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Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness (Review)

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[Intervention Review]

Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

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ABSTRACT

Background

Breathlessness is a common and disabling symptom which affects many people with advanced cardiorespiratory disease and cancer. The most effective treatments are aimed at treating the underlying disease. However, this may not always be possible, and symptomatic treatment is often required in addition to maximal disease-directed therapy. Opioids are increasingly being used to treat breathlessness, although their mechanism of action is still not completely known. A few good sized, high quality trials have been conducted in this area.

Objectives

To determine the effectiveness of opioid drugs in relieving the symptom of breathlessness in people with advanced disease due to malignancy, respiratory or cardiovascular disease, or receiving palliative care for any other disease.

Search methods

We performed searches on CENTRAL, MEDLINE, EMBASE, CINAHL, and Web of Science up to 19 October 2015. We handsearched review articles, clinical trial registries, and reference lists of retrieved articles.

Selection criteria

We included randomised double-blind controlled trials that compared the use of any opioid drug against placebo or any other intervention for the relief of breathlessness. The intervention was any opioid, given by any route, in any dose.

Data collection and analysis

We imported studies identified by the search into a reference manager database. We retrieved the full-text version of relevant studies, and two review authors independently extracted data. The primary outcome measure was breathlessness and secondary outcome measures included exercise tolerance, oxygen saturations, adverse events, and mortality. We analysed all studies together and also performed

subgroup analyses, by route of administration, type of opioid administered, and cause of breathlessness. Where appropriate, we performed meta-analysis. We assessed the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and created three 'Summary of findings' tables.

Main results

We included 26 studies with 526 participants. We assessed the studies as being at high or unclear risk of bias overall. We only included randomised controlled trials (RCTs), although the description of randomisation was incomplete in some included studies. We aimed to include double blind RCTs, but two studies were only single blinded. There was inconsistency in the reporting of outcome measures. We analysed the data using a fixed-effect model, and for some outcomes heterogeneity was high. There was a risk of imprecise results due to the low numbers of participants in the included studies. For these reasons we downgraded the quality of the evidence from high to either low or very low.

For the primary outcome of breathlessness, the mean change from baseline dyspnoea score was 0.09 points better in the opioids group compared to the placebo group (ranging from a 0.36 point reduction to a 0.19 point increase) (seven RCTs, 117 participants, very low quality evidence). A lower score indicates an improvement in breathlessness. The mean post-treatment dyspnoea score was 0.28 points better in the opioid group compared to the placebo group (ranging from a 0.5 point reduction to a 0.05 point increase) (11 RCTs, 159 participants, low quality evidence).

The evidence for the six-minute walk test (6MWT) was conflicting. The total distance in 6MWT was 28 metres (m) better in the opioids group compared to placebo (ranging from 113 m to 58 m) (one RCT, 11 participants, very low quality evidence). However, the change in baseline was 48 m worse in the opioids group (ranging from 36 m to 60 m) (two RCTs, 26 participants, very low quality evidence).

The adverse effects reported included drowsiness, nausea and vomiting, and constipation. In those studies, participants were 4.73 times more likely to experience nausea and vomiting compared to placebo, three times more likely to experience constipation, and 2.86 times more likely to experience drowsiness (nine studies, 162 participants, very low quality evidence).

Only four studies assessed quality of life, and none demonstrated any significant change.

Authors' conclusions

There is some low quality evidence that shows benefit for the use of oral or parenteral opioids to palliate breathlessness, although the number of included participants was small. We found no evidence to support the use of nebulised opioids. Further research with larger numbers of participants, using standardised protocols and with quality of life measures included, is needed.

PLAIN LANGUAGE SUMMARY

Opioids for treating breathlessness at the end of life

Background

People with lung disease may experience breathlessness. Initial treatments should focus on the underlying causes of breathlessness. However, as the disease progresses, it may be better to focus on treating the symptoms. As well as standard care, opioids (e.g. morphine, given either by mouth, by nebuliser, or injected) may help relieve these symptoms. However, opioids also have side effects, such as drowsiness, constipation, nausea (feeling sick), and vomiting.

Review question

We wanted to know if opioid drugs reduced breathlessness in people with lung disease. We also looked at whether opioids improved their ability to exercise, and what side effects people had. We also wanted to know if opioid drugs improved their quality of life.

Study characteristics

We searched for studies up to 19 October 2015, and we included 26 studies with 526 people. These people had breathlessness from different types of lung disease. Some were given opioid drugs and some were given other drugs or a placebo, and studies compared the reporting of breathlessness to see if there was any difference. Some studies also looked at the amount of time people could exercise to see if there were any differences. Some people came from home, and some came from the hospital setting.

Key findings

There was some low quality evidence that showed a benefit of using oral or injectable opioid drugs for the treatment of the symptoms of breathlessness. There was no evidence for opioids by nebuliser. Some people experienced drowsiness, nausea, and vomiting. More research is needed using more people, and looking at effects on quality of life.

Quality of the evidence

We rated the quality of the evidence using one of the following grades: very low, low, moderate, or high. Very low quality evidence means we are uncertain about the results. High quality evidence means we are very certain about the results. For this Cochrane review, we found that the evidence was of low to very low quality. We included randomised controlled trials which were blinded, which means that participants and those people that assessed the results did not know whether the participants had received the opioid drug or a placebo. However, the trials were of small size, and some studies did not give enough information to allow us to assess whether they were of good quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Opioids compared with placebo in people with breathlessness in advanced disease or terminal illness

Patient or population: adults with refractory breathlessness
Setting: inpatient and outpatient setting
Intervention: opioids
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Opioids				
Breathlessness: change from baseline[1]	The mean change from baseline ranged from −2 to 9.7 in the control group	The mean change from baseline was 0.09 points better in the opioids group compared to the placebo group (ranging from a 0.36 point reduction to a 0.19 point increase)	-	117 (7 RCTs)	⊕◯◯◯ **very low**[2,3,4]	A lower score indicates an improvement in breathlessness
Breathlessness: post-treatment score[1]	The mean post-treatment score ranged from −43 to 50 in the control group	The mean post-treatment score was 0.28 points better in the opioid group compared to the placebo group (ranging from a 0.5 point reduction to a 0.05 point increase)	-	159 (11 RCTs)	⊕⊕◯◯ **low**[2,3]	A lower score indicates an improvement in breathlessness

Exercise tolerance: 6MWT[5] - total distance	The total distance in 6MWT was 368m in the placebo group	The total distance in 6MWT was 28 m better in the opioids group compared to placebo (ranging from 113 m to 58 m)	-	11 participants (1 RCT)	⊕○○○ **very low**[2,3,4,6]	-
Exercise tolerance: 6MWT[5]- change from baseline	The change from baseline was from -21m to 37m in the placebo group	The change in baseline was 48 m worse in the opioids group (ranging from 36 m to 60 m)	-	26 (2 RCTs)	⊕○○○ **very low**[1,2,3]	-
Adverse events: constipation	55 per 1000	179 per 1000	RR 3 (95% CI 1.63 to 5.51)	162 (9 RCTs)	⊕○○○ **very low**[2,3]	-
Adverse events: nausea and vomiting	67 per 1000	201 per 1000	RR 4.73 (95% CI 1.73 to 12.97)	104 (7 RCTs)	⊕○○○ **very low**[2,3]	-
Adverse events: drowsiness	58 per 1000	128 per 1000	RR 2.86 (95% CI 1.17 to 7.02)	156 (9 RCTs)	⊕○○○ **very low**[2,3]	-
Quality of life[7]	The change from baseline score in the control group was 2.94	The quality of life change from baseline score in the opioid group was 0.86 points lower (ranging from 9.90 points lower to 8.18 points higher)	-	16 (1 RCT)	⊕○○○ **very low**[2,3,4]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

[1]The study authors assessed breathlessness at variable time points (one hour to six weeks) during the study according to the VAS, Borg scale, and oxygen cost diagram.

[2]There were limitations in the design and implementation of available studies, which suggested a high risk of bias.

[3]There were small study sizes.

[4]There was significant heterogeneity.

[5]The study authors assessed six minute walk test (6MWT) at variable time points (one hour to six weeks).

[6]There were large CIs.

[7]The study authors measured this outcome using the Chronic Respiratory Disease Questionnaire. Only one study included quality of life data that we were able to be include.

Abbreviations: RCT: randomised controlled trial; CI: confidence interval; RR: risk ratio.

BACKGROUND

Description of the condition

Breathlessness may be described as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (ATS 1999). Breathlessness, also termed dyspnoea, shortness of breath, air hunger, awareness of respiratory distress, or laboured breathing, may be variably perceived by different patients, depending on multiple physiological, psychological, social, environmental, and cultural factors (Guz 1997). It is a common symptom at the advanced stages of illness, and may be as disabling to the patient and their families as pain, nausea and vomiting, delirium, and other end of life symptoms (Neuman 2006).

Respiratory motor activity is regulated by automatic centres in the brainstem and voluntary signals from the cortex, and controls chest wall expansion, lung inflation, and ventilation. Feedback is provided by chemoreceptors, mechanoreceptors, and sensory receptors. Breathlessness may be explained by a mismatch between afferent sensory information processed at the cortex and respiratory motor command from the cortex and brainstem. Alterations in arterial blood pH (acidity), partial pressure of carbon dioxide (pCO_2), and partial pressure of oxygen (pO_2) stimulate central chemoreceptors in the medulla and peripheral chemoreceptors in the carotid and aortic bodies, which transmit impulses to the brainstem respiratory centres, and adjust breathing based on acid base homeostasis (Nattie 1995; Fitzgerald 1986). Mechanoreceptors and stretch receptors located in the lung parenchyma and bronchioles sense changes in the expansion of the lung and become irritated by certain mechanical and chemical stimuli, and affect subsequent levels and patterns of breathing (Nishino 2011). Changes in air flow, smooth muscle tone, and impulses from C fibres located adjacent to the alveoli and pulmonary capillaries respond to changes in pulmonary interstitial and capillary pressures (Widdicombe 1982). Sensory receptors in respiratory muscle and the diaphragm involved in spinal and supraspinal reflexes influences central respiratory activity (Bolsher 1987; Bolsher 1988). Each of these mechanisms may contribute to the mismatch of neural activity and consequent mechanical and ventilatory outputs, and create sensations of dyspnoea, air hunger, and increased desire to breathe, which may cause distress.

Recent neuroimaging studies also suggest that neural structures that involve pain and dyspnoea may be shared, further contributing to the affected person's discomfort and distress associated with an increased sensation of ventilation (Brannan 2001; Liotti 2001; Parsons 2001; Peiffer 2001; Evans 2002; von Leupoldt 2009).

There are many currently incurable and progressive cardiopulmonary, neuromuscular, and malignant conditions in which dyspnoea is a common symptom in the advanced stages of disease. The dominant mechanism that leads to dyspnoea may vary between conditions and in many conditions more than one mechanism may be responsible. Illnesses such as interstitial lung disease, pulmonary hypertension, and congestive heart failure stimulate pulmonary receptors (irritant, mechanical, and vascular) leading to an increased respiratory drive and increased afferent input to the respiratory centre. Chronic conditions that are severe enough might also lead to gas exchange abnormalities through mechanisms such as ventilation-perfusion (V/Q) mismatching (e.g. pulmonary vascular disease) or diffusion impairment (e.g. interstitial lung disease) leading to stimulation of chemoreceptors and increased respiratory drive. Conditions that reduce the oxygen-carrying capacity of the blood (e.g. anaemia) or reduce cardiac output (e.g. cardiac failure) also stimulate chemoreceptors. Respiratory muscle weakness in conditions such as motor neurone disease or myopathy, and decreased compliance of the chest wall in conditions such as severe kyphoscoliosis and pleural effusion, impair ventilatory mechanics which reduces the afferent feedback for a given efferent input (Manning 1995). There are multiple potential aetiological factors related to breathlessness in chronic obstructive pulmonary disease (COPD). There is an increased resistive load from narrowing of the airways and increased elastic load from hyperinflation resulting in impaired ventilator mechanics. In addition, hypoxia and or hypercapnia may be present, leading to stimulation of chemoreceptors, and finally dynamic airway compression may stimulate receptors within the airway (Parshall 2012).

Multiple mechanisms for breathlessness have also been described in individuals with advanced cancer. Cancers that involve the lungs may obstruct airways leading to ventilation perfusion mismatch, and pleural effusions are common. Many people with lung cancer also have COPD. Dudgeon 1998 showed that people with terminal cancer often have abnormal spirometry (most commonly a mixed obstructive/restrictive pattern or a restrictive pattern). They also found that respiratory muscle weakness may be an important contributor to dyspnoea and that co-morbidities such as anaemia and cardiac disease are common.

Initial approaches should aim to treat the underlying causes of breathlessness. However, as the disease progresses, such treatments may be less appropriate due to decreased effectiveness and discomfort caused to the person, and a more symptom-based approach may be required.

Many pharmacological and non-pharmacological interventions have been recommended to help alleviate symptoms of breathlessness in advanced disease. Management of symptoms is often multimodal, with varying treatments utilised depending on the person's co-morbidities, and psychosocial, environmental, and cultural factors.

A Cochrane systematic review on non-pharmacological interventions demonstrated efficacy for neuro-electrical muscle stimulation, chest wall vibration, walking aids, breathing training, and use of hand-held fans (Bausewein 2008). Another Cochrane review demonstrated effectiveness of exertional oxygen therapy in non-hypoxaemic COPD patients (Uronis 2011), and suggested a

slight, but not statistically significant, improvement in adults with heart failure, cancer (not end-stage disease), and kyphoscoliosis (Cranston 2008).

Some guidelines recommend opioids as the first-line pharmacological treatment for breathlessness (ATS 1999; Mahler 2010; Parshall 2012; Mahler 2013; Wiseman 2013). A Cochrane review published in 2001 concluded that there was some evidence to support the use of oral and parenteral opioids to palliate breathlessness, but the number of participants studied was small and they recommended that larger trials were needed using standard protocols and incorporating quality of life measures.

A Cochrane review (Simon 2010), found no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD. However, the overall effect size was small and further research is required.

Description of the intervention

Opioids are chemical substances derived from the opium poppy. In the human body they bind to the μ, κ, and δ receptors located in the cerebral cortex, limbic system, midbrain, brainstem, and outside the central nervous system in the bronchioles, alveolar walls, myocardial cells, peripheral sensory nerve fibres, and primary afferent neurons.

How the intervention might work

Exogenous and endogenous opioids specifically bind to the μ receptors to reduce transmission of pain signals (Chahl 1996). Opioids also depress respiratory drive by directly blunting the responsiveness of the brainstem centres, which are affected by hypoxia and hypercapnia. Decreased respiratory output results in a decrease in corollary discharge from the brainstem to perceptual areas in the cerebral cortex and thus reduced the sensation of breathlessness. Corollary discharge describes the hypothesis that a sensory 'copy' of the motor output is sent from the motor cortex to the sensory cortex and imparts a conscious awareness of respiratory effort (Beach 2006).

Opioids may also cause blunting of perceptual sensitivity to sensations of breathlessness. Neuroimaging studies demonstrate that μ opioid receptor agonists can modulate the central processing of breathlessness similar to that of pain relief. Administration of opioids stimulate activity in the anterior cingulate cortex, thalamus, frontal cortex, and brainstem, the same areas which are activated when breathlessness occurs (Banzett 2000; Peiffer 2001; Petrovic 2002; Pattinson 2009).

Peripheral opioid receptors are located in bronchioles and alveolar walls of the respiratory tract (Zebraski 2000). Opioid administration may modulate breathlessness by binding to these opioid receptors. It is theorised that opioid administration could modulate breathlessness by binding to these peripheral opioid receptors. However, to date, studies of nebulised opioids have lacked efficacy compared with systemically administered opioids, and there is a lack of efficacy when nebulised opioids are compared with systemically administered opioids (Polosa 2002; Mahler 2013).

Other effects of opioids include drowsiness, euphoria, confusion, peripheral vasodilation, constipation, nausea and vomiting, and cough suppression.

The choice of preparation and pharmacokinetics of opioids may vary depending on individual needs. Small doses of short-acting opioids may be commenced in opioid-naïve people, and once a stable dose has been achieved, may be switched to long acting preparations. Currow 2011 found that 70% of participants derived benefit from 10 mg sustained-release once-daily preparations. Transmucosal, transdermal, subcutaneous, or intravenous modes may be more appropriate for people whose swallowing is impaired or who are approaching the final stages of end of life. It is unclear if all opioids and all routes are equal in their ability to relieve breathlessness. Opioids differ significantly in their pharmacodynamic properties, from differences in their absorption, to metabolism and affinity for receptors.

Why it is important to do this review

The use of opioids to treat breathlessness in advanced illness is variably accepted in medical practice, and some health professionals and patients have concerns regarding efficacy and side effects (Oxberry 2012; Rocker 2012). Much of the literature around opioids for breathlessness are narrative reviews and opinion pieces, and a systematic review is required to specifically examine the quality of evidence from randomised controlled trials (RCTs), to evaluate efficacy in terms of symptom control and quality of life, and to assess adverse effects.

This review will build on a previous Cochrane systematic review (Jennings 2001). In more recent years, additional RCTs have been published (Mazzocato 1999; Johnson 2002; Abernethy 2003), mechanisms of action have been further elucidated, and guidelines that examine the risk of bias and assessment of heterogeneity in Cochrane reviews have been updated (Higgins 2011).

OBJECTIVES

To determine the effectiveness of opioid drugs in relieving the symptom of breathlessness in patients with advanced disease due to malignancy, respiratory or cardiovascular disease, or receiving palliative care for any other disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group randomised controlled trials (RCTs) compared to either placebo or other treatment, as well as crossover studies in which participants were randomised to order of treatment. We defined 'randomised' as studies that were described by the study author as 'randomised'. There was no language restriction. All identified trials, published and unpublished, were eligible for inclusion.

Types of participants

We considered adults with any type of advanced progressive illness with persistent breathlessness despite optimal or appropriate treatment of reversible factors.
We also included participants suffering from breathlessness due to any type of illness, who were considered to be at an advanced stage of illness, or palliative stage, as defined by the study authors.

Types of interventions

Any opioid drug, given by any route in any dose, for the treatment of breathlessness compared to placebo, or any other pharmacological or non-pharmacological interventions that were directly compared with the opioid treatment.

Types of outcome measures

Primary outcomes

Subjective measurement of breathlessness intensity or severity, including but not limited to Borg and the modified Borg scale, verbal categorical scales of breathlessness, and visual analogue scales (VAS) of breathlessness (O'Donnell 1998).

Secondary outcomes

- Quality of life measure by any scale.
- Any physiological and functional assessments of breathlessness including but not limited to six-minute walk tests (6MWT), shuttle tests, and actigraphy.
- Performance status.
- Pulse oximetry.
- Arterial blood gas analysis.
- Adverse events including constipation, delirium, and others.
- Mortality.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases up to 19 October 2015.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library) Issue 10 of 12, 2015.
- MEDLINE (OVID) 1946 to October week 2 2015.
- EMBASE (OVID) 1974 2015 October 16.
- CINAHL(EBSCO) 1982 to Octpber 2015.
- Web of Science (ISI) to October 2015.

We have presented the search strategies we used in Appendix 1.

Searching other resources

For ongoing studies we searched the following up to 19 October 2015.

- The *meta*Register of Controlled Trials (*m*RCT) (http://www.controlled-trials.com/mrct/).
- ClinicalTrials.gov (http://clinicaltrials.gov/).
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/).

We handsearched reference lists of included studies, relevant chapters, and review articles. We used Google to search for conference abstracts.
We attempted to contact the trial investigators of two studies to determine the potential for inclusion. However, we did not receive a reply by the time we completed this review.

Data collection and analysis

Selection of studies

Two review authors (RM and HB) independently screened all abstracts to determine whether they met the inclusion criteria. We sought the full-text publications of articles that definitely met or may have met the inclusion criteria. Two review authors (RM and HB) then reviewed these full-text articles to determine eligibility. We resolved any disagreement with discussion and consensus. We included a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram in the review to document the screening process (Liberati 2009), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data extraction and management

Two review authors (RM and HB) independently extracted data from the included studies. Where appropriate, we imported data and pooled them in Cochrane's statistical software, Review Manager (RevMan) (Review Manager 2014), for further analysis.
We used a data collection form for study characteristics and outcome data, which we piloted on one study included in the review. We extracted the following data.

- Methods: study design, duration of the study, study setting, and date of study.
- Participants: number, mean age and age range, gender, inclusion and exclusion criteria.
- Intervention: intervention, dose, mode of administration, concomitant medications, and exclusions.
- Outcomes: primary and secondary outcomes as specified, type of scale used, and time points collected.
- Notes: funding for trial and any conflicts of interest for trial authors.
- 'Risk of bias' summary.

We extracted the mean and standard deviation (SD) values from each study. Where the included studies reported standard error or confidence intervals (CIs) were reported, we converted these to SD values according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

Two independent authors (HB and RM) assessed the included studies for risk of bias using the Cochrane's 'Risk of bias' assessment tool (Higgins 2011). We assessed the following: allocation (random sequence generation and allocation concealment); blinding of participants and personnel, blinding of outcome assessors; incomplete outcome data; and other bias. We scored each of these domains separately as either low risk of bias, unclear risk of bias (insufficient information to make a judgement), or high risk of bias as outlined below.

- Generation of allocation sequence:
    - for each included study we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups;
    - we assessed the method used to generate the allocation sequence as either: low risk of bias (any truly random process such as random number table or computer random number generator); or unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies that used a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment:
    - for each included study we described the method used to conceal the allocation sequence in sufficient detail and to determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment;
    - we assessed the methods as either: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); or unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding or masking (checking for possible performance bias):
    - for each included study we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes;
    - 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 either: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); or unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We intended to exclude studies that were at high risk of bias and were not double-blinded.
- Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). We assessed the methods used to deal with incomplete data as either: low risk (information from all participants were included in the main results, any dropouts are reported, any systematic differences between the two treatment arms are reported); unclear risk of bias (used 'last observation carried forward' analysis); or high risk of bias (used 'completer' analysis).

- Selective reporting bias (checking for within study reporting bias, checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods as either low risk of bias (whether the study fully reported all prespecified outcomes); unclear risk of bias (it appeared not all pre-outcomes were fully reported); or high risk of bias (the study highlighted not all prespecified outcomes were reported).

- Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Kjaergard 2001; Nüesch 2010; Dechartres 2013). We considered studies to be at low risk of bias if they had 200 participants or more in each treatment arm; at unclear risk of bias if they had 50 to 200 participants per treatment arm; or at high risk of bias if they had fewer than 50 participants per

treatment arm.

- Free of other bias (bias due to problems not covered elsewhere in the table):
    - for each included study we described any important concerns we had about other possible sources of bias (e.g. baseline imbalance, bias of the presentation data, representation of gender, etc.).

We resolved any disagreement by discussion and consensus.
We performed funnel plot analysis and compared fixed-effect versus random-effects magnitude of effect to determine if there was any suggestion of bias.

Measures of treatment effect

We presented results from continuous variables, such as the breathlessness scales, using a fixed-effect model and calculated standardised mean differences (SMDs) where scales were combined, such as when pooling VAS and Borg scale, with the corresponding 95% CIs. Where scales were not combined, and to assess effect across subgroups, we used the mean difference (MD). Where studies reported results based on a variable range of doses, we used the higher dose.
For dichotomous data, including adverse events, we reported relative risk ratios (RRs) where we could pool the data. Where we were unable to pool these data, we included these results in a descriptive analysis.

Unit of analysis issues

Our unit of analysis was the participant. We did not identify any cluster RCTs. We took measurements from the intervention and control group, and analysed the data as if it was a parallel trial, due to lack of paired data available. We attempted to contact the study authors to obtain paired data. However, due to no response we were unable to obtain original data. Most included studies were crossover trials, and therefore we included the data available in data reports, and acknowledged the limitations of this approach.

Dealing with missing data

Where possible we attempted to contact the principal investigator of the included studies to obtain missing data.

Assessment of heterogeneity

For pooled analyses, we quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of the total variation across trials due to heterogeneity rather than sampling error. We considered significant statistical heterogeneity to be present if the I^2 statistic value was greater than 50%.
Where we identified significant heterogeneity, we further assessed this using predetermined subgroups.

Assessment of reporting biases

Where reporting bias was suggested, we attempted to contact the principal investigator of the included study for missing data.

Data synthesis

A priori, we decided to analyse continuous data according to a fixed-effect model, due to the concerns around the small-study effects on the results of the meta-analysis for all continuous outcomes (Higgins 2011). However, we provided random-effects model data in the sensitivity analysis to compare the sensitivity of the results to different statistical methods. We calculated SMDs where we combined scales, such as when we pooled the VAS and Borg scale data, with the corresponding 95% CIs. Where scales were not combined, and to assess effect across subgroups, we used the MD. Where studies reported results based on a variable range of doses, we used the higher dose.
We used RevMan (Review Manager 2014) to perform meta-analyses and presented our primary outcomes in a 'Summary of findings' table, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using the GRADEPro Guideline Development Tool (GDT) software (GradePro 2015). We assessed the overall quality of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (GradePro 2015) and presented the main findings of the review in a transparent and simple tabular format in the 'Summary of findings' tables. 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 the main outcomes. We chose to present the outcomes stipulated a priori and that which would be clinically meaningful.
The GRADE system uses the following criteria for assigning the grade of evidence based on RCTs.

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

We decreased the grade of evidence if the following occurred.

- 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).
- High probability of reporting bias (−1).

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses.

- Type of illness (e.g. chronic obstructive pulmonary disease (COPD), heart failure, malignancy, and neuromuscular disorders).
- Mode of delivery of opioid drug (e.g. oral, subcutaneous, intravenous, nebulised, intra-nasal, sublingual, buccal, transdermal, and other modes).
- Dose.
- Type of opioid (e.g. morphine, dihydrocodeine, fentanyl).

In the protocol we indicated that we would perform meta-analyses according to the subgroups of dose and 'Risk of bias' assessment. Due to the wide variation and heterogeneity of reported doses we chose to analyse this in a descriptive analysis. We compared the 'Risk of bias' difference in a sensitivity analysis.
Post-hoc we chose to include the type of opioid as a subgroup analysis as we felt this would be an important assessment for clinicians and policy makers.

Sensitivity analysis

We performed sensitivity analyses by systematically excluding studies from the overall analysis based on the potential sources of heterogeneity outlined above, and if homogeneous subgroups have not already been identified and analysed separately. We also compared data from fixed-effect and random-effects models to assess for heterogeneity.

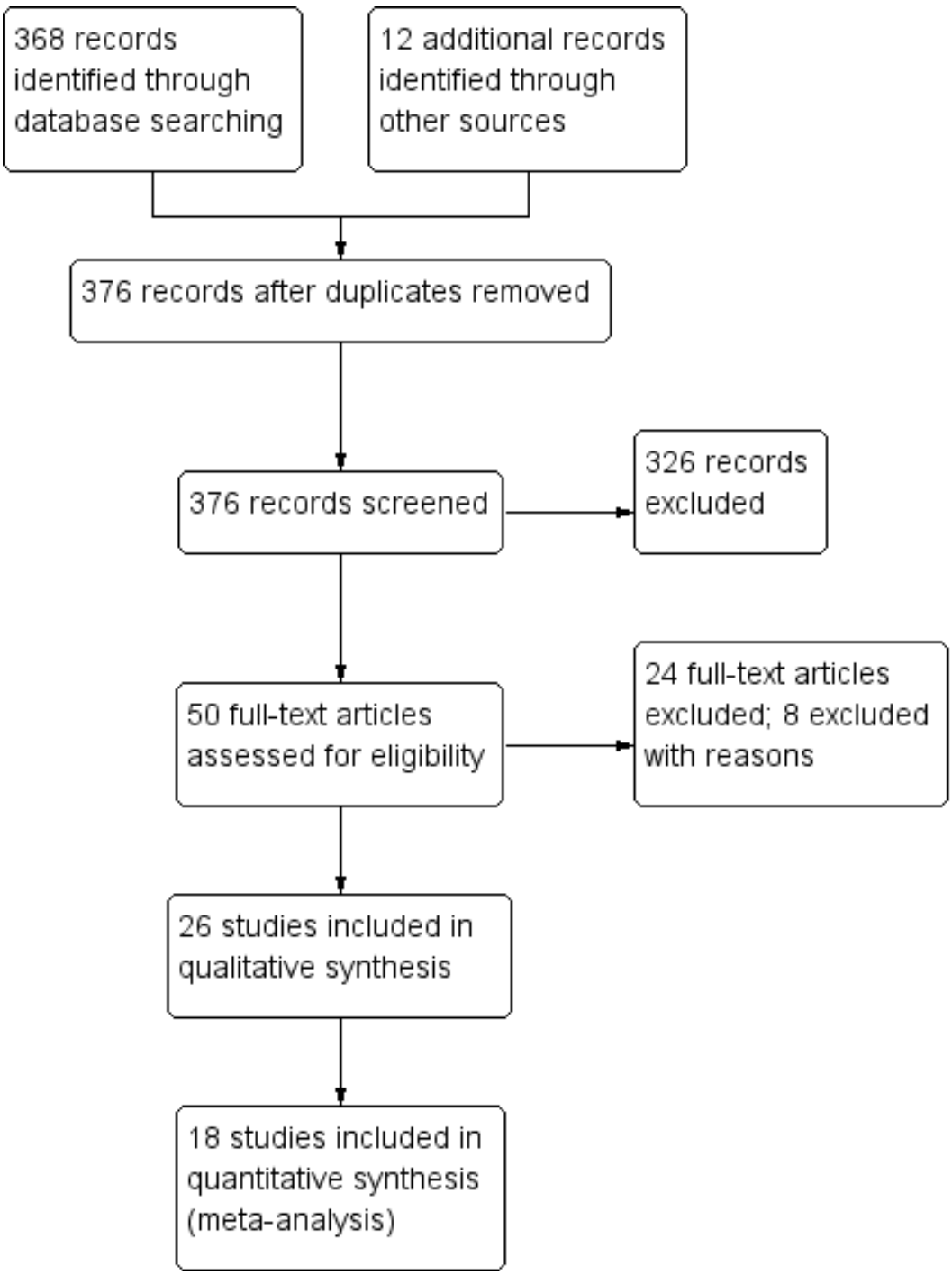
RESULTS

Description of studies

Results of the search

We identified 376 citations by using the search strategy, and selected 50 articles for full-text review after screening the abstracts of the initial search results. See Figure 1 for further details.

Figure 1. Study flow diagram.



We included 26 studies with 526 participants in the review.

Included studies

See the 'Characteristics of included studies' table.

Study characteristics

Eighteen studies with 276 participants provided data for the primary outcome of breathlessness and were included in the meta-analysis (Abernethy 2003; Bar-Or 1982; Bruera 1993; Charles 2008; Chua 1997; Eiser 1991; Harris-Eze 1995; Hui 2014; Jankleson 1997; Jensen 2012; Johnson 1983; Leung 1996; Light 1996; Mazzocato 1999; Noseda 1997; Oxberry 2011; Poole 1998; Woodcock 1981). Four additional studies examined the primary outcome of breathlessness but we were unable to extrapolate data for meta-analysis (Davis 1996; Grimbert 2004; Johnson 2002; Masood 1995). Two additional studies did not report the primary outcome, but reported secondary outcomes (Williams 2003; Young 1989). Two additional studies compared opioids to an intervention other than placebo; Navigante 2010 compared morphine to midazolam, Rice 1987 compared codeine to promethazine. Oxberry 2011 compared morphine with oxycodone and placebo. The other 23 included studies compared opioids to a placebo solution, usually normal saline.

Twenty-four included studies were crossover trials. Hui 2014 was a parallel group RCT that compared subcutaneous fentanyl with placebo, and Navigante 2010 was a parallel RCT that compared morphine to midazolam.

Most included studies were performed over a fixed period during one day or on two consecutive days, with a washout period of only on day. Six studies involved more chronic administration of the drug or placebo, continuing for study periods between four days and six weeks, with a washout period of between three days and two weeks (Woodcock 1981; Johnson 1983; Eiser 1991; Poole 1998; Abernethy 2003; Navigante 2010).

Participants

All included studies were small, with fewer than 50 participants per treatment arm. The number ranged from six to 25 participants, with an average of 19 participants per study. Fifteen studies recruited ambulatory care participants, one study recruited inpatients, one study had a mix of inpatients and outpatients, and nine studies did not specify the participant setting.

Ten studies involved primarily or exclusively participants with chronic obstructive pulmonary disease (COPD) (Abernethy 2003; Bar-Or 1982; Light 1996; Poole 1998; Eiser 1991; Jankleson 1997; Jensen 2012; Johnson 1983; Noseda 1997; Woodcock 1981). Four studies included only participants with malignant disease (Bruera 1993; Charles 2008; Hui 2014; Mazzocato 1999), two studies were comprised primarily of cardiac failure participants (Chua 1997; Oxberry 2011), and one study was comprised of participants with interstitial lung disease (Harris-Eze 1995).

Intervention

Eight studies specifically recruited participants not currently on opioids (Abernethy 2003; Harris-Eze 1995; Jensen 2012; Johnson 1983; Masood 1995; Navigante 2010; Poole 1998; Rice 1987), who were thus opioid naive. Seven studies did not specify whether opioid use was part of the exclusion criteria, or whether it formed part of the co-interventions. Six studies examined participants already on opioids (Bruera 1993; Charles 2008; Grimbert 2004; Hui 2014; Mazzocato 1999; Bruera 2005). Charles 2008, Mazzocato 1999, and Grimbert 2004 used a predefined dose of opioids, regardless of the participant's current opioid use. Bruera 2005 used the participant's usual dose plus half the equivalent dose for the interventional arm and the usual dose plus normal saline for the control arm. Bruera 1993 used 50% more of the participant's usual dose in a PRN (*pro re nata*, or as required) manner. Hui 2014 used a sliding scale of 30 mcg to 350 mcg fentanyl for all interventional participants, and included regular opioids in both the interventional and control arm.

The included studies used the following opioids: oral dihydrocodeine (Bar-Or 1982; Chua 1997; Johnson 1983), oral diamorphine (Eiser 1991), oral morphine (Light 1996; Mazzocato 1999; Poole 1998; Abernethy 2003; Woodcock 1981), nebulised morphine (Charles 2008; Harris-Eze 1995; Leung 1996; Jankleson 1997; Noseda 1997), subcutaneous fentanyl (Hui 2014), nebulised fentanyl (Jensen 2012), oral oxycodone (Oxberry 2011), and hydromorphone (Charles 2008).

The doses of dihydrocodeine ranged from 15 mg three times a day to 60 mg three times a day in 1 mg/1 kg doses. The diamorphine dose ranged from 2.5 to 5 mg four times a day. Sustained release morphine was used in 10 to 20 mg doses. Oxycodone was administered in 2.5 mg doses four times a day. Subcutaneous morphine doses ranged from 2.5 to 10 mg. There was a wide range of nebulised morphine doses used, from 1 mg to 50 mg.

Nine studies delivered the opioids by the oral route (Bar-Or 1982; Eiser 1991; Johnson 1983; Woodcock 1981; Abernethy 2003; Chua 1997; Light 1996; Oxberry 2011; Poole 1998), two studies used parenteral opioids (Bruera 1993; Hui 2014), and ten studies gave the drugs via nebulisation (Davis 1996; Harris-Eze 1995; Masood 1995; Young 1989; Grimbert 2004; Jankleson 1997; Leung 1996; Noseda 1997; Charles 2008; Jensen 2012). Some studies compared different routes of administration.

Eight studies continued regular use of co-interventions including steroids and bronchodilators (Bruera 1993; Masood 1995; Woodcock 1981; Young 1989; Charles 2008; Hui 2014;

Mazzocato 1999; Rice 1987). Two studies involved the use of oxygen inhalation (Leung 1996; Noseda 1997). In both cases the measures were applied to the use of the drug and placebo arm and we felt this did not bias the study results.

Outcomes

Twelve studies performed some form of exercise testing (Bar-Or 1982; Hui 2014; Poole 1998; Chua 1997; Harris-Eze 1995; Leung 1996; Light 1996; Eiser 1991; Jensen 2012; Johnson 1983; Williams 2003; Woodcock 1981). They used a variety of different exercise tests, including incremental treadmill tests, incremental cycle ergometer tests, non incremental treadmill or endurance treadmill tests, and six-minute walk tests (6MWT).

There was significant variety in the reporting of breathlessness outcome measure, but all studies used well-validated scales, including the visual analogue scale (VAS), Borg Scale, and oxygen cost diagram (McGavin 1978; O'Donnell 1998). Several studies did not report breathlessness at a fixed point during exercise (Beauford 1993; Masood 1995). Some studies did not report the primary outcome of breathlessness, did not include sufficient data, did not report standard deviations (SDs) or error, or reported data in such a way that the relevant numbers could not be extrapolated (Young 1989; Davis 1996; Jankleson 1997; Masood 1995; Williams 2003; Grimbert 2004).

In most cases, the studies asked their participants to assess their own levels of breathlessness, by VAS or Borg scale. Some studies asked participants to guess which substance contained the opioid or placebo drug, and other studies offered participants the opportunity to continue on opioid therapy. One study, Poole 1998, used the Chronic Respiratory Disease Questionnaire (CRQ) dyspnoea scale.

Excluded studies

See the 'Characteristics of excluded studies' section.

We excluded eight studies for the following reasons: participants were not randomised (Beauford 1993; Peterson 1996; Shorati 2012; Smith 2009), there was no comparison to a placebo or other intervention (Allard 1999; Bruera 2005; Navigante 2003), or it was a review (Thomas 2010).

Ongoing studies

We identified two ongoing studies (Cuervo Pinna 2012; Daubert 2014).

Risk of bias in included studies

We assessed the risk of bias in the included studies using the Cochrane 'Risk of bias' assessment tool (Higgins 2011), and included the domains of allocation, blinding, incomplete outcome data, and other bias. We judged eight studies to be at an overall low risk of bias. We considered 18 studies to be at an overall unclear risk of bias, that is we had insufficient information to make a judgement, usually due to inadequate descriptions of the methods of randomisation or blinding.

Please see Figure 2 and Figure 3 for a summary of the 'Risk of bias' findings.

Figure 2.

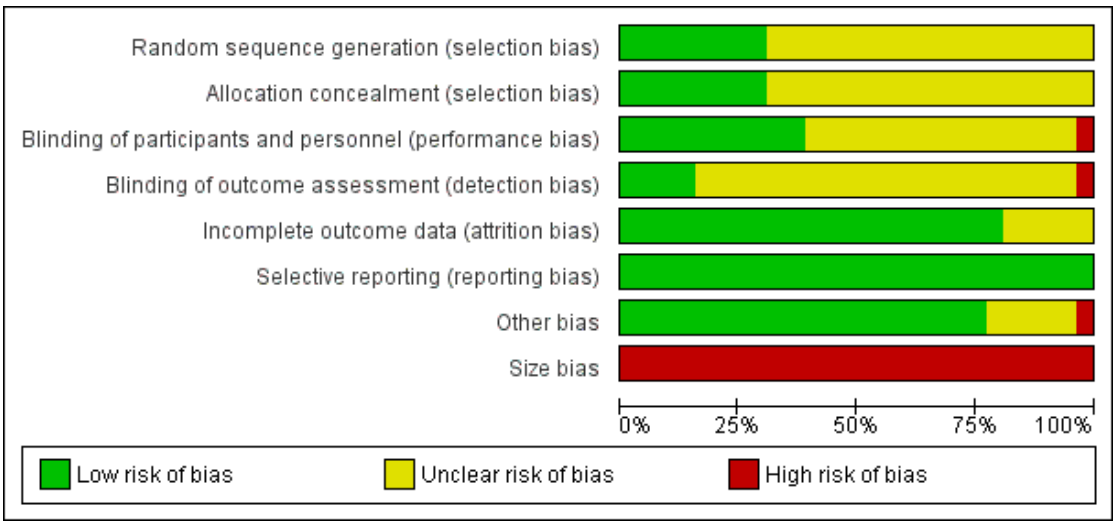
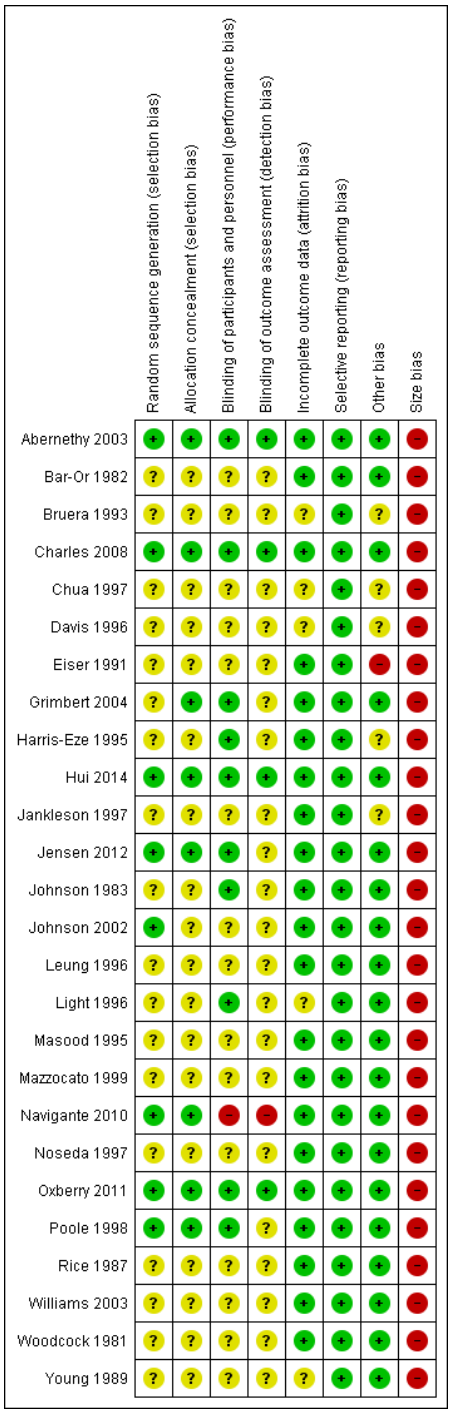


Figure 3.



We assessed the overall quality of the evidence for each outcome using the GRADE system (GradePro 2015) and presented these results in the 'Summary of findings' tables, which shows the main findings of the review 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 the main outcomes.

Allocation

We assessed random sequence generation as adequate (low risk) in eight out of 26 studies (Poole 1998; Johnson 2002; Abernethy 2003; Charles 2008; Navigante 2010; Oxberry 2011; Jensen 2012; Hui 2014). Most studies (18 studies) did not describe the methods of sequence generation (unclear risk of bias).

We judged allocation concealment as adequate (low risk) in eight out of 26 studies (Poole 1998; Abernethy 2003; Grimbert 2004; Charles 2008; Navigante 2010; Oxberry 2011; Jensen 2012; Hui 2014), which suggests that information from most of the studies presented an unclear risk of bias. Many studies did not state the method of allocation concealment, though many of the studies reported their design as randomised.

We did not judge any studies as at high risk of allocation or random sequence generation bias.

Blinding

Blinding of participants and personnel with respect to the intervention was adequate, though blinding of the outcome assessment was overall poor.

We judged the blinding of participants and personnel to be adequate in 10 out of 26 studies, indicating low risk of bias (Johnson 1983; Harris-Eze 1995; Light 1996; Poole 1998; Abernethy 2003; Grimbert 2004; Charles 2008; Oxberry 2011; Jensen 2012; Hui 2014). These studies used placebo interventions, which were reported to have been designed to appear the same as the opioid intervention. We judged blinding of participants and personnel to be at high risk of bias in Navigante 2010 because only the participants were blinded, not the investigators or those that performed the outcome assessment. Of the 15 studies that we assessed as being at an unclear risk of bias for this domain, the studies did not specifically or adequately describe the details to which the intervention and control were blinded, though many studies reported themselves as blinded.

Overall, blinding of the outcome assessment was poor. We assessed only four out of 26 studies as at low risk of bias (Abernethy 2003; Charles 2008; Oxberry 2011; Hui 2014). We judged Navigante 2010 to be at high risk as those performing the outcome assessment were not blinded, and we judged the remaining 21 studies to be at an unclear risk of bias. Most studies did not clearly describe the methods by which the outcome assessment was blinded, though some described themselves as double blinded. This may be in part due to the primary outcome of breathlessness requiring the participant to score their own symptoms.

Incomplete outcome data

The included studies generally reported data completely, with 21 out of 26 studies adequately described. We therefore judged them to be at low risk of bias. We judged the remaining five studies to be at an unclear risk of bias (Bruera 1993; Chua 1997; Davis 1996; Light 1996; Young 1989). The included studies usually recorded adverse events, but generally these did not cause participants to drop out of the study. Most studies were conducted on consecutive days, so loss to follow-up was less likely to occur.

Selective reporting

We judged the risk of selective reporting to be low in all studies. We did not detect any evidence of selective reporting bias.

Other potential sources of bias

We judged 19 studies to be at low risk for this domain (Woodcock 1981; Bar-Or 1982; Rice 1987; Young 1989; Masood 1995; Leung 1996; Light 1996; Noseda 1997; Poole 1998; Mazzocato 1999; Johnson 2002; Abernethy 2003; Williams 2003; Grimbert 2004; Charles 2008; Navigante 2010; Oxberry 2011; Jensen 2012; Hui 2014), and one at high risk of bias because it did not state that it systematically studied adverse events (Eiser 1991). We judged the remaining five studies to be at unclear risk of other bias because insufficient information was available.

Size

The studies were of small sample size, with a mean of 19 participants per study, and with fewer than 50 participants per treatment arm. Thus we judged all 26 studies to be at overall high risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**

Primary outcome: breathlessness

Opioids versus placebo

All studies

The primary outcome of breathlessness was reported in 24 out of 26 included studies. We performed meta-analysis for the main outcome of breathlessness for 18 studies. We analysed change from before and after administration and post-administration measurement. We used standardised mean differences (SMDs) since the studies measured comparable outcomes on different scales (the SMD can be converted to units in a VAS or Borg score by multiplying the SD for a particular study). Where studies presented standard errors of the mean, we correlated them to SD. We took measurements from the intervention and control group, and analysed the data as if it was a parallel trial, due to lack of paired data available. This may increase the unit of analysis error.

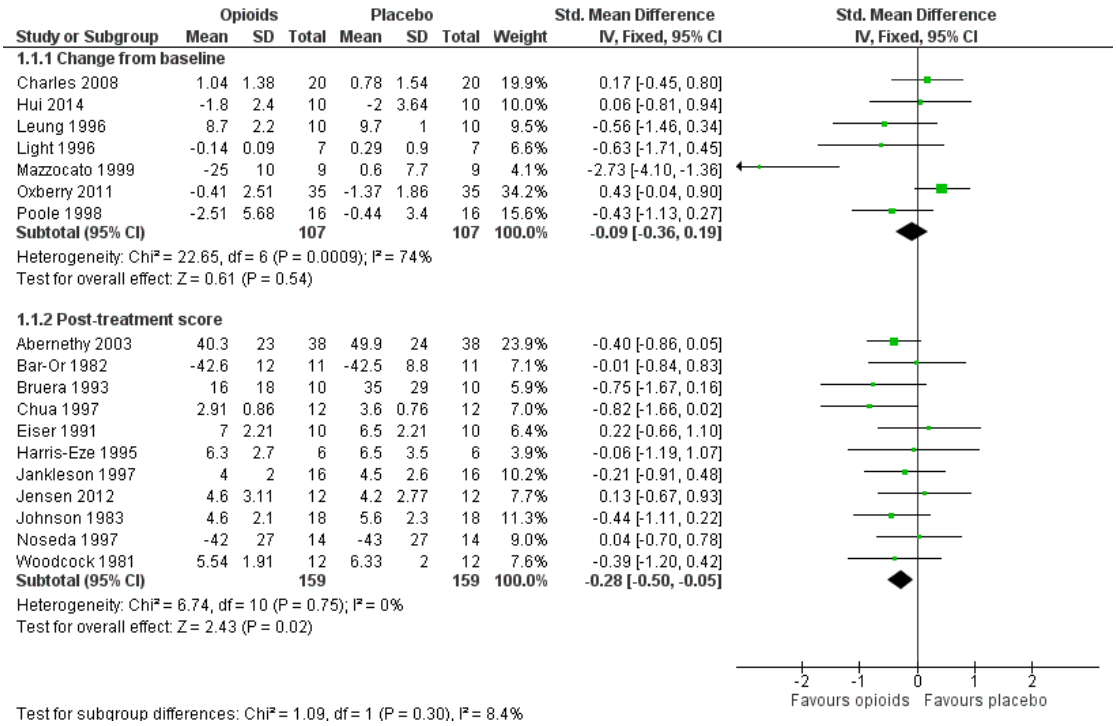
Individually, nine studies reported a statistical benefit using opioids for breathlessness, and 10 studies reported no difference comparing opioids with placebo. Three studies found a significant difference in exercise tolerance, and one found no difference. When we excluded nebulised morphine studies, 10 individual studies found a significant effect on breathlessness, compared to three studies that found no benefit.

We have presented meta-analyses using SMDs in the figures below. We have included fixed-effect meta-analyses for opioids compared with placebo for breathlessness outcome for the following.

- All studies.
- By type of opioid.
- By mode of administration.
- By condition.

Please see Figure 4 for more details.

Figure 4.



The meta-analysis demonstrates a small treatment effect for breathlessness (change from baseline, seven studies, 107 participants; SMD −0.09, 95% confidence interval (CI) −0.36 to 0.19; P = 0.54 (Analysis 1.1); post-treatment score, 11 studies, 159 participants, SMD −0.28, 95% CI −0.50 to −0.05; P = 0.02 (Analysis 1.1)). There was statistically significant heterogeneity between the results of the trials for breathlessness change from baseline (I^2 statistic = 74%, P = 0.0009), but the direction of effect was consistent, and the sample size of the studies was small. We considered the evidence to be of low quality for post-treatment scores and of very low quality for change from baseline breathlessness.

Johnson 2002 presented data using the interquartile range and thus we could not pool these data in the meta-analysis. The study demonstrated a statistically significant improvement in breathlessness from baseline using oral morphine compared to placebo. Masood 1995 presented data using CIs with a very small sample size (12 subjects), so we could not pool its data in the meta-analysis. The study did not demonstrate any statistically significant difference in terms of breathlessness comparing nebulised or intravenous morphine with placebo. Davis 1996 reported a post-treatment score expressed as a percentage of pre-treatment score change from baseline. The ratio for opioids was 0.64 compared to normal saline of 0.84 was statistically significant at P = 0.001, however the difference in ratios between the two groups was not significant (P = 0.17).

We did not analyse breathlessness according to a priori subgroups.

Type of opioid

There was a strong treatment effect for morphine (change from baseline: five studies, 77 participants, SMD −0.18, 95% CI −0.51 to 0.15; P = 0.28 (Analysis 2.1); post-treatment scores: six studies, 96 participants; SMD −0.32, 95% CI −0.60 to −0.03; P = 0.03 (Analysis 2.1)), and for dihydrocodeine (post-treatment score: three studies, 41 participants; SMD −0.74, 95% CI −1.33 to −0.15; P = 0.01 (Analysis 3.1)).

There was no effect for hydromorphone (change from baseline: one study, 20 participants, MD 0.26; 95% CI −0.65 to 1.17; P = 0.57), oral diamorphine (one study, 10 participants; MD 0.50, 95% CI −1.44 to 2.44; P = 0.61), oxycodone (one study, 35 participants; MD −0.08, 95% CI −1.03 to 0.87; P = 0.16 (Analysis 3.1)), or fentanyl (change from baseline: one study, 10 participants, MD −0.20, 95% CI −2.50 to 2.90; P = 0.88 (Analysis 4.1); post-treatment score: one study, 12 participants; MD 0.40, 95% CI −1.96 to 2.76; P = 0.74 (Analysis 4.1)).

Condition

There were insufficient data to suggest opioids would be more beneficial in any specific condition. The effect for COPD was as follows: change from baseline: two studies, 23 participants, SMD −0.49, 95% CI −1.08 to 0.10; P = 0.1; post-treatment scores: eight studies, 131 participants; SMD −0.21; 95% CI −0.45 to 0.04; P =0.1, (Analysis 5.1). For cancer-related dyspnoea it was: change from baseline: three studies, 39 participants, SMD −0.21; 95% CI −0.68 to 0.26; P = 0.21; post-treatment score: one study, 10 participants, SMD −0.75; 95% CI −1.67 to 0.16; P = 0.11 (Analysis 5.1). There was no significant difference overall for heart failure (change from baseline: one study, 35 participants; SMD 0.43, 95% CI −0.04 to 0.90, P = 0.08 favouring placebo; post-treatment score: one study, 12 participants, SMD −0.82, 95% CI −1.66 to 0.02; P = 0.06 favouring opioids), and for interstitial lung disease (one study, six participants; SMD −0.06; 95% CI −1.19 to 1.07; P = 0.92 (Analysis 5.1)).

Mode of administration

The effect for oral opioids was as follows: change from baseline: three studies, 58 participants; SMD 0.07, 95% CI −0.30 to 0.44; P = 0.72; post-treatment score: six studies, 96 participants; SMD −0.27, 95% CI −0.56 to 0.02, P = 0.07 (Analysis 6.1)). For the subcutaneous route it was as follows: change from baseline: one study, 10 participants; MD 0.20, 95% CI −2.50 to 2.90; P = 0.88, post-treatment score: one study, 10 participants; MD −19.00, 95% CI −40.15 to 2.15; P = 0.08 (Analysis 6.2)).

There was no difference in breathlessness for nebulised opioids compared to placebo (change from baseline: two studies, 30 participants; SMD −0.06; 95% CI −0.57 to 0.45; P = 0.81; post-treatment score: four studies, 48 participants; SMD −0.03; 95% CI −0.43 to 0.37; P = 0.87 (Analysis 6.1)).

Opioids versus other interventions

Navigante 2010 included 63 participants and examined morphine versus midazolam. The study found a statistically significant treatment effect that favoured midazolam for the outcome of breathlessness (MD 2.00, 95% CI 1.07 to 2.93; P < 0.0001; Analysis 10.1).

Rice 1987 included seven participants and examined codeine versus promethazine. The effect favoured codeine for breathlessness (MD −0.30; 95% CI −0.83 to 0.23; P = 0.27; Analysis 11.1).

Dose

We attempted to calculate the morphine dose equivalent that would confer relief from breathlessness, but due to significant heterogeneity between trials there was no clear dose threshold. We calculated oral morphine equivalent doses and these are represented in the 'Characteristics of included studies' tables. Light 1996, Oxberry 2011, Bar-Or 1982, and Abernethy 2003 administered 20 mg to 30 mg oral morphine equivalent daily, and three out of four studies found a benefit. Mazzocato 1999, Eiser 1991, and Johnson 1983 administered 13 mg to 15 mg oral morphine equivalent daily, and two out of three studies found a benefit. Woodcock 1981, Johnson 2002, and Chua 1997 administered 5 mg oral morphine equivalent, and all studies found benefit. Poole 1998, Hui 2014, and Bruera 1993 had a wide range of doses and so we could not include these studies in the analysis.

There were few studies that calculated the bioequivalence of nebulised morphine to subcutaneous route. It may be as low as 5% (Masood 1996). Due to a potentially different mode of action, we did not use nebulised opioid doses to calculate bioequivalence.

It is difficult to ascertain the appropriate dose for the relief for breathlessness. It is possible that 5 mg oral morphine daily may confer benefit, but further research is required in this area.

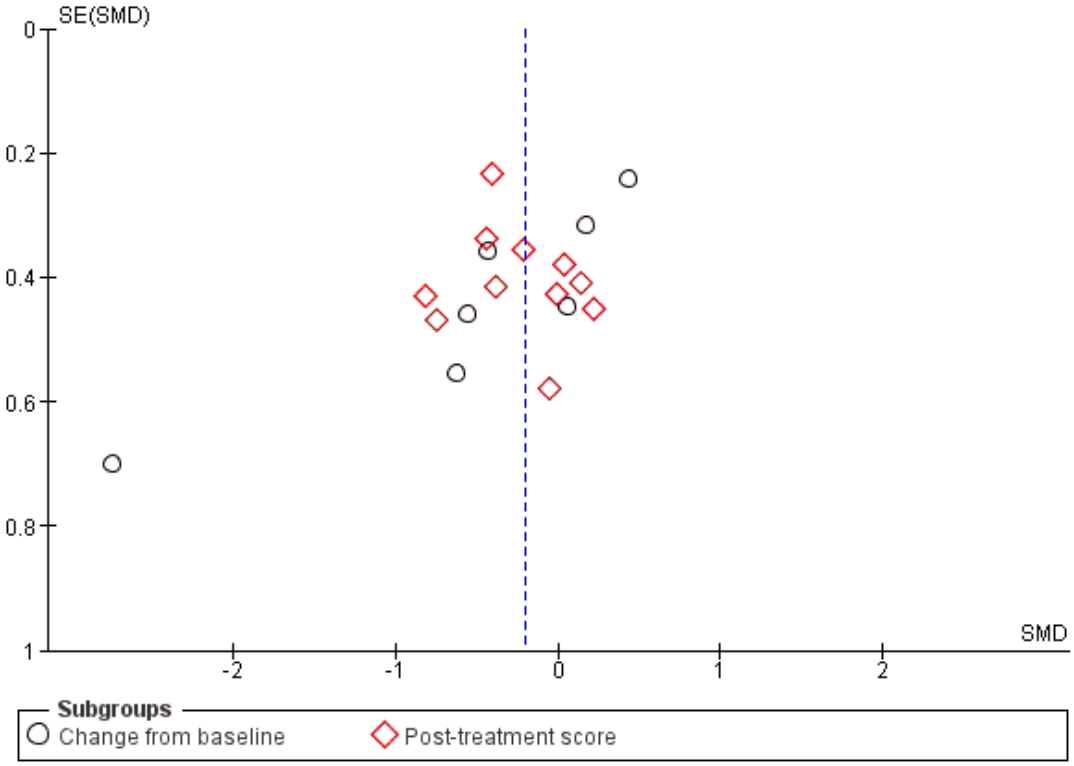
We performed a sensitivity analysis that compared fixed-effect versus random-effects data, and excluded those with an unclear risk of bias. However, it made very little difference to the overall result

(Table 1). We also excluded those studies with an unclear risk of bias, which reduced the effect size.

We performed funnel plot analysis to estimate the risk of bias by comparing the effect of the intervention effect with each study's size or precision. In the setting of an intervention effect, and symmetry of the funnel plot, a low risk of publication bias was suggested.

Please see Figure 5 for more details.

Figure 5. Funnel plot of comparison: 1. Opioids versus placebo, outcome: 1.1 Breathlessness.



Secondary outcomes

Quality of life

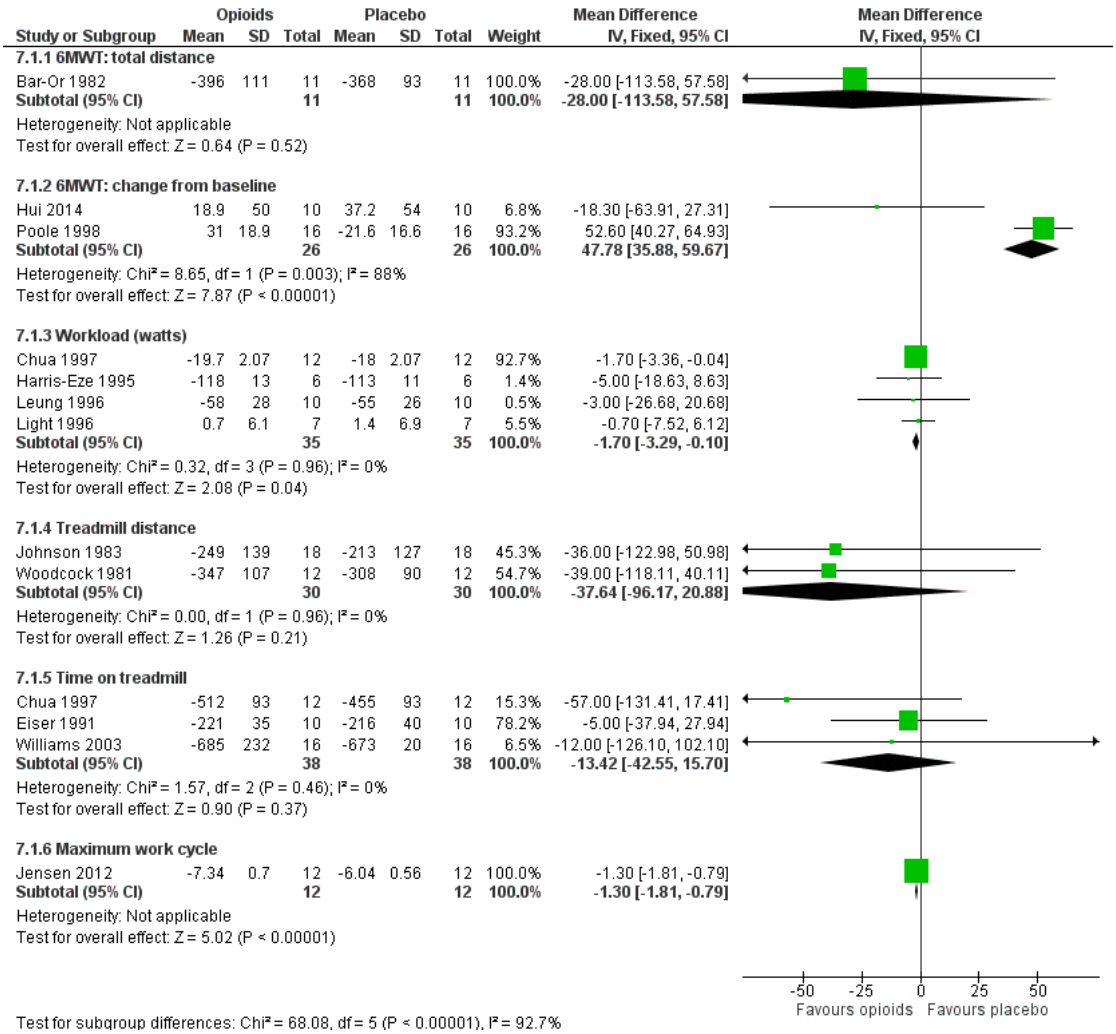
Four studies examined the effects on quality of life. Poole 1998 compared morphine to placebo and used the Chronic Respiratory Disease Questionnaire. The study found no difference in the total score. However, there was a statistically significant difference in the mastery domain scores that favoured placebo, and the study authors suggested that participants may feel less in control when using morphine. This was the only study that presented data that we were able to use for meta-analysis (Analysis 8.1). Eiser 1991 compared morphine to placebo and found no statistically significant difference in well being. Abernethy 2003 compared oral morphine to placebo and reported that there was no significant difference in overall sense of well being, although these data were not reported. Oxberry 2011 comparing oral morphine, oral oxy-

codone, and placebo in heart failure participants and reported no difference in the SF-12, a well-validated 12 question survey for quality of life, although these data were not presented.

Exercise tolerance

Fourteen studies examined exercise tolerance, including 12 studies that compared opioids versus placebo.
Please see Figure 6 for more details.

Figure 6.



Meta-analysis demonstrated a significant improvement in maximal workload achieved (four studies, 35 participants; MD −1.70; 95% CI −3.29 to −0.10; P = 0.04), and in maximum work cycle (one study, 12 participants; MD −1.30; 95% CI −1.81 to −0.79; P < 0.00001) (Analysis 7.1).

There was an improvement of change in treadmill distance of 37.64 m that favoured opioids (two studies, 30 participants; MD −37.64, 95% CI −96.17 to 20.88; P = 0.21), and an improvement in time on treadmill of 13.42 seconds that favoured opioids (three studies, 38 participants; MD −13.42, 95% CI −42.55 to 15.70; P = 0.37).

There were conflicting results for the effect of opioids on the effects of the 6MWT. The change from baseline distance demonstrated a benefit that favoured placebo (two studies, 26 participants; MD 47.78, 95% CI 35.88 to 59.67; P < 0.00001, with significant heterogeneity, I^2 statistic = 88%, P = 0.003), which was largely due one study (Poole 1998). The effect for the 6MWT total distance was as follows; one study, 11 participants; MD −28.00, 95% CI −113.58 to 57.58; P = 0.52) (Analysis 7.1).

Light 1996 assessed minute ventilation in morphine compared with promethazine, and found no difference in workload or minute ventilation.

Rice 1987 assessed a 12-minute walk test in codeine compared to promethazine, and found no statistical significance.

There were no long-term data presented for exercise tolerance.

We graded the evidence as of low methodological quality due to the small size of the included trials, significant heterogeneity across trials, and inconsistency of outcome measurements.

Performance status

No studies examined performance status.

Pulse oximetry

Twelve studies measured pulse oximetry, but all found no difference between opioid and placebo treatment.

Arterial blood gas analysis and end tidal carbon dioxide measurement

Only three studies performed arterial blood gas analysis (Bar-Or 1982; Eiser 1991; Chua 1997). All found no significant difference in arterial oxygen or carbon dioxide levels. Four studies performed end tidal carbon dioxide analysis (Bar-Or 1982; Harris-Eze 1995; Light 1996; Chua 1997). Three studies found no significant difference, and one study found a statistically significant increase in end tidal carbon dioxide levels in the dihydrocodeine group compared to placebo (Chua 1997).

Adverse events

Adverse events from opioids are well recognised, and may be part of the practitioner's reluctance to prescribe in the setting of breathlessness. Only 14 studies reported any adverse events, and only nine studies reported data that we were able to use in meta-analyses (Analysis 9.1; Analysis 9.2; Analysis 9.3). The adverse effects reported included drowsiness, nausea and vomiting, and constipation. In those studies, participants who were 4.73 times more likely to experience nausea and vomiting compared to placebo, three times more likely to experience constipation, and 2.86 times more likely to experience drowsiness. Twelve participants across all studies stopped the trial early due to adverse events in the treatment arm (one participant due to drowsiness and five due to nausea and vomiting (Bar-Or 1982); three participant s withdrew due to morphine related side effects (Abernethy 2003); two participants withdrew from Oxberry 2011 due to bowel and bladder symptoms; and one participant withdrew from Poole 1998 due to severe constipation).

Mortality

Three participants died during the Noseda 1997 study. However, the study authors did not believe that this was related in any way to the study interventions. All of these participants had advanced disease and the deaths were likely to be expected.

Quality of the evidence

We assessed the quality of evidence from the included studies as of low to very low quality. We only included RCTs, although some studies provided an incomplete description of randomisation. We aimed to included double blind RCTs, however two studies were only single blinded. There was inconsistency in the reporting of outcome measures. We analysed the data according to a fixed-effect model due to small study bias, and for some outcomes heterogeneity was high. There was a risk of imprecise results due to the low numbers of included participants. For these reasons we downgraded the quality of the evidence to low for breathlessness post-treatment score, and very low for breathlessness change from baseline.

Please see the 'Summary of findings' tables for more information (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Morphine compared with midazolam in people with breathlessness in advanced disease or terminal illness

Patient or population: adults with refractory breathlessness
Setting: outpatient setting
Intervention: morphine
Comparison: midazolam

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Midazolam	Morphine				
Breathlessness: post-treatment score[1]	The mean dyspnoea score in the midazolam group was 4	The mean post-treatment score was 2 points higher in the opioids group (ranging from 1.07 to 2.93)	-	63 (1 RCTs)	⊕◯◯◯ **very low**[2,3,4]	A lower score indicates an improvement in breathlessness

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

[1]The study authors assessed breathlessness according to the numeric rating scale (NRS) for dyspnoea at 5 days.
[2]Limitations in the design and implementation of available studies suggest a high risk of bias.
[3]There was only one study.
[4]There was evidence of significant heterogeneity.
Abbreviations: RCT: randomised controlled trial; CI: confidence interval; RR: risk ratio.

Codeine compared with promethazine in people with breathlessness in advanced disease or terminal illness

Patient or population: adults with refractory breathlessness
Setting: outpatient setting
Intervention: codeine
Comparison: promethazine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Promethazine	Codeine				
Breathlessness: post-treatment score[1]	The mean dyspnoea score in the promethazine group was 6	The mean post-treatment score was 0.30 points lower in the codeine group (ranging from 0.83 points lower to 0.23 points higher)	-	7 (1 RCT)	⊕◯◯◯ **very low**[2,3,4]	A lower score indicates an improvement in breathlessness

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

[1]Breathlessness was assessed according to the oxygen cost diagram at 1 month.
[2]Limitations in the design and implementation of available studies suggesting a high risk of bias.
[3]Only one study.
[4]Significant heterogeneity.
Abbreviations: RCT: randomised controlled trial; CI: confidence interval; RR: risk ratio.

DISCUSSION

Summary of main results

This Cochrane review demonstrates low quality evidence for a small clinically significant effect for oral and subcutaneous opioids compared to placebo in the relief of breathlessness. There is insufficient evidence at this level to suggest that nebulised opioids are more effective than placebo in relieving breathlessness. This may be explained by the difference in pharmacodynamics of opioids. Not all opioids can be administered via inhaled or intranasal modes. In order to be absorbed by the intranasal or intraoral mucosa, opioids need to be lipophilic. Fentanyl fulfils this criterion as it is highly lipid soluble, whereas morphine is hydrophilic. Therefore, morphine is poorly absorbed via this route (Bausewein 2008).
We found that opioids are inferior for the relief of breathlessness when compared to midazolam, based on one study (Navigante 2010). This is consistent with the Cochrane Review by Simon 2010, which demonstrated a non-significant beneficial effect that favoured benzodiazepines compared to opioids.

Overall completeness and applicability of evidence

The strength of the evidence available is limited by the small sample size of the studies, which involved six to 63 participants with a mean of 19 participants per study, and by the variability of outcome measures utilised, which limits meta-analysis.
Quality and applicability of evidence is also limited in that studies measured the response to intervention shortly after administration, in a crossover study design, often conducted on two consecutive days with the intervention on one day and control the next. Few studies involved multiple doses or titration according to the participants' individual response.
We analysed the data as if all the included studies were parallel group trials, due to lack of paired data available. This may introduce a unit-of-analysis error, the confidence intervals (CIs) may be too wide, and the data may be under weighted, thus disguising clinically important heterogeneity (Elbourne 2002). We analysed the data using a fixed-effect model due to concerns regarding small-study bias, and this may underestimate clinically important differences.
The lack of evidence for nebulised studies may be influenced by the lack of consistency between studies, as nebuliser devices between different studies were not randomised, and particle size and distance from device to mouth varied. Therefore the total amount of opioid reaching the lungs may have varied.
The conclusions we can draw from this review are limited to the dosages used in the included studies. The included studies used a wide range of doses, thus an enhanced effect may be seen with higher doses. However, the risk of adverse events, including drowsiness, may also increase.
The studies on breathlessness used a variety of different outcome measures, including the Borg and visual analogue scale (VAS). The point at which studies measured the data also varied, and may or may not have included an exercise test. The studies reported data variably as either a change from baseline or post-treatment change. This variability in data reporting causes difficulty in interpretation, therefore it is recommended that future studies standardise outcome measures.
Less than half of the studies included assessed pulse oximetry, and only three studies assessed arterial oxygen and carbon dioxide levels. Only one study found a difference in end tidal carbon dioxide levels (Chua 1997). It is unlikely that opioids have a significant impact on oxygen levels in the management of breathlessness.
Not all studies reported adverse outcomes. The most common symptom was drowsiness, followed by nausea and vomiting, and constipation. Adverse effects caused some participants to withdraw from the trial. These trials used high doses of morphine at 20 mg oral morphine daily or more. Further research is required to determine if the same improvement of breathlessness can be achieved at lower doses with a reduction in adverse events.
Very few studies included data on quality of life. This is an important omission as the participants in these studies were all symptomatic, thus quality of life data are particularly relevant.

Quality of the evidence

We assessed the quality of the evidence presented in this Cochrane review using GRADEpro Guideline Development Tool (GDT) software (GradePro 2015) and presented it in the 'Summary of findings' tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). We rated the quality of the evidence using the following grades: very low, low, moderate, or high. Very low quality evidence means we are uncertain about the results. High quality evidence means we are very certain about the results. For this review, we found the evidence to be of low quality.
We only included randomised controlled trials (RCTs), however 17 out of 26 studies had an unclear risk of bias overall, mostly due to inadequate reporting of randomisation and allocation sequence.
We aimed to included double blind RCTs, however two studies were only single blinded.
There was significant heterogeneity between studies for the main outcome of breathlessness (I^2 statistic =74%, P = 0.0009), which may be explained by the small sample size and inconsistency with outcome measures. Therefore, these results should be interpreted with caution.
There was a risk of imprecise results due to the low numbers of included participants.
For these reasons we downgraded the quality of the evidence to low for breathlessness post-treatment score, and very low for breathlessness change from baseline. Further research using larger studies for longer duration, with consistent outcome measures, and adequate randomisation and blinding, is likely to have an important impact on our confidence in the estimate of effect and likely to

change the estimate.

Potential biases in the review process

We conducted this review in accordance with established Cochrane standards. Two review authors independently screened search results and resolved discrepancies by discussion and consensus. We did not restrict the literature search by language and we translated two studies into English to determine suitability for inclusion. Also we contacted the study authors where it was unclear if a study met the inclusion criteria, though none of the study authors responded.

Publication bias is possible, whereby a failure to identify unpublished negative trials could have lead to an overestimation of the effect of opioids for breathlessness.

We analysed the data as if all the included studies were parallel group trials, due to lack of paired data available. This may introduce a unit-of-analysis error, the CIs may be too wide, and the data may be underweighted, thus disguising clinically important heterogeneity (Elbourne 2002).

Agreements and disagreements with other studies or reviews

This review builds on the review by Jennings 2001 "Opioids for the palliation of breathlessness in advanced disease and terminal illness", which concluded that there is evidence in favour of use for oral or parenteral opioid drugs to treat breathlessness, and there is no supporting evidence to support the use of nebulised opioids for the treatment of breathlessness.

This Cochrane review included a further 11 studies, although we chose not to include all studies previously included by Jennings 2001 due to concerns regarding lack of randomisation.

We also undertook further subgroup analyses, and found a particular benefit using morphine.

This Cochrane review also examined the use of opioids compared to other interventions. Our review included one study, Navigante 2010, which found that opioids were inferior when compared to intravenous midazolam for the relief of breathlessness. This is consistent with the Cochrane review by Simon 2010, which compared benzodiazepines to any other intervention, and found a small effect that favoured benzodiazepines over opioids in one study, with an overall small effect size.

AUTHORS' CONCLUSIONS

Implications for practice

For people with breathlessness in advanced disease or terminal illness

- There is low quality evidence showing benefit for the use of oral opioids for the relief of breathlessness in adults with advanced disease and terminal illness.
- Based on this evidence, it is possible that opioids lead to a short-term increase in exercise capacity.
- There is no evidence to support the use of nebulised opioids for the treatment of breathlessness.

For clinicians

- There is low quality evidence showing benefit for the use of oral opioids for the relief of breathlessness in some adults with advanced disease and terminal illness.
- Based on this evidence, it is possible that opioids lead to a short-term increase in exercise capacity.
- It is difficult to draw firm conclusions about the clinical significance of the pooled estimate of treatment effect in our meta-analysis as we used standardised mean difference (SMD) values to combine studies due to the lack of standardised outcome measures but the magnitude of the treatment effect appears small.
- There is no evidence to support the use of nebulised opioids for the treatment of breathlessness.

For policy makers

- There is low quality evidence showing benefit for the use of oral opioids for the relief of breathlessness in adults with advanced disease and terminal illness.
- Based on this evidence, it is possible that opioids lead to a short-term increase in exercise capacity.
- It is difficult to draw firm conclusions about the clinical significance of the pooled estimate of treatment effect in our meta-analysis as we used the SMD to combine studies due to the lack of standardised outcome measures. However, the magnitude of the treatment effect appears small.
- There is no evidence to support the use of nebulised opioids for the treatment of breathlessness.

For funders

- There is low quality evidence showing benefit for the use of oral opioids for the relief of breathlessness in adults with advanced disease and terminal illness.
- Based on this evidence, it is possible that opioids lead to a short-term increase in exercise capacity.
- It is difficult to draw firm conclusions about the clinical significance of the pooled estimate of treatment effect in our meta-analysis as we used the SMD to combine studies due to the lack of standardised outcome measures but the magnitude of the treatment effect appears small.

- There is no evidence to support the use of nebulised opioids for the treatment of breathlessness.
- Given the small sample sizes of these studies, larger trials may assist in providing more robust evidence for opioids for breathlessness.

Implications for research

- Given the small sample sizes of these studies, larger trials including more than 50 participants per treatment arm may assist in providing more robust evidence for opioids for breathlessness.
- Randomised, parallel group trials of longer duration (i.e. greater than one day; for several weeks) are likely to be more clinically appropriate.
- Effective dosing schedules should be elucidated to determine maximum effect with minimum side effects.
- Standardised outcome measures should be used including consistent fixed-point outcome measures of breathlessness, and quality of life measures.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abernethy 2003

Methods	Randomised, double blind crossover study
Participants	Opioid naive adults with dyspnoea despite treatment for reversible factors for end stage respiratory, cardiac or palliative conditions 48 randomised participants Mean age: 76 years 35/48 male Exclusion criteria were recent use of opioids, confusion, obtundation, adverse reactions to opioids, and history of substance misuse
Interventions	20 mg oral sustained release morphine sulphate or placebo tablet Co-interventions included coloxyl and senna
Outcomes	VAS dyspnoea scale Respiratory rate Sedation/obtundation Conspitation
Notes	Outcome measurement at day 4 and day 8 The study authors concluded that sustained release oral morphine at low dosage provides significant symptomatic improvement in refractory dyspnoea in the community setting Dose is equivalent to 20 mg oral morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation and blinding were co-ordinated through the hospital pharmacy's centralised service. This included computerised generation of the allocation sequence in random permuted blocks and blinded disbursement of medication
Allocation concealment (selection bias)	Low risk	Randomisation and blinding were coordinated through the hospital pharmacy's centralised service. This included computerised generation of the allocation sequence in random permuted blocks and blinded disbursement of medication
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. The placebo medication was identical in appearance and taste to the active medication; the bottle indicated

Abernethy 2003 (*Continued*)

		which medication to take each day. Participants were unblinded to the investigators for serious adverse events only. There was no blinding for constipation. To accommodate this, the only investigator aware of the constipation was the study nurse (AM) , who was not involved in the analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The placebo medication was identical in appearance and taste to the active medication; the bottle indicated which medication to take each day. Participants were unblinded to the investigators for serious adverse events only
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study assessed the primary outcome dyspnoea at the end of 4^{th} day of the treatment period only. There were 10 withdrawals during treatment, with some due to adverse events
Selective reporting (reporting bias)	Low risk	The study collected statistical details about some adverse events and some outcomes, such as overall well being and MRC Exercise tolerance scores, but did not report these in detail in the study report except to say there were no significant differences
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There were < 50 participants per treatment arm.

Bar-Or 1982

Methods	Randomised crossover study
Participants	Participants with chronic obstructive pulmonary disease (COPD), otherwise not specifically stated 11 participants
Interventions	30 mg three times daily (TDS) or 60 mg TDS oral dihydrocodeine Compared to oral placebo
Outcomes	Used oxygen cost diagram to measure breathlessness Six-minute walking test (6MWT) Oxygen consumption Adverse events

Bar-Or 1982 (*Continued*)

Notes	Abstract, so limited information provided They concluded that there was a marked improvement in subjective disability when 30 mg TDS was given, but not 60 mg TDS Dose is equivalent to 18 mg oral morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly state the method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly state the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 16 randomised participants and 5 withdrawals due to adverse effects, all discussed but not likely related to the primary outcome measure
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There was a small sample size, and this study is likely to be at high risk of bias; there were < 50 participants per arm

Bruera 1993

Methods	Randomised crossover study
Participants	Terminally ill participants with lung cancer or lung metastases or lymphangitis On supplemental oxygen 10 inpatient participants Normal cognitive function On regular subcutaneous morphine for pain Stable morphine dose for 5 days

Bruera 1993 (*Continued*)

Interventions	Morphine subcutaneous: mean dose 32 mg, standard deviation (SD) 12 mg: 50% higher than regular dose versus placebo 24 hour wash-out period
Outcomes	VAS dyspnoea scale Oxygen saturations Respiratory rate
Notes	VAS at 60 minutes following injection used in results The study authors concluded that treatment is safe and effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not state the methods of randomisation
Allocation concealment (selection bias)	Unclear risk	The study authors did not state the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not state the methods of blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not state the withdrawals, drop-outs and protocol deviations
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting.
Other bias	Unclear risk	It is unclear whether or not there was other risk due to lack of detail in methods
Size bias	High risk	There is size bias as there were only 10 participants in total, and < 50 per treatment arm

Charles 2008

Methods	Double blind, randomised crossover study
Participants	Those with cancer experiencing dyspnoea English speaking, over 18 years, expected prognosis of 7 days, Minimental state exam (MMSE) > 24/30, experiencing dyspnoea with no reversible cause 20 participants

	Mean age: 69 years 11 males, 9 females
Interventions	5 mg nebulised hydromorphone compared to 3 mL nebulised saline Co-interventions were recorded but not stated
Outcomes	VAS dyspnoea scale Respiratory rate Pulse rate Oxygen saturation
Notes	The study measured outcomes at 10, 20, 30 and 60 minutes post-dose The study authors concluded that there were no significant differences between treatments

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study randomised treatment order using a random number generator. To ensure double blinding, a non-clinical research doctor prepared treatments composed of medications (commercially obtained) and blinding agents and checked with a non-clinical nurse, neither of whom was involved with the care of the participant. A research nurse, who was unaware of the order sequence and who was not involved with the clinical care of the participant, subsequently administered preprepared and randomised treatments. The non-clinical research doctor held a master plan of the randomizations so that treatments could be unblinded in an emergency. There were no such emergencies over the course of the study
Allocation concealment (selection bias)	Low risk	This was probably ok as the doctor responsible for randomisation was not involved in the care of the participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Oral medications were administered in orange juice. Blinding as above seems reasonable
Blinding of outcome assessment (detection bias)	Low risk	As above. The VAS was self administered.

Charles 2008 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 5 withdrawals. The study authors did not describe the reasons per initial group allocation but for the whole group. They stated that the reasons were not systematically related to treatments or order of treatments
Selective reporting (reporting bias)	Low risk	There was no evidence of reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There was size bias as there were only 20 participants in total, and < 50 per treatment arm

Chua 1997

Methods	Randomised crossover study Exercise study Incremental treadmill test (modified Bruce protocol)
Participants	Stable chronic heart failure 12 male participants Mean age 65.5 years, (range 58 to 75 years) Average left ventricular ejection fraction (LVEF) 21.3% (range 8% to 39%) New York Heart Association (NYHA) functional class 2 and 3 No chest pain or inducible ischaemia during previous exercise testing No history pulmonary disease All patients on diuretics and ACE inhibitors
Interventions	Dihydrocodeine 1 mg/kg vs placebo Tests took place on separate days
Outcomes	Modified Borg score (dyspnoea) Pulse Systolic blood pressure (BP) End-tidal CO_2 concentration % PaO_2 saturation Modified Borg score (fatigue) Hypoxic chemosensitivity Hypercapnic chemosensitivity Peak O_2 consumption VE-VCO_2 slope Exercise duration

Chua 1997 (*Continued*)

Notes	The study measured outcomes at 3 minutes, 6 minutes, and at peak exercise The study authors concluded that dihydrocodeine was associated with a reduction of exercise ventilation, an improvement in exercise tolerance and a decrease in breathlessness The dose is equivalent to an average of 6 mg oral morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study assessed hypoxic and hypercapnic chemosensitivities in these participants 1 hour after the participants received placebo or dihydrocodeine (1 mg/kg body weight) in a randomised, double-blind design on 2 separate days, followed by treadmill exercise testing on each occasion. The study gave placebo and dihydrocodeine in the form of a drink made up to 200 mL with bitter lemon, which was prepared by the Department of Pharmacy, Royal Brompton Hospital
Allocation concealment (selection bias)	Unclear risk	There were no details other than the above.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was unclear whether or not the participants could tell the difference between the 2 drinks from description above
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not state the number of withdrawals, dropouts, or protocol deviations
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting.
Other bias	Unclear risk	It is unclear whether or not there was other risk due to the lack of detail in the methods
Size bias	High risk	There was size bias as there were only 12 participants in total, and < 50 per treatment arm

Davis 1996

Methods	Randomised crossover study
Participants	People with cancer 79 participants 34 men, 45 women Median age 60 years (range 20 to 81 years)
Interventions	Morphine single nebulised dose, range 5 mg to 50 mg or placebo Interventions made on separate days
Outcomes	VAS score for breathlessness Modified Borg score VAS scores for nausea and drowsiness
Notes	The study measured outcomes at 5, 30, 60, and 90 minutes and at 2, 3, 4, 6, 8, 12, and 24 hours post-treatment The study authors concluded that there was no significant difference in response to nebulised morphine and normal saline Did not provide sufficient information or standard deviations to be included in the meta-analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was an abstract only and did not provide any details regarding randomisation. It is likely that a computer stratified randomisation
Allocation concealment (selection bias)	Unclear risk	The study authors did not report the methods of random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not report the methods of blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not report the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was crossover data for 66 participants only, and the study authors did not state the reason for this
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting.
Other bias	Unclear risk	It is unclear whether or not there was other risk due to lack of detail in methods
Size bias	High risk	There were < 50 participants per treatment arm.

Eiser 1991

Methods	Randomised crossover study Three 2-week periods followed by exercise tests with no wash-out interval Exercise testing (6MW and treadmill test) at end of each study period 4 withdrawals (1 due to chest infection, 1 because of itching on diamorphine, 1 due to constipation on diamorphine, and 1 due to headache due to cerebral metastases)
Participants	Those diagnosed with severe, stable COPD 14 participants 8 men; 6 women Mean age: 65 years Mean forced expiratory volume in one second (FEV1): 32% predicted Mean paO_2 9.0 range 7.1 to 10.9 kPa Mean $paCO_2$ 5.1 range 3.4 to 6.5 kPa
Interventions	Diamorphine 2.5 mg qds, or diamorphine 5 mg qds or placebo
Outcomes	Daily diary cards with 10 cm VAS for dyspnoea, feeling of well-being, drowsiness, number of bronchodilator puffs At the end of each 2 week period: FEV1 PaO_2 $PaCO_2$ A-aPO_2 (alveolar-arterial oxygen tension difference) 6MW VAS dyspnoea for 6MWT Time on treadmill VAS dyspnoea for treadmill O_2 saturation End-tidal PCO_2 Morphine levels
Notes	Dyspnoea assessed "at completion of each type of exercise" The study authors detected no significant effect of opioid compared with placebo The dose is equivalent to 15 mg oral morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was double-blind, randomised, and cross-over with no wash-out intervals. The study authors did not provide any further details for the methods
Allocation concealment (selection bias)	Unclear risk	The study authors did not state the method of allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	The study authors did not clearly state the methods of blinding of participants

Eiser 1991 (*Continued*)

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the first study there were 4 drop outs, 2 due to unrelated reasons and 2 due to side effects in the diamorphine group. However, this is unlikely to influence the results of the assessment of breathlessness
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting.
Other bias	High risk	The study authors did not state that adverse events were systematically studied (apart from drowsiness)
Size bias	High risk	There were only 14 participants in total, and < 50 per treatment arm

Grimbert 2004

Methods	Randomised crossover study
Participants	Participants receiving palliative care for lung cancer, experiencing dyspnoea 12 participants Mean age 63 years 11 men, 1 woman Exclusion criteria: heart failure, asthma, allergy to morphine, previous addiction to morphine
Interventions	Nebulised morphine sulphate 20 mg, compared to nebulised saline 48 hours of treatment with 24 hours washout period
Outcomes	VAS dyspnoea scale - no interpretable data Respiratory rate Oxygen saturation
Notes	The study authors concluded that both nebulised morphine and nebulised saline produced the same improvement in dyspnoea We translated this study into English The primary outcome data was unable to be extrapolated from the figures so this was not included in the meta-analysis
Risk of bias	

Grimbert 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not state the methods of random sequence generation
Allocation concealment (selection bias)	Low risk	The study concealed allocation, collected from pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pharmacy prepared the intervention as a clear, colourless solution
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study did not clearly state the blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study authors reported all follow-up of participants.
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There was a small sample size of only 12 participants and a high size bias. There were< 50 participants per treatment arm

Harris-Eze 1995

Methods	Randomised crossover study Exercise study Incremental cycle ergometer
Participants	Insterstitial lung disease (ILD) 6 participants: 5 male, 1 female Mean age: 49 years FEV1 2.54, SD 0.69 Stable, no change in medication over 2 months No history of opioid abuse No opioid drugs for 1 month
Interventions	Morphine 2.5 mg, morphine 5 mg, or placebo 15 minutes before exercise test 3-day washout period

Harris-Eze 1995 (*Continued*)

Outcomes	Modified Borg Scale-mean value at end exercise Exercise duration Heart rate Maximal workload ECG SaO_2 O_2 uptake (VO_2) CO_2 output (VCO_2) End-tidal CO_2 minute ventilation (VI) Respiratory frequency Tidal volume
Notes	The study authors measured outcomes at 15 minutes post-dose The study authors reported no significant effect of nebulised morphine compared with placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly describe the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly describe the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study participants were given the nebulized study medication (saline (control), morphine 2.5 mg, or morphine 5.0 mg) in randomised, double-blinded fashion. An attendant who was not involved in the remainder of the protocol prepared the study medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The adequacy of blinding was unclear, and we were unable to tell whether unblinding was possible from the description (see above), could influence measurement of Borg scale but not some of the exercise test parameters
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting.

Harris-Eze 1995 (*Continued*)

Other bias	Unclear risk	It is unclear whether or not there was other bias.
Size bias	High risk	There were only 6 participants in total, which is a small sample size; there were < 50 participants per treatment arm

Hui 2014

Methods	Double blinded, randomised parallel placebo controlled study 6MWT
Participants	People diagnosed with cancer, aged ≥ 18 years, with breakthrough dyspnoea > 3/10, ambulatory, Karnovsky score > 50%, on a stable opioid dose 20 participants Mean age 50 years (range 30 to 75 years) 11 female 70% Caucasian, 15% black, 15% Hispanic Exclusion criteria: dyspnoea > 7/10, supplemental oxygen > 6L, delirium, allergy to fentanyl, substance abuse, recent coronary disease
Interventions	Subcutaneous fentanyl, dosed on a sliding scale, dose ranging from 30 mcg to 350 mcg compared to subcutaneous saline Co-interventions included regular opioids, bronchodilators, steroids
Outcomes	NRS dyspnoea scale Borg fatigue scale Heart rate Respiratory rate Oxygen saturation Blood pressure Adverse events
Notes	The study measured outcomes before and after the 6MWT The study authors concluded that prophylactic fentanyl was safe and improved dyspnoea, fatigue, walk distance, and respiratory rate, and that there was also a large placebo effect The dose is equivalent to 1.5 mg to 9 mg oral morphine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer randomised sequence generation.
Allocation concealment (selection bias)	Low risk	Allocation was concealed by using a secured Web site that was only accessible to the study pharmacist after participant enrol-

Hui 2014 (*Continued*)

		ment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded. Both the participants and research staff conducting the study assessments were blinded to the study intervention and the randomisation sequence
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both the participants and research staff conducting the study assessments were blinded to the study intervention and the randomisation sequence
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study with no loss of follow up
Selective reporting (reporting bias)	Low risk	There was no evidence of selective reporting.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This was a parallel trial with 20 participants in each arm (< 50 participants per treatment arm)

Jankleson 1997

Methods	Double blind, randomised crossover study Exercise study 6MWT
Participants	Exercise tolerance limited by dyspnoea in the setting of stable COPD 16 participants 11 male, 5 female Mean age 69 years (range 61 to 85 years) Mean FEV1 0.93 Mean forced vital capacity (FVC) 2.21 Mean PaO_2 9.6 kPa Mean $PaCO_2$ 5.4 kPa
Interventions	Nebulised morphine 20 mg or morphine 40 mg or placebo immediately before and 1 hour before exercise test Tests separated by 1 or 2 days
Outcomes	Modified Borg score 6MWT SaO_2 Heart rate

Jankleson 1997 (*Continued*)

	Plasma morphine levels	
Notes	The study authors reported no significant effect of opioid compared with placebo	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study followed a double-blind cross-over, placebo-controlled design. The hospital pharmacist prepared and allocated 3 test solutions, morphine sulphate (20 and 40 mg in 5 mL solutions with 0.9% saline) and placebo (5 mL 0.9% saline), in a double-blind, random order on each of 3 test days, which were no more than 2 days apart
Allocation concealment (selection bias)	Unclear risk	The study followed a double-blind cross-over, placebo-controlled design. The hospital pharmacist prepared and allocation the 3 test solutions, morphine sulphate (20 and 40 mg in 5 mL solutions with 0.9% saline) and placebo (5 mL 0.9% saline), in a double-blind, random order
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See above - it may be sufficient but we cannot tell how similar the placebo and morphine nebs were
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop outs.
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting.
Other bias	Unclear risk	It was unclear if there was any other bias.
Size bias	High risk	There was a small sample size, and this study was at high risk of bias with < 50 participants per study arm

Jensen 2012

Methods	Randomised, double blind, placebo controlled crossover study
Participants	Diagnosed with COPD, aged 40 years or older, cigarette smokers FEV1 < 0.7 12 participants Mean age 70 years (range ± 2.3 years) 7 males, 5 females Exclusion criteria: those with significant diseases other than COPD, those with sleep disordered breathing, those who has used opioids in the last 2 days
Interventions	Nebulised 50 mcg fentanyl citrate compared to nebulised saline Participants withdrew from beta-agonists, anticholinergics, caffeine, and theophylline prior to the trial
Outcomes	Dyspnoea on the Borg scale Exercise time Dyspnoea unpleasantness Leg discomfort Heart rate Oxygen saturation VO_2 VCO_2 VE VT FR
Notes	The study authors measured outcomes at pre-exercise, isotime (highest equivalent of exercise time achieved), and peak exercise They concluded that single-dose inhalation of fentanyl citrate was associated with significant and potentially clinically important improvements in exercise tolerance in people with COPD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The hospital pharmacist performed randomization, blinding, and dispensing of study medications. This person was an unblinded third party who was not affiliated with either subject recruitment or data collection and analysis
Allocation concealment (selection bias)	Low risk	Double blinded. The hospital pharmacist performed randomization, blinding, and dispensing of study medications. This person was an unblinded third party who was not affiliated with either subject recruitment or data collection and analysis

Jensen 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	This is likely to have been adequate given both placebo in fentanyl solutions were the same volume and dispensing was independent of those involved in conducting the study. However, it is not entirely clear whether the placebo and drug had the same appearance/taste
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly reported. There were 3 drop outs in the placebo group: 2 were due to side effects (before exercise test) and 1 due to protocol violation. There was 1 drop out in intervention group due to side effects prior to exercise test. Balanced and unlikely to affect the results
Selective reporting (reporting bias)	Low risk	We did not find any evidence of selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There was a small sample size, and high risk of bias; there were < 50 participants per study arm

Johnson 1983

Methods	Randomised, double blind, crossover study 2 consecutive 1 week periods followed by exercise test Incremental treadmill test 1 drop-out: developed chest infection and right heart failure on dihydrocodeine
Participants	Those with stable COPD with severe breathlessness, and severe airflow obstruction 19 participants 15 men, 3 women Mean age 64.9 years, SD 9.1 years FEV1 830, SD 260 mL PaO_2 9.3 SD 0.8 kPa; $PaCO_2$ 4.8 SD 0.5 kPa At least Grade 3 breathlessness (MRC scale) No recent hospital admissions No sedative drugs Continued usual bronchodilators and steroids

Johnson 1983 (*Continued*)

Interventions	Dihydrocodeine 15 mg or placebo over 2 consecutive 1 week periods Drug to be taken 30 minutes before exercise up to 3 times daily Tests at end of each week period
Outcomes	Pedometer distance for 1 week Daily VAS for breathlessness PEFR FEV1 FVC Incremental treadmill test Distance walked VAS for breathlessness at 75% distance walked on placebo day
Notes	The study authors concluded that dihydrocodeine 15 mg 30 minutes before exercise offers appreciable benefit to participants with severe breathlessness due to chronic airflow obstruction Dose is equivalent to 4.5 oral morphine, up to 3 times daily

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly state the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors reported allocation concealment but did not clearly state the methods
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were given similar solutions of tablets with opioid or placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study authors clearly stated the methods of withdrawals, drop outs, and reasons, which did not appear to change the study outcomes
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting bias.
Other bias	Low risk	We did not detect any other bias.

Johnson 1983 (*Continued*)

Size bias	High risk	There was a small sample size, and high risk of bias; there were < 50 participants per arm Measured interquartile range so could not be included in the meta-analysis

Johnson 2002

Methods	Randomised, double blind, placebo controlled crossover study
Participants	NYHA Class III or IV heart failure, clinically stable, medically optimised 10 participants Mean age 67 years (range 45 to 85 years) All male Exclusion criteria: renal impairment, malignant disease
Interventions	5 mg oral morphine solution unless creatinine > 200ml/dL, then 2.5 mg was administered Compared to oral placebo solution
Outcomes	VAS breathlessness score Sedation score Constipation Nausea Quality of life Blood pressure Pulse Respiratory rate Catecholamines
Notes	Outcomes measured at 1 hour, day 2, 3, and 4 The study authors concluded that morphine relieves breathlessness due to chronic heart failure The dose is equivalent to 5 mg oral morphine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study authors used a random number table.
Allocation concealment (selection bias)	Unclear risk	Hospital pharmacy but not clear if allocation concealed as no further details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors stated that the study was to be double blind but gave no further details about blinding or the nature of the placebo

Johnson 2002 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study authors accounted for all participants. They recruited 10 participants and reported on 10 participants
Selective reporting (reporting bias)	Low risk	The study authors reported all primary and secondary outcomes, including withdrawals
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were fewer than 50 participants per study arm

Leung 1996

Methods	Randomised, double blind, crossover study Exercise study Incremental cycle ergometer
Participants	COPD (1 pt ILD) 10 participants 6 male, 4 female Mean age 62 years, (range 51 to 71 years) Mean FEV1 = 1.12 Exclusion criteria: CO_2 retention and ischaemic heart disease
Interventions	Morphine 5 mg in 5mL or placebo 15 minutes before exercise test 100% O_2 inhaled during exercise test Tests on separate days
Outcomes	Modified Borg score Maximum power output VE max Heart rate
Notes	The study authors reported no significant effect of opioid compared with placebo

Risk of bias

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

Leung 1996 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly state the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly state the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited participants remained in the study.
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were fewer than 50 participants per study arm

Light 1996

Methods	Randomised, crossover study Exercise study Incremental cycle ergometer
Participants	COPD 7 male participants Mean age 66.4 years SD 3.25 years FEV1 0.99 SD 0.3 FEV1/FVC 0.35 SD 0.07 Exercise limited by breathlessness Stable disease Exclusion criteria: $PaCO_2$ > 45 mmHg, FEV1 > 1.39 L, long-term oxygen supplementation, cardiac disease, history of narcotic abuse, other significant disease affecting exercise performance, use of tranquillisers, hypnotics, mood altering drugs or opioids in week prior to study, alcoholism in past 5 years
Interventions	Morphine 30 mg or placebo once orally 60 minutes before exercise test, compared to 30 mg morphine plus 10 mg prochlorperazine, or compared to 30 mg morphine plus 25 mg promethazine

Light 1996 (*Continued*)

	Tests on separate days
Outcomes	Modified Borg score each minute of exercise Workload Exercise duration VO_2 VCO_2 VE $PETO_2$ $PETCO_2$ Heart rate SaO_2
Notes	The study authors concluded that the administration of 30 mg morphine plus promethazine significantly improved the exercise tolerance of participants with COPD, without significantly impairing the mental capabilities of the participants The dose is equivalent to 30 mg oral morphine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study authors did not state the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not state the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebos were identical in appearance; the participants were blinded to the intervention and the placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not state the number of participants enrolled or recruited, and only provided a statement about the number that completed the study. It is unclear whether or not this had impact on the trial outcomes
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Light 1996 (*Continued*)

Size bias	High risk	This study had a small sample size; there were < 50 participants per arm

Masood 1995

Methods	Double blind, randomised, crossover study Exercise study Incremental cycle ergometer
Participants	Stable severe COPD with disabling breathlessness 12 men ADLs limited by breathlessness FEV1 < 1.51 Exclusion criteria: exacerbations needing antibiotics, change in oral steroid dose or hospital admission within 2 months, overt cardiac disease, contra-indication to exercise testing, pCO_2 > 7.0, use of opioids, benzodiazepines, or other sedative agent within 1 month
Interventions	Morphine 10 mg nebulised or morphine 25 mg nebulised or morphine 1 mg intravenous or morphine 2.5 mg intravenous or placebo nebulised or placebo intravenous 15 minutes before exercise tests Each test was separated by at least 48 hours
Outcomes	Heart rate Respiratory rate VO_2 RER SaO_2 VAS for breathlessness Exercise duration Plasma morphine levels Ventilation
Notes	Nebulised Beta 2 agonist given before exercise tests Authors conclude no significant effect of opioid compared with placebo on exercise tolerance or breathlessness The primary outcome did not include standard deviation therefore could not be included in the meta-analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study authors did not state the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not state the methods of allocation concealment

Masood 1995 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not state whether or not they blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not state the methods of blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All recruited participants remained in the study.
Selective reporting (reporting bias)	Low risk	The study authors presented all primary and secondary outcomes described in methods
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were < 50 participants per arm

Mazzocato 1999

Methods	Randomised crossover study
Participants	Those with dyspnoea due to advanced cancer Normal limits on MMSE, absence of brain tumour, acute incapacitating respiratory decompensation 9 participants Mean age 73 years (range 66 to 83 years) 4 female, 5 male
Interventions	Subcutaneous morphine 5 mg, compared to subcutaneous saline Continued usual co-interventions
Outcomes	VAS dyspnoea scale Borg dyspnoea scale Pain Somnolence Anxiety Respiratory effort score (respiratory frequency, presence of cyanosis, and utilisation of accessory respiratory muscles) Oxygen saturations
Notes	Outcomes measured at 45 minutes on day 1, and crossover on day 2 The study authors concluded that morphine appears effective for cancer dyspnoea, and it does not compromise respiratory function at the dose level used

Mazzocato 1999 (*Continued*)

	The dose was equivalent to 15 mg oral morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Nine participants gave their informed consent. Seven opioid-naive participants were randomised to 5 mg subcutaneous morphine or placebo on day 1. The study authors described this study as a double blind cross over study
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly state the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors gave the methods of blinding of participants as "our study was done under double-blind conditions" but did not provide any further details to assess the adequacy of this. Note that some participants in the morphine group received different doses of morphine if they were already taking oral morphine and it is unclear how this was concealed or blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state whether or not they performed blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The graph (figure 1) with data for primary outcome shows data collected on all participants enrolled
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were < 50 participants per arm

Navigante 2010

Methods	Randomised parallel study
Participants	Ambulatory participants with moderate to severe dyspnoea at rest Mean age 55 years 31 participants in the morphine arm and 32 participants in the midazolam arm

Interventions	Oral morphine: 3 mg then incremental steps at 30 minutes until 50% reduction in dyspnoea Compared to oral midazolam: 2 mg up titrated 25% until 50% reduction in dyspnoea
Outcomes	Dyspnea intensity Adverse events
Notes	Compared morphine to midazolam

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (using a random number generator in 1:1 ratio in blocks of 6) to 1 of the 2 treatment groups. Numbered envelopes that were used to implement the randomisation were concealed until interventions were assigned
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned (using a random number generator in 1:1 ratio in blocks of 6) to 1 of the 2 treatment groups. Numbered envelopes that were used to implement the randomisation were concealed until interventions were assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was single blinded, that is only participants were blinded. However, adequacy was unclear - similarity of preparation - morphine group given laxatives
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was single blinded, and only participants were blinded. The investigators were aware of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was only 1 withdrawal in each group, which was unrelated to the intervention
Selective reporting (reporting bias)	Low risk	The study authors appear to have reported all outcome data.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There were 30 participants per treatment arm and the study was designed as a parallel trial; there were < 50 participants per treatment arm

Noseda 1997

Methods	Placebo-controlled, double blind, randomised crossover study There were 3 drop outs: 3 participants died over the study period, during the night: the study authors did not consider their deaths to be related to the treatment
Participants	Hospital inpatients with severe lung disease, experiencing distressing dyspnoea not relieved by medical therapy Mean age 69 years (± 11 years) Mean FEV1 0.92 SD 0.18 Normal cognitive function 17 participants
Interventions	Nebulised morphine 10 mg + O_2 or morphine 20 mg + O_2, or morphine 10 mg or placebo + O_2 at 2L/min Tests took place over consecutive days
Outcomes	VAS for breathlessness SaO_2% Respiratory rate
Notes	Results using morphine alone were not analysed The study authors reported no benefit of morphine compared with placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly describe the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly describe the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	All morphine and saline solutions were prepared and coded independently in the hospital pharmacy. However, the study authors did not provide any further description. For the 10 mg/no oxygen group, prongs were applied but no oxygen and it is not possible to determine whether or not the participants or investigators were truly blinded to the intervention based on the description above
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not state the methods of blinding of outcome assessment

Noseda 1997 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	This study had incomplete data due to deaths during the trial, which were clearly reported and would be expected in this study type. The deaths occurred overnight and were unlikely to be related to the intervention, which took place during the day
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were < 50 participants per arm

Oxberry 2011

Methods	Controlled double blind crossover study	
Participants	Those with heart failure LVEF < 45%, on standard medical therapy 35 participants Mean age 70 years (± 11 years) Male 8% Exclusion criteria: co-existing respiratory illness, peak expiratory flow (PEF) < 150 L/min, opioid sensitivities, renal impairment i.e. eGFR < 30 mL/min	
Interventions	Oral morphine 5 mg QID compared to oral oxycodone 2.5 mg four times daily (QID) compared to oral placebo Treatment arm 4 days with 3 day washout period	
Outcomes	NRS dyspnoea scale NRS coping NRS satisfaction	
Notes	Outcomes assessed daily The study authors concluded that there was no benefit over placebo for the relief of breathlessness with short-term low-dose oral opioids for congestive heart failure The dose is equivalent to 20 mg oral morphine	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Oxberry 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	The study drug manufacturer (Calderdale and Huddersfield NHS Pharmacy Manufacturing Unit, Huddersfield, UK) randomised the order of interventions for each participant using a random number generation programme. It did not use block design and there were 6 possible sequence combinations. The pharmacy dispensed all 3 medications for use in the required sequence with identical labels except for the treatment order. Hence the investigators and participants remained blinded to the treatment sequence and allocation was conducted distant to the research team
Allocation concealment (selection bias)	Low risk	The placebo was designed to have very similar characteristics to the active medications (a clear, colourless liquid with the same viscosity and similar taste)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pharmacy dispensed all 3 medications for use in the required sequence with identical labels except for the treatment order. Hence the investigators and participants remained blinded to the treatment sequence and allocation was conducted distant to the research team
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded to outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was a small number of drop outs, which were all completely reported and unlikely to influence results and reasons stated
Selective reporting (reporting bias)	Low risk	The study was registered prior to recruitment and audited study. The study reported all prespecified outcomes
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	There were < 50 participants per treatment arm.

Poole 1998

Methods	Randomised, double blind, crossover study Two 6-week treatment periods followed by exercise tests 2-week wash-out period 6MWT 2 drop-outs
Participants	Those with breathlessness caused by COPD, following pulmonary rehabilitation 16 participants 11 men, 5 women Mean age 70.7 years, SD 1.6 years FEV1 0.6, SD 0.4 Mean pO_2 9.8 mean pCO_2 5.3 Exclusion criteria: CCF, $paCO_2$ > 5.4, FEV1 > 1.49, alcoholism, psychiatric disorder, on opiates, change in drugs in past month, or hospitalised in past 2 months
Interventions	Oral morphine sulphate sustained release 10 mg to 20 mg daily-BD or placebo Average dose 25 mg over 24 hours Tests at end of treatment periods
Outcomes	Chronic Respiratory Disease Questionnaire 6MWT SaO_2 Spirometry Breathlessness scores on Likert scale before and at the end of six minutes walk Side effects
Notes	The study authors concluded that there was no significant difference after opioid administration The dose is equivalent to 15 mg morphine, uptitrated to BD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The Auckland Hospital Pharmacy performed randomization in blocks of 4. They maintained the randomisation schedule, stored the study medicines in a controlled drug safe, and dispensed them at study visits according to the regulations governing the use of controlled medicines
Allocation concealment (selection bias)	Low risk	The placebo capsules were identical in appearance but were filled only with lactose
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pharmacy supplied identical tablets.

Poole 1998 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Staff involved in administering questionnaires and 6MWTs were not blinded to adverse events and therefore may have guessed the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 2 dropouts from the morphine group, but this is unlikely to affect the results
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were < 50 participants per arm

Rice 1987

Methods	Double blind crossover study
Participants	Clinically stable males with COPD FEV < 60% 7 participants 3 withdrawals (1 due to side effects of codeine, 1 due to worsening respiratory function) Age range 59 to 79 years All male Exclusion criteria: PCO_2 > 55, history of chemical dependence
Interventions	30 mg codeine QID compared to 25 mg promethazine QID Co-interventions: beta agonists, theophylline, prednisolone Outcomes measured at baseline and at 1 month
Outcomes	VAS dyspnoea scale Breathlessness rating
Notes	The study authors concluded that the benefits of codeine or promethazine are uncertain

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Subjects were randomised in sets of 4 in a double-blind fashion to begin oral treatment with identical pills that contained either 30 mg codeine or 25 mg promethazine, both taken 4 times daily. There were limited details in

Rice 1987 (*Continued*)

		the study report
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly report the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not clearly state whether they blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state whether there was blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant dropped out on the third day of the first study arm after developing acute urinary retention while taking codeine. Three participants had marked worsening of their respiratory symptoms and required hospitalisation. Two participants were receiving codeine, 1 on the first study arm and 1 on the second arm. The third subject was receiving promethazine during the first arm There was a small number of drop outs but also a small total number of participants. There were roughly similar reasons per group
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We did not detect any other bias.
Size bias	High risk	This study had a small sample size despite it being a parallel study; there were < 50 participants per arm

Williams 2003

Methods	Randomised crossover study
Participants	Stable heart failure Age range 38 to 75 years Mostly male (N = 15)
Interventions	Diamorphine 1 or 2 mg given intravenously Compared to intravenous saline
Outcomes	Primary outcome of breathlessness was not measured Oxygen consumption Exercise duration Respiratory rate
Notes	Naloxone 0.4 mg was given at the end of the test

Williams 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly state the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly state the methods of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not clearly state whether they blinded participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state whether or not they performed blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study authors reported all follow-up and completion data
Selective reporting (reporting bias)	Low risk	We did not detect any selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size; there were < 50 participants per treatment arm

Woodcock 1981

Methods	Randomised, crossover study Exercise study Incremental treadmill test
Participants	Those with severe airway obstruction with breathlessness on exertion 12 participants 10 men, 2 women Mean age 62 years No recent hospital admissions At least Grade 3 breathlessness (MRC scale) Normal or low pCO_2 FEV1 0.73, SD 0.31 paO_2 72.6, SD 6.86 $paCO_2$ 35.3, SD 2.4 All ex-smokers stopped smoking at least 6 months before the study

Woodcock 1981 (*Continued*)

Interventions	Dihydrocodeine 1 mg/kg given once, orally, 45 minutes before treadmill test (incremental speed to exhaustion) or alcohol or caffeine Placebo Tests on consecutive days
Outcomes	VAS for breathlessness during treadmill test (measured at 75% of distance walked on day of placebo) Exercise tolerance (distance walked to exhaustion on treadmill) Ventilation O_2 consumption FVC FEV1
Notes	Salbutamol 200 mcg, inhaled, 30 minutes before study The study authors concluded that opioids may be valuable in the treatment of breathlessness The dose is equivalent to an average of 6 mg oral morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not clearly state whether they performed random sequence generation
Allocation concealment (selection bias)	Unclear risk	The study authors did not clearly state whether they performed allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not clearly state whether they performed blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not clearly state whether they performed blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study, although the study authors did not specifically state the number of participants enrolled
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias

Woodcock 1981 (*Continued*)

Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were < 50 participants per arm

Young 1989

Methods	Cross-over study Exercise study Cycle endurance test Nebulised opioid
Participants	COPD (9) or idiopathic pulmonary fibrosis (2) Mean age 58.4 years (39 to 74) Exercise tolerance limited by dyspnoea FEV1 0.4 to 1
Interventions	Morphine 5 mg or placebo neb 15 mins before exercise test Tests on separate days 100% O_2 inhaled during exercise test
Outcomes	Cycle ergometer exercise test at 80% of pre-determined E_{max} Endurance time Ventilation during last minute of exercise FEV1
Notes	The study authors did not use dyspnoea as an outcome measure, although they selected participants because exercise was limited by dyspnoea They initially studied 18 participants and 7 excluded on run-in day because exercise was limited by other factors: the participants were excluded from the study authors' and from this review analysis Mean endurance time increased by 64 seconds: 1 participant had an increase of 400 seconds. If the study authors had excluded that participant from their analysis, the mean increase would have been approximately 25 seconds and not statistically significant The study authors concluded that morphine had a significant effect on exercise endurance time vs placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study authors did not state the methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The hospital pharmacist performed allocation, but the study authors did not further describe the method used to conceal allocation

Young 1989 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study authors did not state whether they performed blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study authors did not state whether they performed blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study authors did not clearly report complete participant data and dropouts
Selective reporting (reporting bias)	Low risk	We did not detect any evidence of selective reporting bias.
Other bias	Low risk	We judged that this trial appeared to be free of other sources of bias
Size bias	High risk	This study had a small sample size, and was at high risk of bias; there were < 50 participants per arm

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

Study	Reason for exclusion
Allard 1999	This study did not compare the intervention to a placebo or any other intervention
Beauford 1993	This study doesn't appear to be randomised, and we were unable to contact the study authors
Bruera 2005	This study did not compare the intervention to a placebo.
Navigante 2003	This study compared morphine plus midazolam to oxygen therapy
Peterson 1996	This study doesn't appear to be randomised.
Shorati 2012	This study doesn't appear to be randomised. We were unable to contact the study authors
Smith 2009	This was a pilot trial of 2 participants only, and it doesn't appear to have randomised participants to treatment
Thomas 2010	This was a review of 2 randomised controlled trials.

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

Cuervo Pinna 2012

Trial name or title	Cuervo Pinna 2012
Methods	This is a crossover clinical trial in which the study population will do the 6MWT with the study drug and placebo
Participants	Patients with advanced cancer. Patients must have dyspnoea at rest or dyspnoea moderate effort with an intensity of at least 3 on a scale from 0 to 10
Interventions	Oral Transmucosal Fentanyl Citrate versus placebo
Outcomes	Primary variable: VAS scale change from baseline. Improvement of the severity of dyspnoea after completion of the 6MWT in patients with advanced cancer. Response to treatment was considered an improvement greater than or equal to two points on the previous level of dyspnea.The evaluation and determination of changes in the level of severity of dyspnoea is done through Visual Analogue Scale (VAS) included in the Edmonton Symptom Assessment System (ESAS) Secondary variables:
Starting date	2012
Contact information	Cuervo Pinna M. Extremadura, Palliative Care Support Team, Badajoz, Spain
Notes	

Daubert 2014

Trial name or title	Daubert 2014
Methods	Prospective, randomised, double blind controlled trial, randomly assigned to either receive lorazepam or morphine. Symptom relief will be evaluated using the Edmonton Symptom Assessment Scale. Patients will receive treatment for 14 days
Participants	People greater than 18 years of age, enrolled in a hospice service, diagnosed with dyspnoea, able to take oral medications
Interventions	opioids compared to benzodiazepines
Outcomes	The primary outcome will be the change in patients' perception of their quality of life. This will be assessed using the Functional Assessment of Chronic Illness Therapy-Palliative Care scale, which patients will complete prior to initiation of therapy and after 7 and 14 days of treatment. An intention to- treat analysis will be performed and the change in quality of life observed will be compared between groups using a multivariable logistic regression analysis to adjust for confounding variables
Starting date	Research is in progress from 2014
Contact information	Daubert E, Bolesta S, Wilkes University, E-mail: eliza.daubert@wilkes.edu

Daubert 2014 (*Continued*)

Notes	

DATA AND ANALYSES

Comparison 1. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	18		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Change from baseline	7	214	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.36, 0.19]
1.2 Post-treatment score	11	318	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.50, -0.05]

Comparison 2. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	11		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Morphine: change from baseline	5	154	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.51, 0.15]
1.2 Morphine: post-treatment score	6	192	Std. Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.60, -0.03]

Comparison 3. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Hydromorphone: change from baseline	1	40	Mean Difference (IV, Fixed, 95% CI)	0.26 [-0.65, 1.17]
1.2 Oral diamorphine: post-treatment score	1	20	Mean Difference (IV, Fixed, 95% CI)	0.5 [-1.44, 2.44]
1.3 Oxycodone: change from baseline	1	70	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-1.03, 0.87]
1.4 Dihydrocodeine: post-treatment score	3	82	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.33, -0.15]

Comparison 4. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Fentanyl: change from baseline	1	20	Mean Difference (IV, Fixed, 95% CI)	0.20 [-2.50, 2.90]
1.2 Fentanyl: post-treatment score	1	24	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.96, 2.76]

Comparison 5. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	17		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 COPD: change from baseline	2	46	Std. Mean Difference (IV, Fixed, 95% CI)	-0.49 [-1.08, 0.10]
1.2 COPD: post-treatment score	8	262	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.45, 0.04]
1.3 Heart failure: change from baseline	1	70	Std. Mean Difference (IV, Fixed, 95% CI)	0.43 [-0.04, 0.90]
1.4 Heart failure: post-treatment score	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.66, 0.02]
1.5 Insterstitial lung disease	1	12	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-1.19, 1.07]
1.6 Cancer-related dyspnoea: change from baseline	3	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.68, 0.27]
1.7 Cancer-related dyspnoea: post-treatment score	1	20	Std. Mean Difference (IV, Fixed, 95% CI)	-0.75 [-1.67, 0.16]

Comparison 6. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	15		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Oral: change from baseline	3	116	Std. Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.30, 0.44]
1.2 Oral: post-treatment score	6	190	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.56, 0.02]
1.3 Nebulised: change from baseline	2	60	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.57, 0.45]
1.4 Nebulised: post-treatment score	4	96	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.43, 0.37]
2 Breathlessness	2	40	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-2.79, 2.57]
2.1 Subcutaneous: change from baseline	1	20	Mean Difference (IV, Fixed, 95% CI)	0.20 [-2.50, 2.90]

2.2 Subcutaneous: post-treatment score	1	20	Mean Difference (IV, Fixed, 95% CI)	-19.0 [-40.15, 2.15]

Comparison 7. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise tolerance	12		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 6MWT: total distance	1	22	Mean Difference (IV, Fixed, 95% CI)	-28.0 [-113.58, 57.58]
1.2 6MWT: change from baseline	2	52	Mean Difference (IV, Fixed, 95% CI)	47.78 [35.88, 59.67]
1.3 Workload (watts)	4	70	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-3.29, -0.10]
1.4 Treadmill distance	2	60	Mean Difference (IV, Fixed, 95% CI)	-37.64 [-96.17, 20.88]
1.5 Time on treadmill	3	76	Mean Difference (IV, Fixed, 95% CI)	-13.42 [-42.55, 15.70]
1.6 Maximum work cycle	1	24	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-1.81, -0.79]

Comparison 8. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life	1	32	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-9.90, 8.18]

Comparison 9. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events: constipation	9	324	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [1.63, 5.51]
2 Adverse events: nausea and vomiting	7	208	Odds Ratio (M-H, Fixed, 95% CI)	4.73 [1.73, 12.97]
3 Adverse events: drowsiness	9	312	Odds Ratio (M-H, Fixed, 95% CI)	2.86 [1.17, 7.02]

Comparison 10. Morphine versus midazolam

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	1	63	Mean Difference (IV, Fixed, 95% CI)	2.0 [1.07, 2.93]

Comparison 11. Codeine versus promethazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness	1	14	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.83, 0.23]

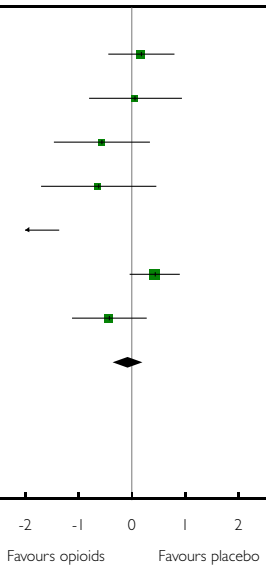
Analysis 1.1. Comparison 1 Opioids versus placebo, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 1 Opioids versus placebo

Outcome: 1 Breathlessness

Study or subgroup	Opioids N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Change from baseline							
Charles 2008	20	1.04 (1.38)	20	0.78 (1.54)		19.9 %	0.17 [-0.45, 0.80]
Hui 2014	10	-1.8 (2.4)	10	-2 (3.64)		10.0 %	0.06 [-0.81, 0.94]
Leung 1996	10	8.7 (2.2)	10	9.7 (1)		9.5 %	-0.56 [-1.46, 0.34]
Light 1996	7	-0.14 (0.09)	7	0.29 (0.9)		6.6 %	-0.63 [-1.71, 0.45]
Mazzocato 1999	9	-25 (10)	9	0.6 (7.7)		4.1 %	-2.73 [-4.10, -1.36]
Oxberry 2011	35	-0.41 (2.51)	35	-1.37 (1.86)		34.2 %	0.43 [-0.04, 0.90]
Poole 1998	16	-2.51 (5.68)	16	-0.44 (3.4)		15.6 %	-0.43 [-1.13, 0.27]
Subtotal (95% CI)	**107**		**107**			**100.0 %**	**-0.09 [-0.36, 0.19]**
Heterogeneity: Chi^2 = 22.65, df = 6 (P = 0.00092); I^2 =74%							
Test for overall effect: Z = 0.61 (P = 0.54)							
2 Post-treatment score							



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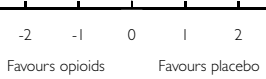
Study or subgroup	Opioids N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Abernethy 2003	38	40.3 (23)	38	49.9 (24)		23.9 %	-0.40 [-0.86, 0.05]
Bar-Or 1982	11	-42.6 (12)	11	-42.5 (8.8)		7.1 %	-0.01 [-0.84, 0.83]
Bruera 1993	10	16 (18)	10	35 (29)		5.9 %	-0.75 [-1.67, 0.16]
Chua 1997	12	2.91 (0.86)	12	3.6 (0.76)		7.0 %	-0.82 [-1.66, 0.02]
Eiser 1991	10	7 (2.21)	10	6.5 (2.21)		6.4 %	0.22 [-0.66, 1.10]
Harris-Eze 1995	6	6.3 (2.7)	6	6.5 (3.5)		3.9 %	-0.06 [-1.19, 1.07]
Jankleson 1997	16	4 (2)	16	4.5 (2.6)		10.2 %	-0.21 [-0.91, 0.48]
Jensen 2012	12	4.6 (3.11)	12	4.2 (2.77)		7.7 %	0.13 [-0.67, 0.93]
Johnson 1983	18	4.6 (2.1)	18	5.6 (2.3)		11.3 %	-0.44 [-1.11, 0.22]
Noseda 1997	14	-42 (27)	14	-43 (27)		9.0 %	0.04 [-0.70, 0.78]
Woodcock 1981	12	5.54 (1.91)	12	6.33 (2)		7.6 %	-0.39 [-1.20, 0.42]
Subtotal (95% CI)	**159**		**159**			**100.0 %**	**-0.28 [-0.50, -0.05]**

Heterogeneity: Chi^2 = 6.74, df = 10 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Chi^2 = 1.09, df = 1 (P = 0.30), I^2 =8%

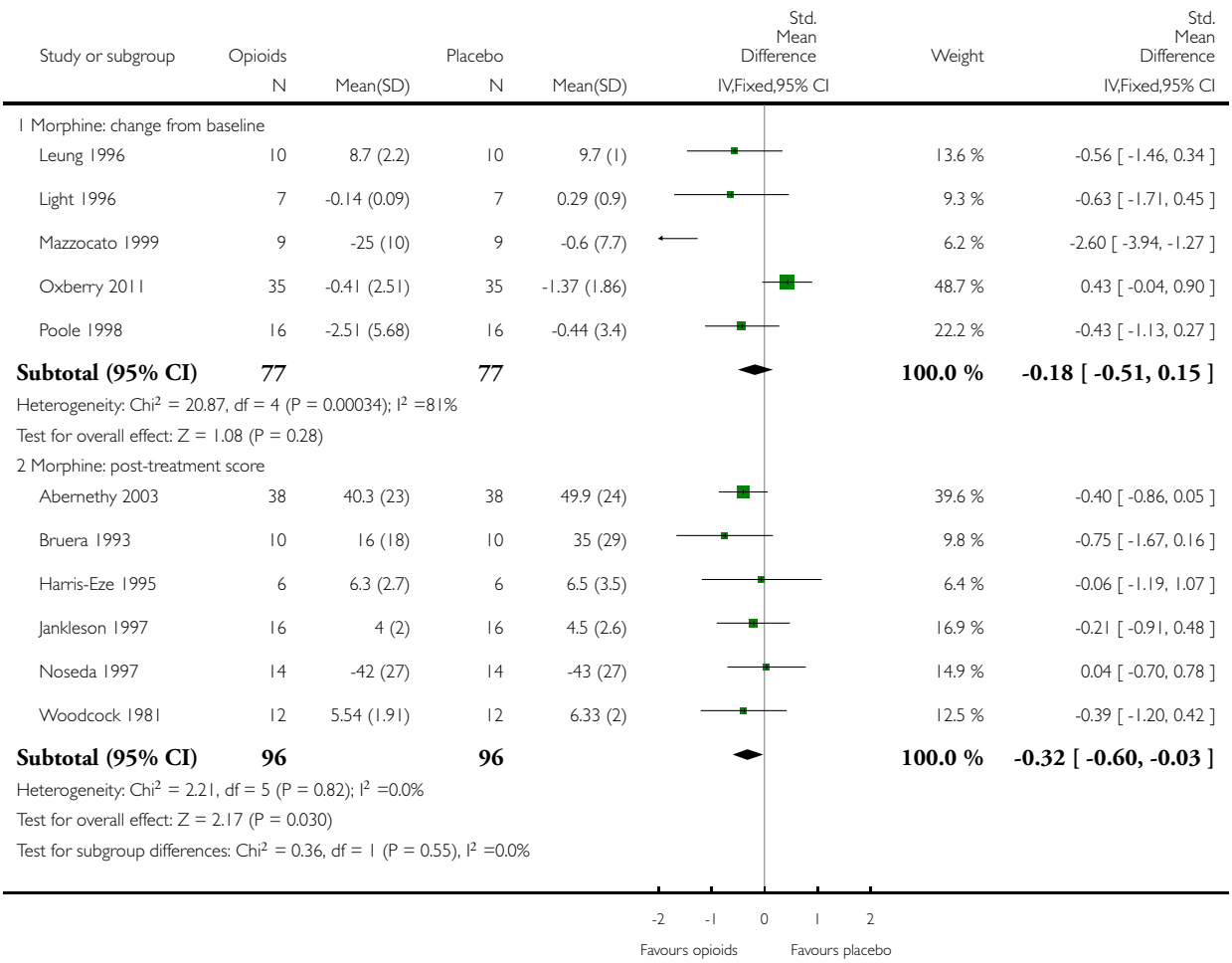


Analysis 2.1. Comparison 2 Opioids versus placebo, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 2 Opioids versus placebo

Outcome: 1 Breathlessness

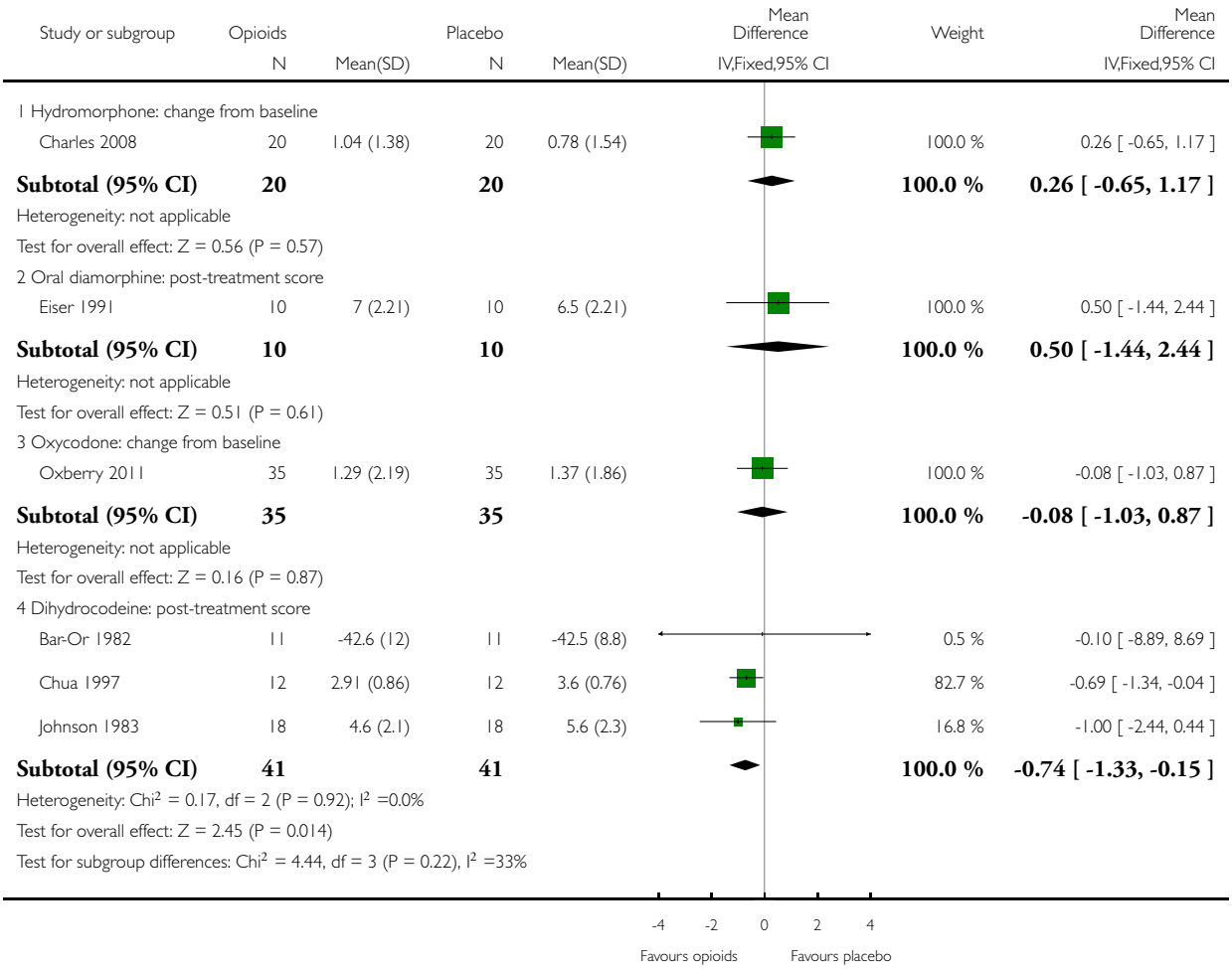


Analysis 3.1. Comparison 3 Opioids versus placebo, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 3 Opioids versus placebo

Outcome: 1 Breathlessness

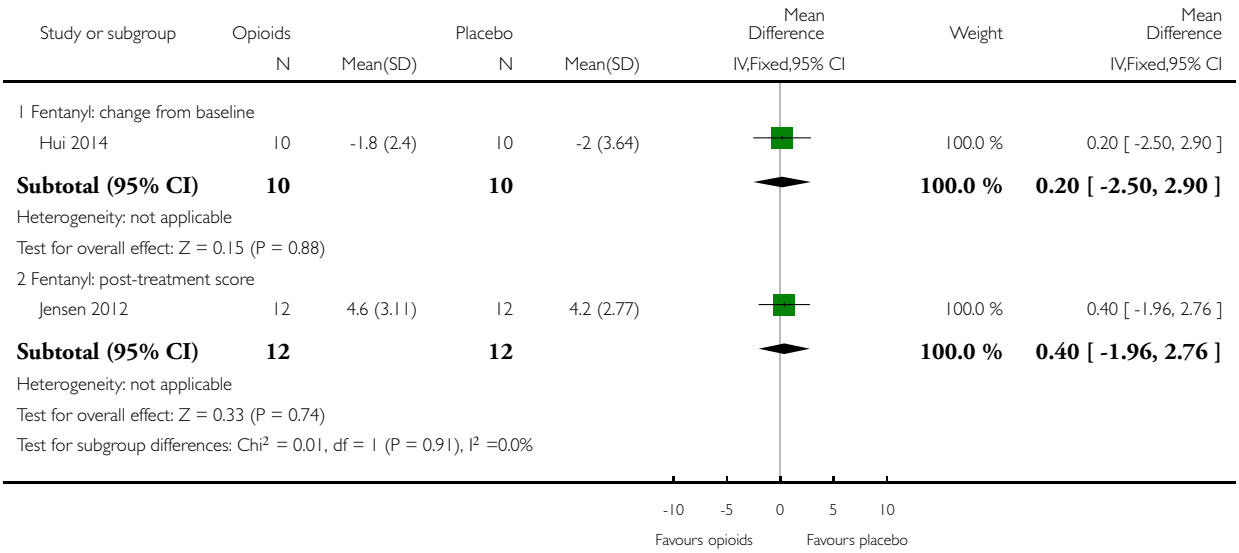


Analysis 4.1. Comparison 4 Opioids versus placebo, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 4 Opioids versus placebo

Outcome: 1 Breathlessness

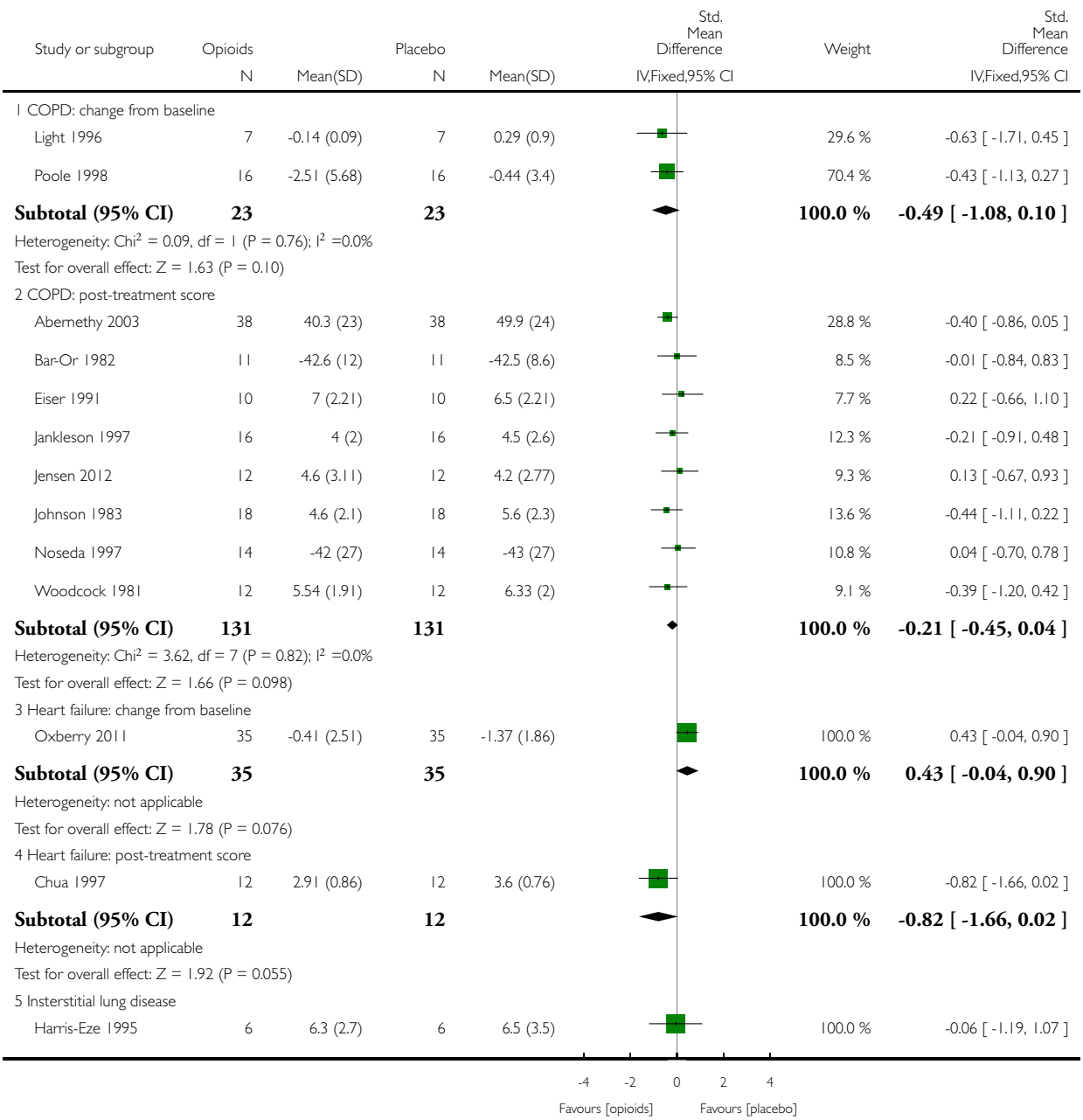


Analysis 5.1. Comparison 5 Opioids versus placebo, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 5 Opioids versus placebo

Outcome: 1 Breathlessness



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Study or subgroup	Opioids N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**6**		**6**			**100.0 %**	**-0.06 [-1.19, 1.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.10 (P = 0.92)							
6 Cancer-related dyspnoea: change from baseline							
Charles 2008	20	1.04 (1.38)	20	0.78 (1.54)		58.6 %	0.17 [-0.45, 0.80]
Hui 2014	10	-1.8 (2.4)	10	-2 (3.64)		29.4 %	0.06 [-0.81, 0.94]
Mazzocato 1999	9	-25 (10)	9	0.6 (7.7)		12.1 %	-2.73 [-4.10, -1.36]
Subtotal (95% CI)	**39**		**39**			**100.0 %**	**-0.21 [-0.68, 0.27]**
Heterogeneity: Chi^2 = 14.88, df = 2 (P = 0.00059); I^2 =87%							
Test for overall effect: Z = 0.86 (P = 0.39)							
7 Cancer-related dyspnoea: post-treatment score							
Bruera 1993	10	16 (18)	10	35 (29)		100.0 %	-0.75 [-1.67, 0.16]
Subtotal (95% CI)	**10**		**10**			**100.0 %**	**-0.75 [-1.67, 0.16]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.62 (P = 0.11)							
Test for subgroup differences: Chi^2 = 11.26, df = 6 (P = 0.08), I^2 =47%							

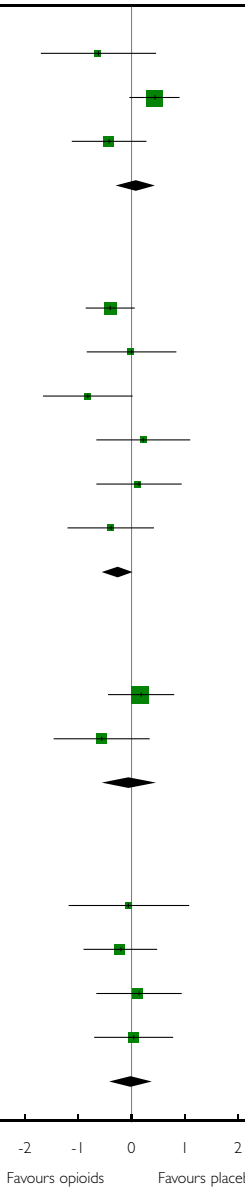
Analysis 6.1. Comparison 6 Opioids versus placebo, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 6 Opioids versus placebo

Outcome: 1 Breathlessness

Study or subgroup	Opioids N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Oral: change from baseline							
Light 1996	7	-0.14 (0.09)	7	0.29 (0.9)		11.6 %	-0.63 [-1.71, 0.45]
Oxberry 2011	35	-0.41 (2.51)	35	-1.37 (1.86)		60.7 %	0.43 [-0.04, 0.90]
Poole 1998	16	-2.51 (5.68)	16	-0.44 (3.4)		27.7 %	-0.43 [-1.13, 0.27]
Subtotal (95% CI)	**58**		**58**			**100.0 %**	**0.07 [-0.30, 0.44]**
Heterogeneity: Chi^2 = 5.77, df = 2 (P = 0.06); I^2 =65%							
Test for overall effect: Z = 0.36 (P = 0.72)							
2 Oral: post-treatment score							
Abernethy 2003	38	40.3 (23)	38	49.9 (24)		40.1 %	-0.40 [-0.86, 0.05]
Bar-Or 1982	11	-42.6 (12)	11	-42.5 (8.6)		11.9 %	-0.01 [-0.84, 0.83]
Chua 1997	12	2.91 (0.86)	12	3.6 (0.76)		11.8 %	-0.82 [-1.66, 0.02]
Eiser 1991	10	7 (2.21)	10	6.5 (2.21)		10.7 %	0.22 [-0.66, 1.10]
Johnson 1983	12	4.6 (3.11)	12	4.2 (2.77)		12.9 %	0.13 [-0.67, 0.93]
Woodcock 1981	12	5.54 (1.91)	12	6.33 (2)		12.7 %	-0.39 [-1.20, 0.42]
Subtotal (95% CI)	**95**		**95**			**100.0 %**	**-0.27 [-0.56, 0.02]**
Heterogeneity: Chi^2 = 4.59, df = 5 (P = 0.47); I^2 =0.0%							
Test for overall effect: Z = 1.83 (P = 0.067)							
3 Nebulised: change from baseline							
Charles 2008	20	1.04 (1.38)	20	0.78 (1.54)		67.6 %	0.17 [-0.45, 0.80]
Leung 1996	10	8.7 (2.2)	10	9.7 (1)		32.4 %	-0.56 [-1.46, 0.34]
Subtotal (95% CI)	**30**		**30**			**100.0 %**	**-0.06 [-0.57, 0.45]**
Heterogeneity: Chi^2 = 1.74, df = 1 (P = 0.19); I^2 =43%							
Test for overall effect: Z = 0.24 (P = 0.81)							
4 Nebulised: post-treatment score							
Harris-Eze 1995	6	6.3 (2.7)	6	6.5 (3.5)		12.5 %	-0.06 [-1.19, 1.07]
Jankleson 1997	16	4 (2)	16	4.5 (2.6)		33.2 %	-0.21 [-0.91, 0.48]
Jensen 2012	12	4.6 (3.11)	12	4.2 (2.77)		25.0 %	0.13 [-0.67, 0.93]
Noseda 1997	14	-42 (27)	14	-43 (27)		29.2 %	0.04 [-0.70, 0.78]
Subtotal (95% CI)	**48**		**48**			**100.0 %**	**-0.03 [-0.43, 0.37]**



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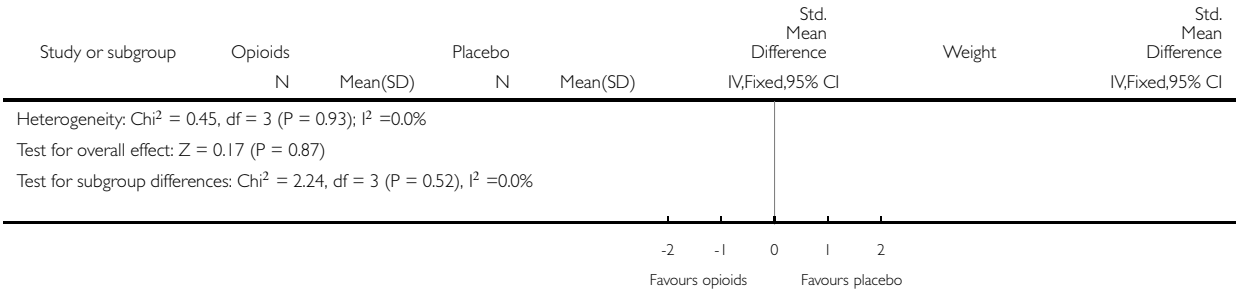
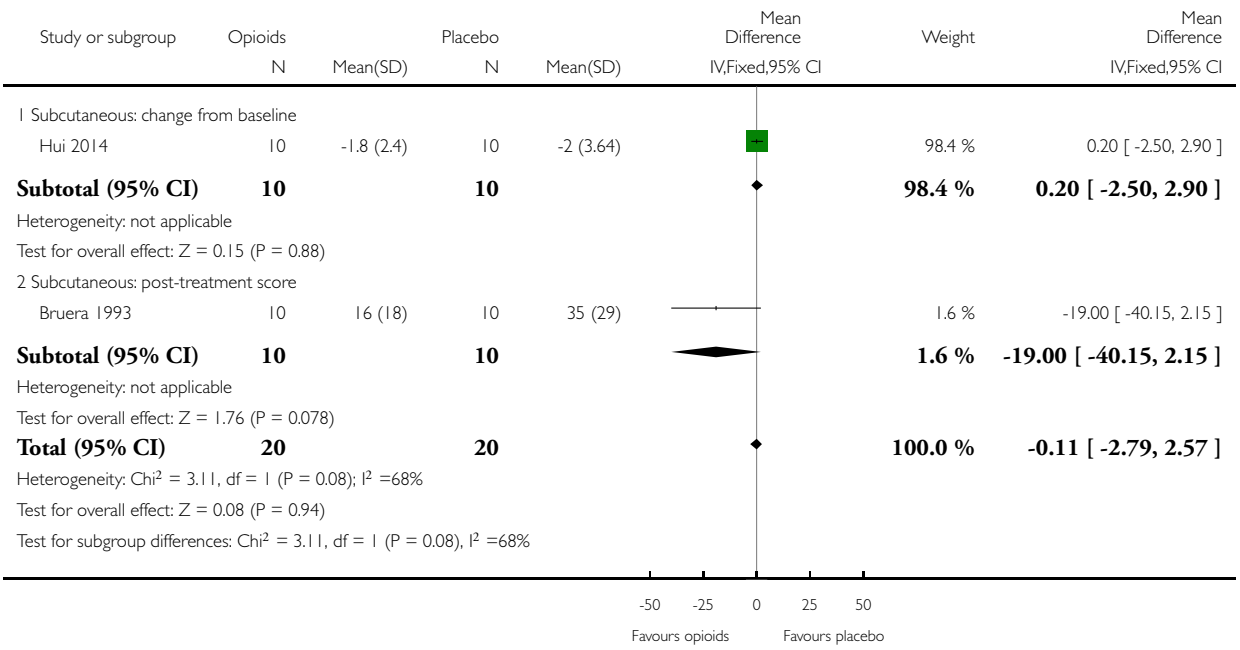


Analysis 6.2. Comparison 6 Opioids versus placebo, Outcome 2 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 6 Opioids versus placebo

Outcome: 2 Breathlessness

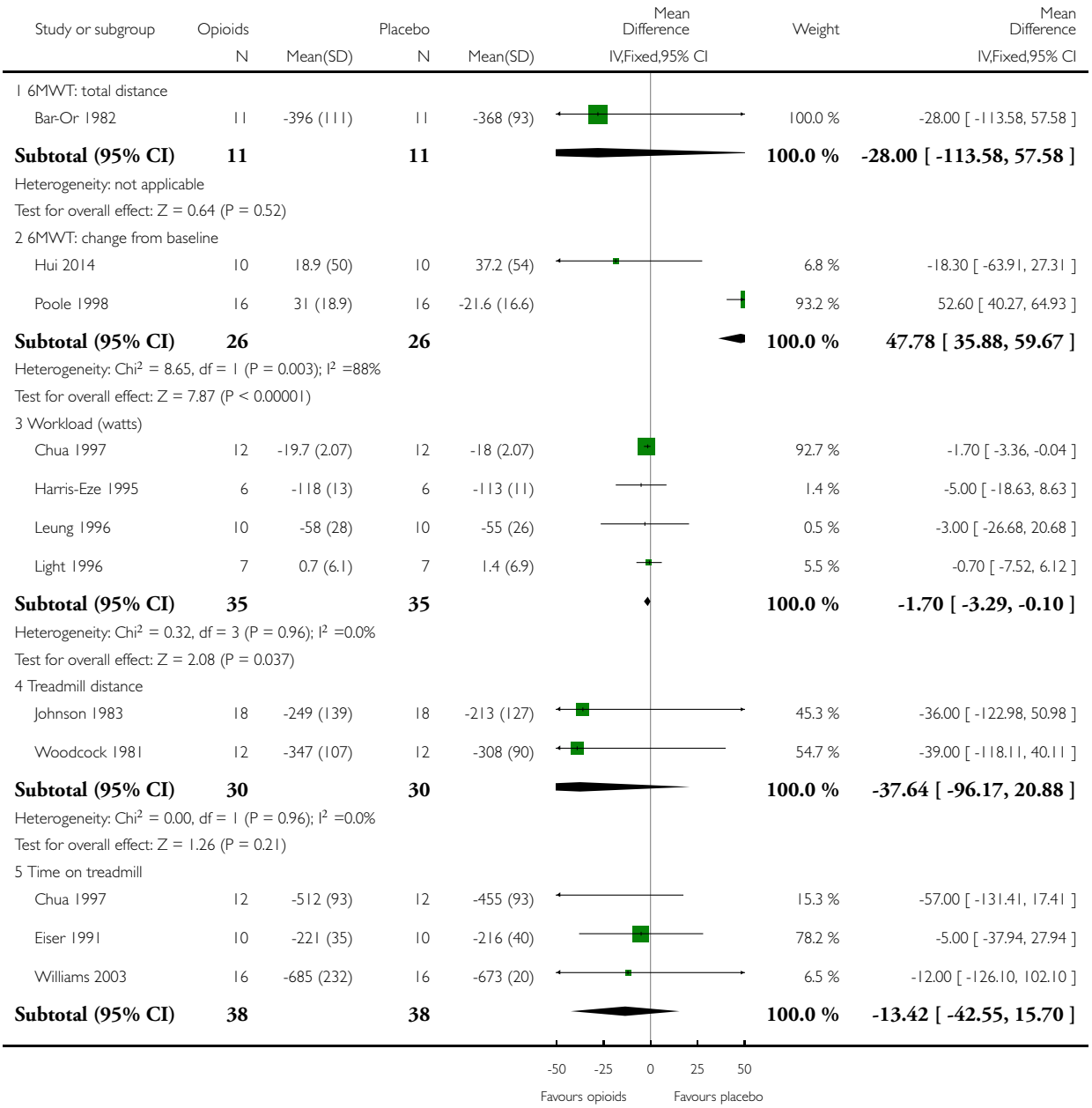


Analysis 7.1. Comparison 7 Opioids versus placebo, Outcome 1 Exercise tolerance.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 7 Opioids versus placebo

Outcome: 1 Exercise tolerance



Study or subgroup	Opioids N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 6MWT: total distance							
Bar-Or 1982	11	-396 (111)	11	-368 (93)		100.0 %	-28.00 [-113.58, 57.58]
Subtotal (95% CI)	**11**		**11**			**100.0 %**	**-28.00 [-113.58, 57.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.64 (P = 0.52)							
2 6MWT: change from baseline							
Hui 2014	10	18.9 (50)	10	37.2 (54)		6.8 %	-18.30 [-63.91, 27.31]
Poole 1998	16	31 (18.9)	16	-21.6 (16.6)		93.2 %	52.60 [40.27, 64.93]
Subtotal (95% CI)	**26**		**26**			**100.0 %**	**47.78 [35.88, 59.67]**
Heterogeneity: Chi^2 = 8.65, df = 1 (P = 0.003); I^2 =88%							
Test for overall effect: Z = 7.87 (P < 0.00001)							
3 Workload (watts)							
Chua 1997	12	-19.7 (2.07)	12	-18 (2.07)		92.7 %	-1.70 [-3.36, -0.04]
Harris-Eze 1995	6	-118 (13)	6	-113 (11)		1.4 %	-5.00 [-18.63, 8.63]
Leung 1996	10	-58 (28)	10	-55 (26)		0.5 %	-3.00 [-26.68, 20.68]
Light 1996	7	0.7 (6.1)	7	1.4 (6.9)		5.5 %	-0.70 [-7.52, 6.12]
Subtotal (95% CI)	**35**		**35**			**100.0 %**	**-1.70 [-3.29, -0.10]**
Heterogeneity: Chi^2 = 0.32, df = 3 (P = 0.96); I^2 =0.0%							
Test for overall effect: Z = 2.08 (P = 0.037)							
4 Treadmill distance							
Johnson 1983	18	-249 (139)	18	-213 (127)		45.3 %	-36.00 [-122.98, 50.98]
Woodcock 1981	12	-347 (107)	12	-308 (90)		54.7 %	-39.00 [-118.11, 40.11]
Subtotal (95% CI)	**30**		**30**			**100.0 %**	**-37.64 [-96.17, 20.88]**
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%							
Test for overall effect: Z = 1.26 (P = 0.21)							
5 Time on treadmill							
Chua 1997	12	-512 (93)	12	-455 (93)		15.3 %	-57.00 [-131.41, 17.41]
Eiser 1991	10	-221 (35)	10	-216 (40)		78.2 %	-5.00 [-37.94, 27.94]
Williams 2003	16	-685 (232)	16	-673 (20)		6.5 %	-12.00 [-126.10, 102.10]
Subtotal (95% CI)	**38**		**38**			**100.0 %**	**-13.42 [-42.55, 15.70]**

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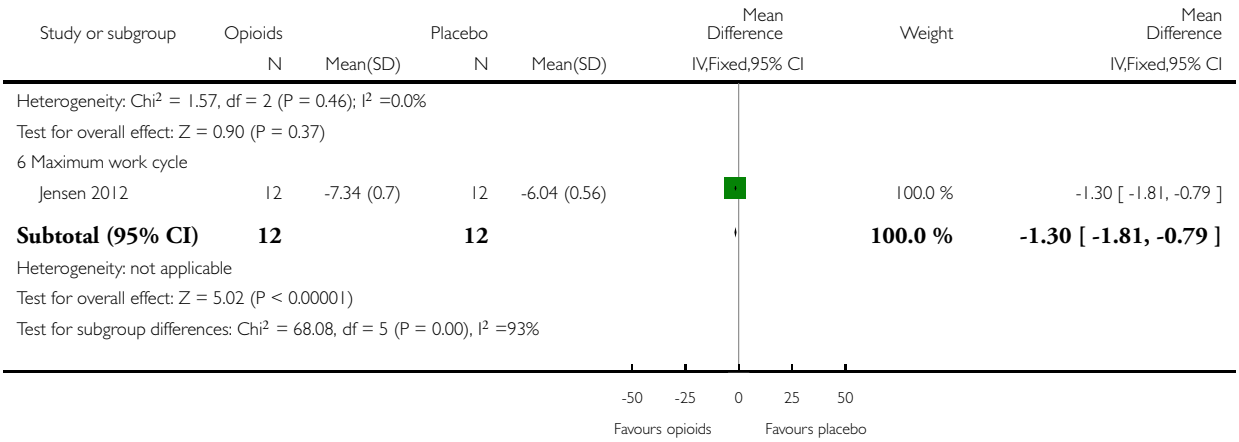
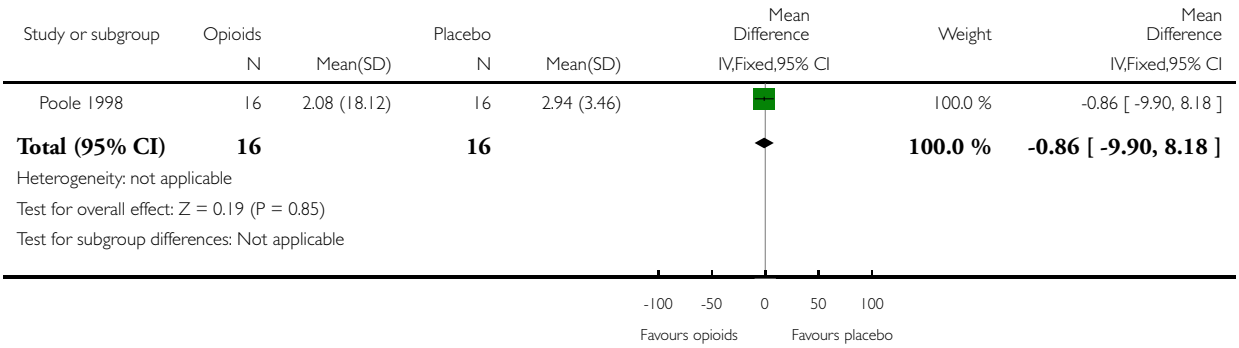


Analysis 8.1. Comparison 8 Opioids versus placebo, Outcome 1 Quality of life.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 8 Opioids versus placebo

Outcome: 1 Quality of life



Analysis 9.1. Comparison 9 Opioids versus placebo, Outcome 1 Adverse events: constipation.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 9 Opioids versus placebo

Outcome: 1 Adverse events: constipation

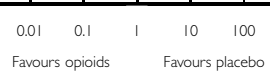
Study or subgroup	Opioids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abernethy 2003	9/38	4/38		40.0 %	2.25 [0.76, 6.68]
Bar-Or 1982	2/12	0/12		5.0 %	5.00 [0.27, 94.34]
Hui 2014	0/10	0/10			Not estimable
Johnson 1983	4/18	0/18		5.0 %	9.00 [0.52, 155.86]
Johnson 2002	0/10	0/10			Not estimable
Mazzocato 1999	0/9	0/9			Not estimable
Noseda 1997	0/14	0/14			Not estimable
Oxberry 2011	0/35	0/35			Not estimable
Poole 1998	14/16	5/16		50.0 %	2.80 [1.32, 5.93]
Total (95% CI)	**162**	**162**		**100.0 %**	**3.00 [1.63, 5.51]**

Total events: 29 (Opioids), 9 (Placebo)

Heterogeneity: $Chi^2 = 0.99$, df = 3 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 3.54 (P = 0.00040)

Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9 Opioids versus placebo, Outcome 2 Adverse events: nausea and vomiting.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 9 Opioids versus placebo

Outcome: 2 Adverse events: nausea and vomiting

Study or subgroup	Opioids n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bar-Or 1982	5/10	0/10		6.7 %	21.00 [0.97, 453.91]
Hui 2014	0/10	0/10			Not estimable
Johnson 2002	0/10	0/10			Not estimable
Mazzocato 1999	1/9	0/9		11.3 %	3.35 [0.12, 93.83]
Noseda 1997	0/14	0/14			Not estimable
Oxberry 2011	3/35	2/35		48.7 %	1.55 [0.24, 9.88]
Poole 1998	12/16	5/16		33.3 %	6.60 [1.40, 31.05]
Total (95% CI)	**104**	**104**		**100.0 %**	**4.73 [1.73, 12.97]**

Total events: 21 (Opioids), 7 (Placebo)

Heterogeneity: $Chi^2 = 2.52$, df = 3 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 3.02 (P = 0.0025)

Test for subgroup differences: Not applicable

Analysis 9.3. Comparison 9 Opioids versus placebo, Outcome 3 Adverse events: drowsiness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 9 Opioids versus placebo

Outcome: 3 Adverse events: drowsiness

Study or subgroup	Opioids n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Abernethy 2003	0/38	0/38			Not estimable
Bar-Or 1982	2/12	0/12		6.8 %	5.95 [0.26, 138.25]
Hui 2014	0/10	0/10			Not estimable
Jensen 2012	0/12	0/12			Not estimable
Johnson 2002	0/10	0/10			Not estimable
Mazzocato 1999	1/9	0/9		7.2 %	3.35 [0.12, 93.83]
Noseda 1997	0/14	0/14			Not estimable
Oxberry 2011	7/35	4/35		54.2 %	1.94 [0.51, 7.33]
Poole 1998	10/16	5/16		31.8 %	3.67 [0.85, 15.84]
Total (95% CI)	**156**	**156**		**100.0 %**	**2.86 [1.17, 7.02]**

Total events: 20 (Opioids), 9 (Placebo)

Heterogeneity: $Chi^2 = 0.66$, df = 3 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 2.30 (P = 0.021)

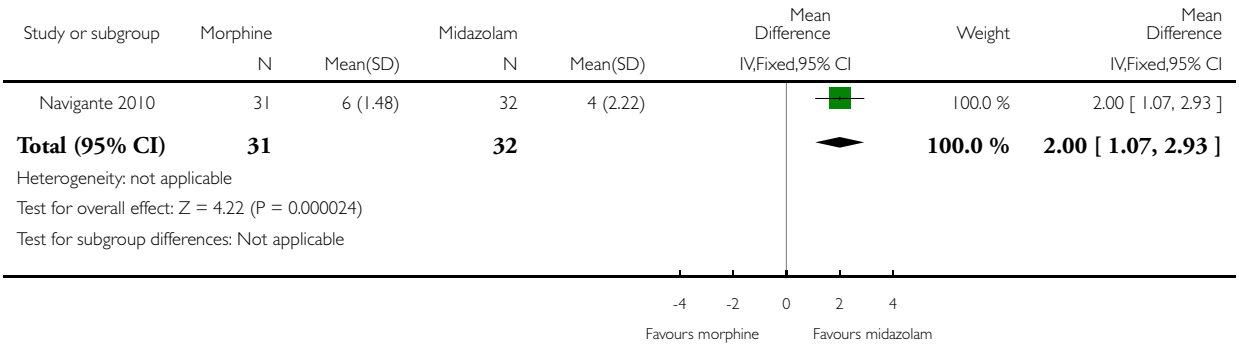
Test for subgroup differences: Not applicable

Analysis 10.1. Comparison 10 Morphine versus midazolam, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 10 Morphine versus midazolam

Outcome: 1 Breathlessness

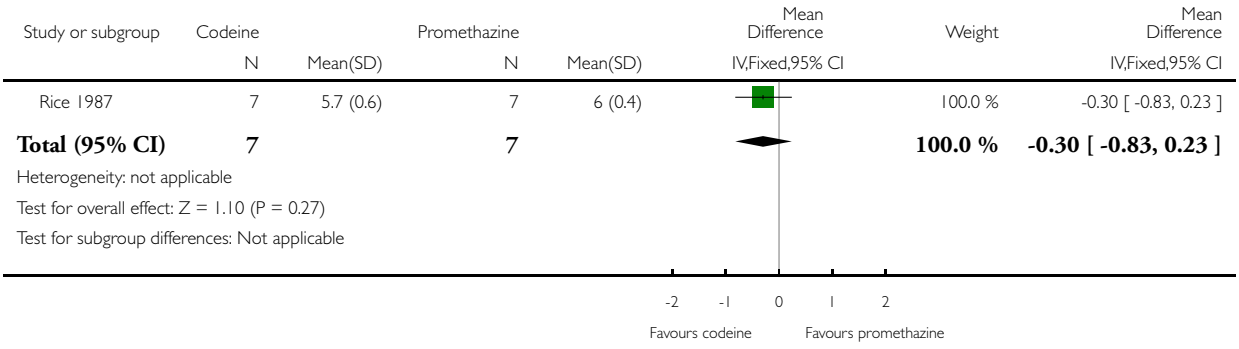


Analysis 11.1. Comparison 11 Codeine versus promethazine, Outcome 1 Breathlessness.

Review: Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness

Comparison: 11 Codeine versus promethazine

Outcome: 1 Breathlessness



ADDITIONAL TABLES

Table 1. Sensitivity analysis: breathlessness

Meta-analysis	Number of studies	Pooled SMD	Confidence interval	P value for SMD	Heterogeneity test
All studies, fixed-effect Change from baseline	7	−0.09	−0.36 to 0.19	0.54	I^2 statistic = 74%, P = 0.0009
All studies, random-effects Change from baseline	7	−0.36	−0.94 to 0.21	0.21	I^2 statistic = 74%, P = 0.0009
All studies, fixed-effect Post-treatment score	11	−0.28	−0.50 to −0.05	0.02	I^2 statistic = 0%, P = 0.75
All studies, random-effects Post-treatment score	11	−0.28	−0.50 to −0.05	0.02	I^2 statistic = 0%, P = 0.75
Studies excluded with unclear bias Change from baseline	5	0.01	−0.29 to 0.31	0.95	I^2 statistic = 80%, P = 0.0006
Studies excluded with unclear bias Post-treatment score	5	0.20	−0.50 to 0.10	0.20	I^2 statistic = 0%, P = 0.76

Abbreviations: SMD: standardised mean difference.

APPENDICES

Appendix 1. Search strategies

CENTRAL (the Cochrane Library)

#1 MeSH descriptor: [Analgesics, Opioid] this term only
#2 (papaveretum or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid* or opiate* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine):ti,ab,kw (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [Dyspnea] this term only
#5 (dyspnoea* or breathless* or (short* near/2 breath*)):ti,ab,kw (Word variations have been searched)
#6 #4 or #5
#7 #3 and #6

MEDLINE (OVID)

1 Analgesics, Opioid/
2 (papaveretum or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid* or opiate* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).tw.
3 Dyspnea/
4 (dyspnoea* or breathless* or (short* adj2 breath*)).tw.
5 or/1-2
6 or/3-4
7 5 and 6
8 randomised controlled trial.pt.
9 controlled clinical trial.pt.
10 randomized.ab.
11 placebo.ab.
12 drug therapy.fs.
13 randomly.ab.
14 trial.ab.
15 or/8-14
16 exp animals/ not humans.sh.
17 15 not 16
18 7 and 17

EMBASE (OVID)

1. Analgesics, Opioid/
2. (papaveretum or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid* or opiate* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine).tw.
3. Dyspnea/
4. (dyspnoea* or breathless* or (short* adj2 breath*)).tw.
5. or/1-2
6. or/3-4
7. 5 and 6
8. random$.tw.

9. factorial$.tw.
10. crossover$.tw.
11. cross over$.tw.
12. cross-over$.tw.
13. placebo$.tw.
14. (doubl$ adj blind$).tw.
15. (singl$ adj blind$).tw.
16. assign$.tw.
17. allocat$.tw.
18. volunteer$.tw.
19. Crossover Procedure/
20. double-blind procedure.tw.
21. Randomized Controlled Trial/
22. Single Blind Procedure/
23. or/8-22
24. (animal/ or nonhuman/) not human/
25. 23 not 24
26. 7 and 25

Web of Science (ISI)

#8 #7 AND #3
Indexes=SCI-EXPANDED, A&HCI, SSCI, CPCI-SSH, CPCI-S Timespan=All years
#7 #6 OR #5 OR #4
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
#6 TOPIC: ((((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*))))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
#5 TOPIC: (((controlled clinical trial OR controlled trial OR clinical trial OR placebo)))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
#4 TOPIC: (((randomised OR randomised OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomised controlled trial)))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
#3 #2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
#2 TS=((dyspnoea* or breathless* or (short* NEAR/2 breath*)))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years
#1 TOPIC: ((papaveretum or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid* or opiate* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine))
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All years

CINAHL (EBSCO)

S17 S7 AND S16
S16 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S15 (allocat* random*)
S14 (MH "Quantitative Studies")
S13 (MH "Placebos")
S12 placebo*
S11 (random* allocat*)
S10 (MH "Random Assignment")
S9 (Randomi?ed control* trial*)

S8 (singl* blind*) or (doubl* blind*) or (tripl* blind*) or (trebl* blind*) or (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)
S7 (S3 AND S6)
S6 S4 OR S5
S5 (dyspnoea* or breathless* or (short* N2 breath*))
S4 (MH "Dyspnea")
S3 S1 OR S2
S2 (papaveretum or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid* or opiate* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil
or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine)
S1 (MH "Analgesics, Opioid")#1 MeSH descriptor: [Analgesics, Opioid] this term only
#2 (papaveretum or morphine or fentanyl or hydromorphone or oxycodone or pentazocine or methadone or opioid* or opiate* or codeine or dextromoramide or OTFC or diamorphine or dihydrocodeine or dextropropoxyphene or meptazinol or sufentanil or alfentanil or remifentanil or nalbuphine or meptazinol or dipipanone or pethidine or tramadol or buprenorphine):ti,ab,kw (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [Dyspnea] this term only
#5 (dyspnoea* or breathless* or (short* near/2 breath*)):ti,ab,kw (Word variations have been searched)
#6 #4 or #5
#7 #3 and #6

CONTRIBUTIONS OF AUTHORS

HB and RM drafted the protocol. HB and RM screened the abstracts, and full-text articles for inclusion, extracted the data, and drafted the review. JM and NS provided comments and revisions of the review. HB will be responsible for updating this Cochrane review.

DECLARATIONS OF INTEREST

HB has no relevant conflicts of interest to declare.

JM has no relevant conflicts of interest to declare.

NS has no relevant conflicts of interest to declare.

RM has no relevant conflicts of interest to declare.

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we indicated that we would perform meta-analyses according to the subgroups of dose and 'Risk of bias' assessments. Due to the wide variation and heterogeneity of reported doses we chose to analyse this in a descriptive analysis. We compared the 'Risk of bias' difference in a sensitivity analysis.

Post-hoc we chose to include the type of opioid as a subgroup analysis as we felt this would be an important assessment for clinicians and policy makers.