) – dyspnoea mean past 24 hours; fatigue, drowsiness and appetite (Hui 2016; Yennurajalingam 2013).
- Modified Dyspnea Borg Scale (0 to 10) (0 = no shortness of breath at all) (Hui 2016).
- Cancer Dyspnea Scale 1 to 5 (higher score indicates a greater intensity of dyspnoea) (Hui 2016).
- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 – dyspnoea past week (Hui 2016).
- Global Symptom Evaluation (Hui 2016).

Excluded studies

We excluded 16 studies and 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 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 item presented as percentages across all included studies.

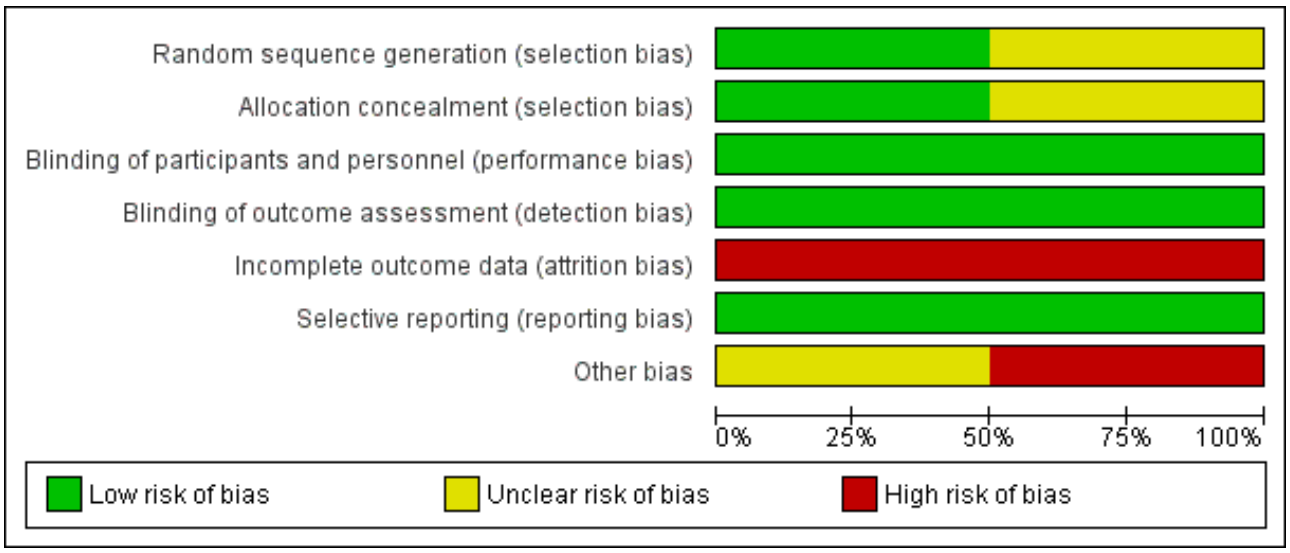
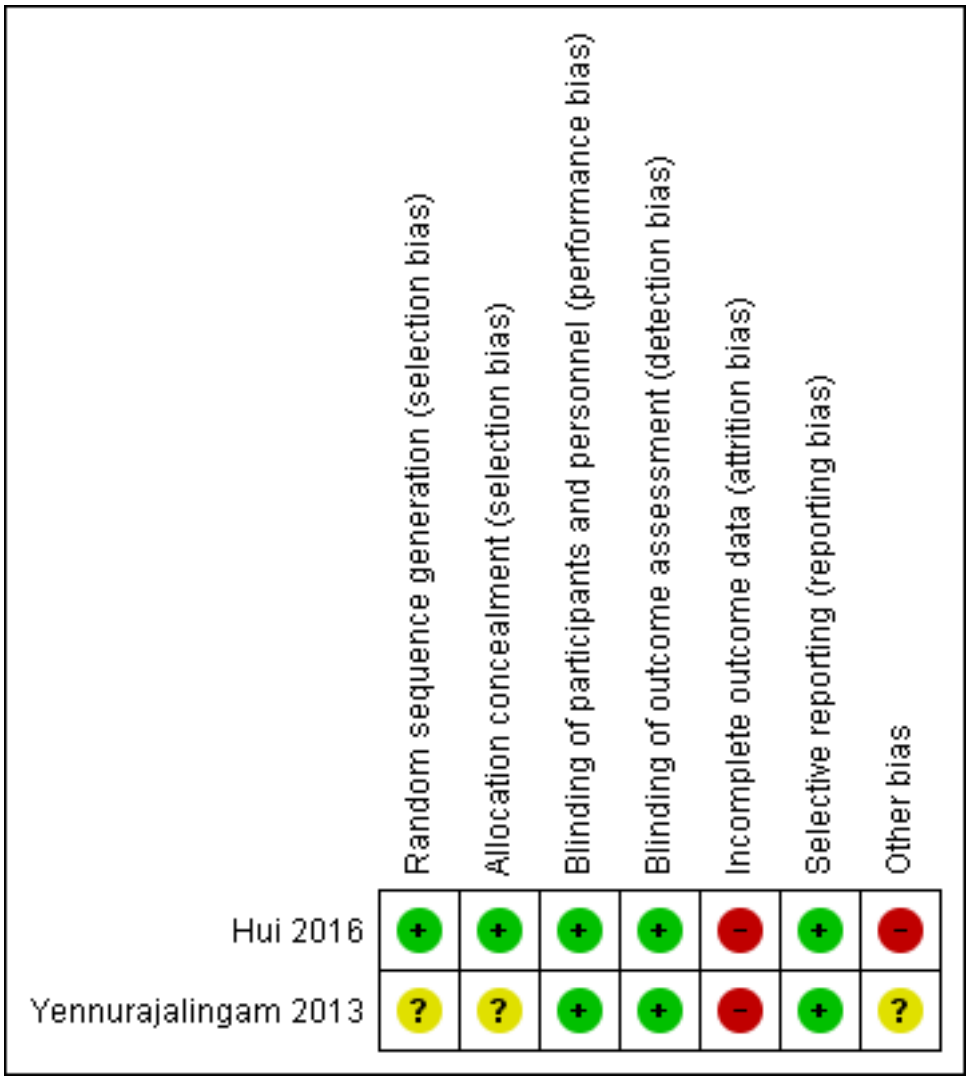


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Both included studies reported that they were randomised. Only one study described the method used to generate their random sequence (Hui 2016), thus we judged the second study to have an unclear risk of bias (Yennurajalingam 2013).

Allocation concealment

For allocation concealment, only one study used pharmacy randomisation and was at low risk in this regard (Hui 2016). The other study was at unclear risk, as there was insufficient information on the method of allocation concealment (Yennurajalingam 2013).

Blinding

Both studies were at low risk, with blinding of participants, personnel and outcome assessments reported (Hui 2016; Yennurajalingam 2013).

Incomplete outcome data

The two studies were at high risk for attrition bias, as greater than 10% of participants could not be evaluated, thereby leaving a gap in the evidence (i.e. 6/19 participants receiving the intervention and 3/18 participants receiving placebo (Hui 2016); 19/62 participants receiving the intervention, and 17/58 participants receiving placebo (Yennurajalingam 2013)).

Selective reporting

Neither study identified reporting gaps. Therefore, we judged these studies 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. Neither study was 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). The other study was at high risk of bias because of their small number

of participants (fewer than 50 participants per treatment arm) (Hui 2016).

Effects of interventions

See: **Summary of findings for the main comparison** Systemic corticosteroids compared with placebo for the management of cancer-related breathlessness (dyspnoea)

Primary outcome

Participant-reported dyspnoea intensity, quality and burden

For the meta-analysis, both studies provided change in dyspnoea intensity score (on a scale of 0 to 10; lower score = less breathlessness) and the standard deviation at one week (Hui 2016; Yennurajalingam 2013). The studies included 157 participants at baseline and 114 participants after one week of corticosteroid treatment (dexamethasone). After one week, the dexamethasone group reported less dyspnoea intensity than the control group (MD −0.85, 95% CI −1.73 to 0.03; P = 0.06; Analysis 1.1), although we were uncertain as to whether corticosteroids truly had an important effect on dyspnoea as results were imprecise.

Both studies used a numeric rating scale to assess the intensity of dyspnoea 'now' – an 11-point dyspnoea numeric rating scale (0 to 10).

We judged the quality of the evidence for the primary outcome of dyspnoea relief (intensity) to be very low (see Summary of findings for the main comparison). We downgraded the quality of the evidence once for imprecision due to the small number of participants in the included studies, and twice for very serious study limitations (likely selection and attrition bias).

One study measured affective distress/quality of dyspnoea (Hui 2016), using the Cancer Dyspnea Scale effort, discomfort and anxiety variables (Domain 2 of Parshall's 'Domains of Dyspnoea Measurement') and results were similar between groups. We judged the quality of the evidence for the primary outcome of dyspnoea relief (quality) to be very low. We downgraded the quality of the evidence three times for imprecision due to the small number of participants in the included study, inconsistency, and serious study limitations (likely attrition bias).

Both studies assessed impact of dyspnoea on function/quality of life. Hui 2016 assessed dyspnoea quality and burden/impact on function and quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36 (EORTC QLQ-C30) dyspnoea 'past week,' which favoured dexamethasone compared to placebo at day four, but not at day seven. However, it was unclear whether dexamethasone had a significant effect on dyspnoea as results were imprecise. In Yennurajalingam 2013, FACIT physical well-being scores showed significantly better improvement at days eight (P = 0.007) and 15 (P = 0.002) in the dexamethasone group compared with the control group, however there were no significant changes for FACIT social/family, emotional or functional scales. We judged the quality of the evidence for the primary outcome of dyspnoea relief (burden) to be very low. We downgraded the quality of the evidence three times for imprecision due to the small number of participants in the included studies, inconsistency, and serious study limitations (likely selection and attrition bias).

Secondary outcomes

Serious adverse events

The severity of adverse events was not properly defined, making it difficult to assess this outcome. Hence we evaluated reported 'adverse events'. In both studies, the frequency of adverse events was similar between groups, and dexamethasone was generally well tolerated. We judged the quality of the evidence for this outcome to be very low. We downgraded the quality of the evidence three times due to serious study limitations (likely selection and attrition bias), inconsistency, and imprecision due to the small number of participants in the included studies.

Participant satisfaction with treatment

Neither study measured participant satisfaction with treatment.

Participant withdrawal

There were 6/41 (15%) participant withdrawals in Hui 2016, and 48/132 (36%) in Yennurajalingam 2013. We judged the quality of the evidence for this outcome to be very low. We downgraded the quality of the evidence three times from high to very low due to serious study limitations (likely selection and attrition bias), inconsistency, and imprecision due to the small number of participants in the included studies.

DISCUSSION

Summary of main results

The objective of this systematic review was to assess the effects of corticosteroids on dyspnoea in adults with cancer-related dyspnoea. Two studies with 157 participants met the inclusion criteria, of whom 114 were evaluable. The included studies assessed dexamethasone (4 mg/day or up to 16 mg/day) compared to placebo.

Both studies were evaluated for relief of dyspnoea in the meta-analysis (Hui 2016; Yennurajalingam 2013). We reported data after one week of intervention, since this was the only time that could be standardised across both trials. The following conclusion regarding the effectiveness of corticosteroids for relief of dyspnoea should be interpreted with consideration of the small number of eligible studies with small numbers of participants in each treatment arm, and difference in dexamethasone dose. The quality of evidence was very low due to very serious study limitations and imprecision.

- There was no clear difference in favour of dexamethasone over placebo (MD −0.85, 95% −1.73 to 0.03) for dyspnoea at one week of intervention (P = 0.06).
- There were insufficient data to evaluate different subgroups, such as drug type, route of administration, dosage and different primary disease types.

Overall completeness and applicability of evidence

We identified two studies that met the inclusion criteria and included these studies in the meta-analysis for dyspnoea relief/change in dyspnoea intensity from baseline. There was a lack of studies for planned comparisons, and insufficient data for subgroup analyses. The results were also influenced by differences in dosages, comparators and heterogeneity of study populations. The studies excluded people with overlying conditions that would be expected to respond to corticosteroids (e.g. COPD and superior

vena cava obstruction). Comparators included in the meta-analysis included dexamethasone compared to placebo. We also included trials where dyspnoea was not the primary outcome.

Quality of the evidence

The quality of evidence for breathlessness intensity was very low, downgraded once for imprecision due to the small number of participants in the included studies, and twice for very serious study limitations (likely selection and attrition bias). Both studies measured participant-reported dyspnoea relief/intensity of dyspnoea at similar time points, and burden of dyspnoea/impact on function and quality of life (Hui 2016; Yennurajalingam 2013). Only one study measured affective distress/quality of dyspnoea (Hui 2016). We judged the quality of the evidence for the outcomes breathlessness quality and burden to be very low, downgraded three times for imprecision due to the small number of participants in the included studies, inconsistency, and serious study limitations.

We judged the quality of the evidence for the outcomes adverse events and withdrawals to be very low, downgraded three times due to serious study (likely selection and attrition bias), inconsistency, and imprecision due to the small number of participants in the included studies. Neither study measured participant satisfaction with treatment.

Other concerns regarding quality of the evidence included the fact that one study was an inadequately powered pilot study with greater than 10% dropouts in both arms prior to day seven (Hui 2016). The other study had a very high participant withdrawal from trial, with approximately 30% dropouts by day 15 (Yennurajalingam 2013). Therefore, the current body of evidence does not allow a robust conclusion. We have very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect.

Potential biases in the review process

To minimise bias, three review authors independently extracted data and five authors assessed risk of bias. Due to the lack of studies we were unable to determine if there was evidence of small-study effects.

Agreements and disagreements with other studies or reviews

We found no other studies or reviews that assessed the quality of evidence and effects of systemic corticosteroid use for the management of cancer-related dyspnoea in adults.

AUTHORS' CONCLUSIONS

Implications for practice

For people with dyspnoea

There is insufficient evidence to support or refute the suggestion that systemic corticosteroids have any efficacy in cancer-related breathlessness (dyspnoea) in adults.

For clinicians

There is insufficient evidence to support or refute the suggestion that systemic corticosteroids have any efficacy in cancer-related breathlessness (dyspnoea) in adults. This may be particularly relevant when considering the potential toxicity of corticosteroids, especially following prolonged use.

For policy makers

There is insufficient evidence to support or refute the suggestion that systemic corticosteroids have any efficacy in cancer-related breathlessness (dyspnoea) in adults.

For funders

There is insufficient evidence to support or refute the suggestion that systemic corticosteroids have any efficacy in cancer-related breathlessness (dyspnoea) in adults (that is not related to a number of specific respiratory or inflammatory (or both) conditions).

Implications for research

General implications

This review has highlighted a marked paucity of research in the subject area. Future robust, double-blind randomised trials with significant numbers of participants (e.g. over 200 per treatment arm) are needed to evaluate the safety and effectiveness of systemic corticosteroids in the management of cancer-related dyspnoea in adults.

Design

There are few randomised controlled trials assessing the benefit of systemic corticosteroids in cancer-related dyspnoea. There is a need for further research to observe the effects of systemic corticosteroids on all three domains of dyspnoea measurement (i.e. dyspnoea intensity, dyspnoea quality and dyspnoea burden/impact on function) alongside participant satisfaction with treatment, and assessment of serious adverse events. Further trials with increased number of participants are needed to evaluate the effectiveness of corticosteroids for the management of dyspnoea in adults with cancer-related breathlessness. Comparators should include placebo versus combinations of dexamethasone with other antidyspnoea agents, since the mechanism of cancer-related dyspnoea is not well understood and involves multiple sites of action in the body.

Measurement (endpoints)

There is currently no standard outcome measure for the measurement of cancer-related dyspnoea. This must be determined prior to future studies. Appropriate time points for measuring the effect of corticosteroids on breathlessness also need to be determined.

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CHARACTERISTICS OF STUDIES

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

Hui 2016

Methods	Randomised, double-blind, parallel, placebo-controlled trial Single-institution Country: USA Year: 2013–2015 Study duration: randomised trial for 7 days with an open-label extension phase for another 7 days
Participants	37 adults (19 intervention, 18 control) with a diagnosis of cancer with clinical or radiological evidence of lung involvement. Exclusion criteria: people with delirium, oxygen saturation < 90% despite supplemental oxygen > 6 L/minute, diabetes mellitus uncontrolled on oral hypoglycaemic agents or insulin, severe anaemia, open wound that had not healed, infection requiring antibiotics or major surgery within the past 2 weeks, chronic obstructive pulmonary disease exacerbation and heart failure exacerbation, receiving active or recent chronic systemic corticosteroids (> 14 days), or using megestrol acetate, or receiving chemotherapy or expected to start within 1 week of study enrolment.
Interventions	Participants randomised into 2 groups. Intervention: dexamethasone 8 mg (2 × 4 mg capsules) orally twice a day for 4 days, then 4 mg given orally twice a day for 3 days Control: identical-appearing placebo capsules After 1 week, all participants received dexamethasone 4 mg orally twice a day for 7 days in an open-label extension.
Outcomes	Primary outcome: proportion of participants who completed the blinded phase of the study (35/37 participants). Dyspnoea assessed at baseline, days 4 (SD 2) and days 7 (SD 2) using the ESAS, Modified Dyspnea Borg Scale, Cancer Dyspnea Scale and 1 item on dyspnoea from the EORTC Quality of Life Questionnaire. Secondary outcomes: fatigue, drowsiness and appetite using ESAS.
Notes	Dexamethasone was associated with rapid improvement in dyspnoea and was well tolerated; however, sample size was small and the study was not powered for between-arm comparisons. Funding: MD Anderson Cancer Center Institutional Research Grant. Authors also supported in part from American Cancer Society Mentored Research Scholar Grant in Applied and Clinical Research and National Institutes of Health Grants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed using permuted blocks.
Allocation concealment (selection bias)	Low risk	Used a secured website for allocation that was only accessible to the study pharmacist.
Blinding of participants and personnel (performance bias)	Low risk	Placebo capsules were identical in appearance.

Hui 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both participants and research staff conducting the study assessments were blinded to the randomisation sequence and the study intervention."
Incomplete outcome data (attrition bias) All outcomes	High risk	Used 'completer' analysis. 2 participants did not complete the 7-day intervention and 4 participants did not complete from the placebo group.
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 Outpatients at 3 study centres Country: USA Year: not described Study duration: 14 days
Participants	120 (62 intervention, 58 control) people with advanced cancer with ≥ 3 symptoms during the previous 24 hours (e.g. fatigue, pain, nausea, loss of appetite, depression, anxiety or sleep disturbance) with mean intensity of ≥ 4/10 on the ESAS.
Interventions	Participants randomised into 2 groups Intervention: dexamethasone 4 mg orally twice per day for 14 days. Control: placebo orally twice per day for 14 days.
Outcomes	Primary outcome: fatigue, measured by a change in the FACIT-F subscale from baseline to day 15. Secondary outcomes: anorexia, anxiety, depression, shortness of breath and symptom distress scores. Used the FACIT-F, ESAS, Hospital Anxiety and Depression Scale, and Functional Assessment of Cancer Therapy-Anorexia-Cachexia instruments.
Notes	Dexamethasone was more effective than placebo in improving cancer-related fatigue and quality of life. There was a non-significant improvement in shortness of breath at days 8 and 15. Funding: American Cancer Society Mentored Research Scholar Grant.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not specified.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described.

Yennurajalingam 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
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	19/62 participants receiving dexamethasone were not evaluable. 17/58 participants receiving placebo were not evaluable.
Selective reporting (reporting bias)	Low risk	None detected
Other bias	Unclear risk	Sample size: 120 participants; 50–199 participants per treatment arm.

EORTC: European Organization for Research and Treatment of Cancer; ESAS: Edmonton Symptom Assessment System; FACIT-F: Functional Assessment of Chronic Illness – Fatigue; SD: standard deviation; VAS: visual analogue scale.

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

Study	Reason for exclusion
Davidson 2010	Not an RCT. Literature review on management of refractory dyspnoea.
Delgado 1986	Did not study breathlessness.
Elsayem 2007	Case studies only.
Jantarakupt 2005	Not an RCT. Literature review on dyspnoea management in lung cancer.
Lui 2013	Not a double-blind study.
McCannon 2012	Not an RCT. Literature review about dyspnoea management in lung cancer.
North 2003	Wrong intervention. Used intrapleural administration of methylprednisolone acetate for malignant pleural effusion.
Ripamonti 1999	Not an RCT. Literature review of dyspnoea in advanced cancer.
Simoff 2013	Not an RCT. Literature review of symptom management in people with lung cancer.
Simon 2012	Systematic review of refractory dyspnoea, but found no studies of corticosteroids.
Skřičková 2013	Not an RCT. Literature review about management of respiratory symptoms in people with advanced lung cancer.
Thomas 2002	Not an RCT. Literature review on management of dyspnoea.
Viola 2008	Systematic review of management of dyspnoea in people with cancer. Found no studies of systemic corticosteroids.
White 1984	Not an RCT. All participants received corticosteroids for bleomycin-induced pneumonitis.

Study	Reason for exclusion
Yennu 2015	Abstract only. Studied symptom clusters, and not breathlessness as an individual outcome.
Yennurajalingam 2016	Studied symptom clusters, and not breathlessness as an individual outcome.

RCT: randomised controlled trial.

DATA AND ANALYSES

Comparison 1. Breathlessness (dyspnoea) at one week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness (dyspnoea)	2	114	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.73, 0.03]

Analysis 1.1. Comparison 1 Breathlessness (dyspnoea) at one week, Outcome 1 Breathlessness (dyspnoea).

Study or subgroup	Dexamethasone N	Dexamethasone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hui 2016	16	-1.8 (2.8)	14	-1.3 (1.9)		26.74%	-0.5[-2.2,1.2]
Yennurajalingam 2013	43	-1.6 (2.4)	41	-0.6 (2.4)		73.26%	-0.98[-2.01,0.05]
Total ***	**59**		**55**			**100%**	**-0.85[-1.73,0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.22, df=1(P=0.64); I^2=0%							
Test for overall effect: Z=1.9(P=0.06)							

ADDITIONAL TABLES

Table 1. Primary sites of disease

Study	Breast	Head, neck and lung	Gastrointestinal	Gynaecological	Genitourinary	Sarcoma	Not specified
Hui 2016	—	37	—	—	—	—	4
Yennurajalingam 2013	13	45	39	9	10	9	7

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#2 MeSH descriptor: [Betamethasone] explode all trees

#3 MeSH descriptor: [Fludrocortisone] explode all trees

#4 MeSH descriptor: [Dexamethasone] explode all trees

#5 MeSH descriptor: [Methylprednisolone] explode all trees

#6 MeSH descriptor: [Prednisolone] explode all trees

#7 MeSH descriptor: [Triamcinolone] explode all trees

#8 MeSH descriptor: [Beclomethasone] explode all trees

#9 (corticoid* or corticosteroid* or glucocorticoid* or betamethasone or fludrocortisone or cortisone or deflazacort or dexamethasone or hydrocortisone or methylprednisolone or prednisolone or triamcinolone or beclomethasone)

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

#11 MeSH descriptor: [Dyspnea] explode all trees

#12 (dysp* or breathless* or ((short or labor* or difficult*) near/3 breath*)):ti,ab

#13 #11 or #12

#14 MeSH descriptor: [Neoplasms] explode all trees

#15 (cancer* or carcinoma* or malignan* or adenocarcinoma* or mesothelioma* or tumour* or tumor*)

#16 #14 or #15

#17 #10 and #13 and #16

Appendix 2. MEDLINE via 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.

17. Prednisolone/

18. prednisolone.tw.

19. Triamcinolone/

20. triamcinolone.tw.

21. exp Mometasone Furoate/

22. exp Fluticasone/

23. exp Beclomethasone/

24. exp Budesonide/

25. exp Fluocinolone Acetonide/ai [Antagonists & Inhibitors]

26. exp Androstadienes/

27. exp Pregnenediones/

28. exp Pregnadienediols/

29. budesonide.tw.

30. mometasone.tw.

31. beclomethasone.tw.

32. flunisolide.tw.

33. fluticasone.tw.

34. 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 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

35. "malignan*".tw.

36. "tumour*".tw.

37. "tumor*".tw.

38. "cancer*".tw.

39. "carcinoma*".tw.

40. "adenocarcinoma*".tw.

41. exp Neoplasms/

42. 35 or 36 or 37 or 38 or 39 or 40 or 41

43. exp Dyspnea/

44. "dyspn*".tw.

45. (short* adj2 breath*).tw.

46. (breath* adj2 difficult*).tw.

47. (labo*r* adj2 breath*).tw.

48. "breathless*".tw.

49. 43 or 44 or 45 or 46 or 47 or 48

50. randomized controlled trial.pt.

51. controlled clinical trial.pt.

52. randomized.ab.

53. randomised.ab.

54. placebo.ab.

55. randomly.ab.

56. trial.ab.

57. groups.ab.

58. drug therapy.fs.

59. 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58

60. exp animals/ not humans.sh.

61. 59 not 60

62. 34 and 42 and 49 and 61

Appendix 3. Embase search strategy

(('corticosteroid'/exp OR ('betamethasone'/exp OR betamethasone:ti,ab) OR ('cortisone'/exp OR cortisone:ti,ab) OR ('deflazacort'/exp OR deflazacort:ti,ab) OR ('fludrocortisone'/exp OR fludrocortisone:ti,ab) OR ('dexamethasone'/exp OR dexamethasone:ti,ab) OR ('hydrocortisone'/exp OR hydrocortisone:ti,ab) OR ('methylprednisolone'/exp OR methylprednisolone:ti,ab) OR ('prednisolone'/exp OR prednisolone:ti,ab) OR ('triamcinolone'/exp OR triamcinolone:ti,ab)) OR beclometasone:ti,ab OR beclomethasone:ti,ab)

AND

(('neoplasm'/exp OR tumor*:ti,ab OR tumour*:ti,ab OR cancer*:ti,ab OR carcinoma*:ti,ab OR adenocarcinoma*:ti,ab OR malignan*:ti,ab) OR mesothelioma)

AND

(random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti)

AND

('cheyne stokes breathing'/exp OR dyspn*:ti,ab OR breathless*:ti,ab OR (short* NEAR/2 breath*):ti,ab OR **'dyspnea'/exp/mj)**

Appendix 4. CINAHL search strategy

S47 S34 NOT S46

S46 S34 AND S45

S45 S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44

S44 (MH "Quantitative Studies")

S43 (MH "Placebos")

S42 TX placebo

S41 TX random* W1 allocat*

S40 (MH "Random Assignment")

S39 TX random* control* trial*

S38 TX (trebl* OR tripl* OR doubl* OR singl*) N1 (blind* OR mask*)

S37 TX clinic* N1 trial*

S36 PT Clinical Trial

S35 (MH "Clinical Trials+")

S34 S32 AND S33

S33 S20 AND S23

S32 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31

S31 TX breathless*

S30 TX labo#r* N2 breath*

S29 labo#r* N2 breath*

S28 TX breath N2 difficult*

S27 TX short* n2 breath*

S26 TX cheyne stokes

S25 TX dyspn*

S24 (MH "Dyspnea+")

S23 S21 OR S22

S22 TX malignan* OR tumor* OR tumour* OR cancer* OR carcinoma* OR adenocarcinoma* OR mesothelioma*

S21 (MH "Neoplasms+")

S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19

S19 TX beclomethasone

S18 (MH "Beclomethasone")

S17 (MH "Triamcinolone")

S16 TX triamcinolone

S15 (MH "Prednisolone+")

S14 TX methylprednisolone

S13 (MH "Methylprednisolone")

S12 TX hydrocortisone

S11 (MH "Hydrocortisone")

S10 (MH "Dexamethasone")

S9 TX dexamethasone

S8 TX deflazacort

S7 TX cortisone

S6 TX fludrocortisone

S5 TX betamethasone

S4 (MH "Betamethasone")

S3 TX adrenal N2 hormon*

S2 TX corticoid* OR corticosteroid* OR glucocorticoid*

S1 (MH "Adrenal Cortex Hormones+")

Appendix 5. Science Citation Index (ISI Web of Science) search strategy

TOPIC: (corticoid* OR corticosteroid* OR glucocorticoid* OR betamethasone OR Fludrocortisone OR cortisone OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR triamcinolone OR beclomethasone) *AND* **TOPIC:** (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumour* OR tumor*) *AND* **TOPIC:** (dyspn* OR breath*)

Appendix 6. LILACS search strategy

1. w:((dyspnoea OR dyspnea) AND (cancer OR malignancy OR malignant OR tumours OR tumors OR carcinoma) AND (corticosteroids OR glucocorticoids OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR betamethasone)) AND (instance:"regional") AND (type_of_study:("clinical_trials"))

tw:((mh:(adrenal cortex hormones)) OR (tw:(corticosteroid* OR corticoid* OR glucocorticoid* OR betamethasone OR fludrocortisone OR cortisone OR dexamethasone OR hydrocortisone OR methylprednisolone OR prednisolone OR triamcinolone OR beclomethasone)) AND (mh:(neoplasms)) OR (tw:(cancer* OR malignan* OR carcinoma* OR adenocarcinoma* OR tumour* OR tumor* OR mesothelioma)) AND (mh:(respiratory physiological phenomena)) OR (tw:(dyspn* OR "cheyne stokes" OR breathless*))) AND (instance:"regional") AND (db:("LILACS") AND type_of_study:("cohort" OR "case_control" OR "clinical_trials"))

CONTRIBUTIONS OF AUTHORS

Draft the protocol	AH, JD
Develop and run the search strategy	KR PaPaS Information Specialist provided support
Obtain copies of studies	KR
Select which studies to include	JH, PG, PVB, JD
Extract data from studies	AH, SK, JD
Enter data into Review Manager 5	AH
Assess risk of bias	AH, SK, JH, PG, JD
Carry out the analysis	AH, SK
Interpret the analysis	JH, PG, AH, SK, JD
Draft the final review	AH, KR, JD
Update the review	AH, JH, PG, KR

DECLARATIONS OF INTEREST

AH: none known.

JD: none known; JD is a trainee physician in palliative medicine and manages patients with dyspnoea due to advanced cancer.

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

SK: none known.

KR: none known.

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

JH: none known; JH is a specialist palliative medicine physician and manages patients with dyspnoea due to advanced cancer. JH receives royalties from Oxford University Press.

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- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had planned for two authors to independently extract data and perform assessments. At review stage, three review authors (AH, SK, JD) independently extracted data from the studies. Five review authors (AH, SK, JH, PG, JD) independently assessed the risk of bias of each included study.

We stated our intention to search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), but this database is under review and not available to search.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Adrenal Cortex Hormones [administration & dosage] [adverse effects] [*therapeutic use]; Dexamethasone [administration & dosage] [adverse effects] [*therapeutic use]; Dyspnea [*drug therapy] [etiology]; Neoplasms [*complications]

MeSH check words

Adult; Humans