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

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

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

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

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 patients 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 dyspnoeic patients than in patients 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 an individual’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 (SVC) 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, 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 individual’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 (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). Non-pharmacological techniques are thus 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 (Johnson 2014) postulate 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”. 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 patients with dyspnoea (Booth 2006; Booth 2011; Farquhar 2010; Farquhar 2014). From an anxiety reduction training point of view, cognitive behavioral therapy, simple relaxation therapy, distraction methods, music, or mindfulness (Lok 2016) may also help patients feel more control 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 patient is experiencing significant anxiety), alongside other non-pharmacological strategies (ERS Monograph 2016), oxygen (if a patient 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), nau-

sea and vomiting (Wayne-Bossert 2016), 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- α 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 patients 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). As dyspnoea is likely to be multifactorial in the context of cancer however, 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 cancer patients 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 patients 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 side effects (Matsuo 2011), especially following long-term use. There is little objective evidence in the literature to support the use of systemic corticosteroids for symptom control however (ERS Monograph 2016; Viola 2008), and concerns have been raised about the 'uncontrolled' use of steroids in cancer patients (Haywood 2015; Levy 2016; Wayne-Bossert 2016).

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 will include studies if they are randomised controlled trials (RCTs) with double-blind assessment of participant outcomes. We will include studies with full journal publication, as well as on-line clinical trial results and summaries of otherwise unpublished clinical trials or abstracts with sufficient data for analysis. We will exclude studies that are non-randomised, case reports and clinical observations. We will not include short abstracts (usually meeting reports).

Types of participants

Participants with cancer suffering from 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 indication, compared to placebo or any active comparator including supportive care or alternate non-pharmacological treatment. We will exclude studies assessing inhaled corticosteroids.

Types of outcome measures

We anticipate that studies may use a variety of outcome measures, and will include any study that reports any of the following outcome measures assessing dyspnoea, as outlined below.

Primary outcomes

Our primary outcome is 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. judgments 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 will use both standardised, mean pre-post change in breathlessness scores after the intervention (comparator), as well as post-intervention standardised mean difference in breathlessness scores between intervention and comparator groups. We will 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 will 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. A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect (ICH 1994).
- Patient satisfaction with treatment.
- Participant withdrawal from trial.

Search methods for identification of studies

Electronic searches

We will search the following databases without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library).
- MEDLINE (via Ovid).
- Embase.com.
- CINAHL (via EBSCOhost).
- Science Citation Index (Web of Science).
- Latin America and Caribbean Health Sciences (LILACS).

Medical subject headings (MeSH) or equivalent and text word terms will be used. Where appropriate, MeSH terms will be exploded. We will apply 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 will be tailored to individual databases. The search strategy for MEDLINE is in Appendix 1.

Searching other resources

We will search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, reference lists of reviews and retrieved articles will be checked for additional studies and citation searches will be performed on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact authors where necessary for additional information.

Data collection and analysis

Selection of studies

Three review authors (JH, PG, PVB) will independently determine eligibility by reading the abstract of each study identified by

the search. Independent review authors will eliminate studies that clearly do not satisfy inclusion criteria, and obtain full copies of the remaining studies. Two review authors (PG, PVB) will read these studies independently to select relevant studies, and in the event of disagreement, a third author will adjudicate (JH). We will not anonymise the studies in any way before assessment. We will include a PRISMA flow chart in the full review which will show the status of identified studies (Moher 2009) as recommended in Part 2, Section 11.2.1 of the *Cochrane Handbook* (Higgins 2011). We will include studies in the review irrespective of whether measured outcome data are reported in a usable way.

Data extraction and management

Two review authors (AH, SK) will independently extract data using a standard form and check for agreement before entry into Review Manager (RevMan 2014). We will resolve any discrepancies by discussion and will consult a third review author (JH) if necessary. We will consider different dyspnoea scales equivalent if they are based on a 0 to 10 scale and we will normalise them to such a scale. We will include information about the three domains of dyspnoea (intensity, quality, and impact on function), serious adverse events, patient satisfaction with treatment, and participant withdrawal from the trial. We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will collect characteristics of the included studies in sufficient detail to populate a table of 'Characteristics of included studies' in the full review.

Assessment of risk of bias in included studies

Two authors (AH, SK) will independently assess risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by Cochrane Pregnancy and Childbirth, with any disagreements resolved by discussion and adjudication by a third author (JH) if necessary. We will complete a 'Risk of bias' table for each included study using the 'Risk of bias' tool in RevMan (RevMan 2014).

We will assess the following for each study.

- Random sequence generation (checking for possible selection bias). We will assess 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); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) will be excluded.
- Allocation concealment (checking for possible 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 will assess 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). Studies that do not conceal allocation (e.g. open list) will be excluded.

- Blinding of participants and personnel (checking for possible performance bias). We will assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess methods as: low risk of bias (study states that it was blinded and describes 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 states that it was blinded but does not provide an adequate description of how it was achieved). Studies that were not double-blind are considered to have high risk of bias.

- Blinding of outcome assessment (checking for possible detection bias). We will assess the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We will assess the methods as: low risk of bias (study has a clear statement that outcome assessors were unaware of treatment allocation, and ideally describes how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacks a clear statement on how it was achieved). Studies where outcome assessment was not blinded would be considered as having a high risk of bias.

- Selective reporting (checking for reporting bias). We will assess whether primary and secondary outcome measures were prespecified and whether these were consistent with those reported. We will assess the methods as: low risk of bias (study protocol is available and all of the study's prespecified primary and secondary outcomes that are of interest are reported in the prespecified way, or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that are prespecified); high risk of reporting bias (not all of the study's prespecified primary outcomes are reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that are not prespecified; one or more reported primary outcomes are not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in 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).

- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation

carried forward' analysis); high risk of bias (used 'completer' analysis).

- Size of study (checking for possible biases confounded by small size). We will assess studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

For dichotomous outcomes between groups, we will estimate and compare the risk ratio (RR) using 95% confidence intervals (CIs). For continuous outcomes between groups, we will measure arithmetic mean and standard deviation (SD) and report the mean difference (MD) with 95% CI. When an outcome was derived with different instruments measuring the same construct, we will use standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

We will only include studies in which randomisation is by the individual patient; this may include cross-over or $n = 1$ studies. For trials containing multiple arms, we will only include pair-wise comparisons of each intervention arm to the control arm.

Dealing with missing data

We will endeavour to contact authors to request additional data in cases where an intended outcome has not been reported or where relevant summary statistics for summary data are missing. If intention-to-treat (ITT) analyses were not performed, we will perform the ITT analyses provided that the necessary data are available for this purpose.

Assessment of heterogeneity

We will assess statistical heterogeneity by visually examining forest plots and quantify it using the I^2 statistic. We will consider I^2 values above 50% to represent substantial heterogeneity in line with Higgins 2011 and we will assess potential sources of heterogeneity through subgroup analyses.

Assessment of reporting biases

We will use funnel plot symmetry to interpret the results of the statistical analysis. If there is evidence of small study effects, we will consider publication bias as only one of a number of possible explanations.

Data synthesis

We will use Review Manager (RevMan 2014) for data extraction and synthesis. We will display a meta-analysis of outcomes only if participants, interventions, comparisons and outcomes can be judged to be sufficiently similar to ensure an answer that is clinically meaningful. We will synthesise dichotomous outcomes by calculating the RR, and continuous variables by calculating the MD as an estimate of effect size, using a fixed-effect model with 95% CIs. If continuous variables are measured on different scales, we will calculate the SMD. We will use a random-effects model for meta-analysis if there is significant clinical or statistical (or both) heterogeneity and it is considered appropriate to combine studies.

Quality of the evidence

Two review authors (AH, SK) will independently rate the quality of the outcomes of dyspnoea relief using the three domains of dyspnoea, serious adverse events, and patient satisfaction with treatment. We will use the GRADE system to rank the quality of the evidence using the GRADEprofiler 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).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: 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: 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; or downgraded observational studies; or case series/case reports.

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

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

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

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

We will decrease the grade rating by one (-1) or two (-2) (up to a maximum of -3 to 'very low') if we identify:

- 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 plan to include a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we will include 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), serious adverse events, patient satisfaction with treatment, and participant withdrawal from trial.

Subgroup analysis and investigation of heterogeneity

Where possible, we will conduct subgroup analyses based on: type of systemic corticosteroid, dose, type of cancer, and length of the trial. Sensitivity analyses will be performed by including and excluding studies with a high risk of bias to determine the impact that inclusion of studies of poorer methodological quality has on the outcomes. Where significant heterogeneity is identified, we will also conduct sensitivity analyses using a random-effects model versus a fixed-effect model.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategy for MEDLINE via Ovid

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. budesonide.tw.
27. mometasone.tw.
28. beclomethasone.tw.
29. flunisolide.tw.
30. fluticasone.tw.
31. 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
32. "malignan*".tw.
33. "tumour*".tw.
34. "tumor*".tw.
35. "cancer*".tw.
36. "carcinoma*".tw.
37. "adenocarcinoma*".tw.
38. exp Neoplasms/
39. 32 or 33 or 34 or 35 or 36 or 37 or 38
39. exp Dyspnea/
40. "dyspn*".tw.
41. (short* adj2 breath*).tw.
42. (breath* adj2 difficult*).tw.
43. (labo*r* adj2 breath*).tw.
44. "breathless*".tw.
45. 39 or 40 or 41 or 42 or 43 or 44
46. randomized controlled trial.pt.

47. controlled clinical trial.pt.
48. randomized.ab.
49. randomised.ab.
50. placebo.ab.
51. randomly.ab.
52. trial.ab.
53. groups.ab.
54. drug therapy.fs.
55. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. exp animals/ not humans.sh.
57. 55 not 56
58. 31 and 39 and 45 and 57

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 RevMan	AH
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.

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