Opioids for the palliation of breathlessness in advanced disease and terminal illness. (Review)

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[Intervention Review]

Opioids for the palliation of breathlessness in advanced disease and terminal illness.

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ABSTRACT

Background

Breathlessness is a common symptom in people with advanced disease. The most effective treatments are aimed at treating the underlying cause of the breathlessness but this may not be possible and symptomatic treatment is often necessary. Strategies for the symptomatic treatment of breathlessness have never been systematically evaluated. Opioids are commonly used to treat breathlessness: the mechanisms underlying their effectiveness are not completely clear and there have been few good-sized trials in this area.

Objectives

To determine the effectiveness of opioid drugs given by any route in relieving the symptom of breathlessness in patients who are being treated palliatively.

Search strategy

An electronic search was carried out of Medline, Embase, CINAHL, *T he Cochrane L ibrary*, Dissertation Abstracts, Cancercd and SIGLE. Review articles and reference lists of retrieved articles were hand searched. Date of most recent search: May 1999.

Selection criteria

Randomised double-blind, controlled trials comparing the use of any opioid drug against placebo for the relief of breathlessness were included. Patients with any illness suffering from breathlessness were included and the intervention was any opioid, given by any route, in any dose.

Data collection and analysis

Studies identified by the search were imported into a reference manager database. The full texts of the relevant studies were retrieved and data were independently extracted by two review authors. Studies were quality scored according to the Oxford Quality scale. The primary outcome measure used was breathlessness and the secondary outcome measure was exercise tolerance. Studies were divided into non-nebulised and nebulised and were analysed both separately and together. A qualitative analysis was carried out of adverse effects of opioids. Where appropriate, meta-analysis was carried out.

Main results

Eighteen studies were identified of which nine involved the non-nebulised route of administration and nine the nebulised route. A small but statistically significant positive effect of opioids was seen on breathlessness in the analysis of studies using non-nebulised opioids. There was no statistically significant positive effect seen for exercise tolerance in either group of studies or for breathlessness in the studies using nebulised opioids.

Authors' conclusions

There is evidence to support the use of oral or parenteral opioids to palliate breathlessness although numbers of patients involved in the studies were small. No evidence was found to support the use of nebulised opioids. Further research with larger numbers of patients, using standardised protocols and with quality of life measures is needed.

PLAIN LANGUAGE SUMMARY

Opioids (chemical substance) for palliation for breathlessness in terminal illness

There is evidence in favour of using oral or injectable opioid drugs for the palliative treatment of breathlessness. Breathlessness is common in people with advanced disease and opioid drugs are often used to treat it. A review to assess the effectiveness of opioids in these patients found a small but statistically significant positive effect when opioids were administered orally or subcutaneously. However, there was no evidence to support the use of nebulised (inhaled) opioids for the treatment of breathlessness. There was a lack of consistent evidence in support of the use of opioids administered via any route to improve exercise tolerance.

BACKGROUND

Breathlessness or dyspnoea is a common symptom affecting people with advanced disease from many causes (Reuben 1986). It is a distressing sensation which significantly affects quality of life. In advanced cancer, patients with any tumour type may experience breathlessness, although it is most common in primary lung tumours and in patients with metastatic lung disease. In chronic lung disease and heart failure, despite maximal treatment, many patients continue to experience disabling dyspnoea. Breathlessness can also be a feature of renal failure and motor neurone disease. This review examines the use of opioids for the palliation of breathlessness in terminal illness: terminal illness is defined as any life threatening illness for which a cure is not possible.

The most effective treatments for dyspnoea are aimed at identifying and treating the underlying cause of the breathlessness, for example, treating the underlying tumour with chemotherapy or radiotherapy, treating infection with antibiotics, anaemia with a blood transfusion, fluid overload with diuretics or draining a pleural effusion. In many cases, this is not possible as there may be either no effective treatment or no specific treatable cause. For example, although chemotherapy can be relatively effective in some tumour types such as small cell lung cancer or lymphoma, in other tumours there may be no specific effective treatment. In motor neurone disease, except where debility is complicated by infection, specific treatment that will have a beneficial effect in the short term is not currently available.

Specific treatment may be inappropriate in severely ill patients. Pleural tap, for instance, may be unjustifiably traumatic if a patient is close to death, and a relatively straightforward procedure, such as blood transfusion, may be inappropriate in a dying patient when this may be seen to be an unwelcome and futile attempt to prolong life. In some cases, even investigation of a symptom may cause unacceptable distress for patients and relatives. Treatment may, therefore, of necessity, be directed at symptomatic relief only (Fishbein 1989; Ripamonti 1998).

There has been no systematic evaluation of the evidence of the effectiveness of symptomatic treatments for breathlessness. Many treatments for breathlessness have been based on anecdote or case reports (Tooms 1993). Commonly used drug treatments for dyspnoea include opioids, benzodiazepines, oxygen therapy, and beta-agonists. Opioids are prescribed in varying doses and by different routes, and there is little in the way of objective evidence for their use (Bruera 1993; Cohen 1991; Krasnow 1994; Robin 1986). A variety of different opioids, both weak and strong, have been used. In current practice, oral morphine is perhaps most commonly prescribed in palliative care, although other drugs, such as dihydrocodeine, codeine and diamorphine are also used.

The mechanisms underlying the sensation of breathlessness have not been fully elucidated and it is not clear how the opioid drugs exert their effect (Bellofiore 1990; McQueen 1983; Wanke 1993).They may be useful in relieving breathlessness because they reduce the effect of carbon dioxide and oxygen levels on ventilation. Some studies of normal subjects have shown opioid drugs to reduce oxygen consumption both at rest and during exercise (Eckenhoff 1960; Santiago 1977; Santiago 1979; Weil 1975) although other studies have not confirmed this effect (Stark 1983a). Inhaled opioids have been used for palliating breathlessness on the assumption from experimental data that there are intrapulmonary opioid receptors accessible through inhalation which avoid some systemic side effects of the drugs (Adcock 1991; Belvisi 1988; Bostwick 1987; Cabot 1994; Neudeck 1998; Rogers 1989). Finally, it is possible that opioids alter the central perception of breathlessness in a way similar to that by which they alter the perception of pain.

There are few good sized randomised controlled trials in this area, particularly involving cancer patients. This is partly because of the difficulty in accruing large numbers of patients able to participate in a study. It is hard to find patients with advanced disease who are either well enough to perform exercise tests or who are breathless at rest and well enough to be able to participate in a study. This raises ethical issues about randomised trials at end of life: some clinicians are reluctant to enter terminally ill patients into randomised trials. Patients who are already very unwell may die during the study period for reasons unrelated to the treatment.

OBJECTIVES

The objective of this review was to determine the effectiveness of opioid drugs in relieving the symptom of breathlessness in patients with either advanced malignancy, or with advanced respiratory or cardiovascular disease, or receiving palliative care for any other disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, parallel group placebo-controlled trials were included as were double-blind cross-over studies in which patients were randomised to order of treatment. 'Randomised' is defined as studies which were described by the authors as 'randomised' anywhere in the manuscript.

There was no language restriction. All identified trials, published and unpublished, were potentially eligible for inclusion.

Types of participants

The population addressed by the review included patients of any age who suffered from breathlessness. Patients with any illness could be included.

Healthy volunteers were not covered by the inclusion criteria as the Steering Group felt that they might not behave in the same way as sick patients. Both in-patient and out-patient studies in any setting were included, for example, home, hospice, or hospital.

Types of interventions

The intervention considered in this review was the trial of any opioid drug, given by any route, in any dose, for the relief of breathlessness. The opioid had to be compared with placebo. Studies which involved the use of oxygen either during an exercise test or during the administration of both drug and placebo were also eligible for inclusion. Much of the work in the field involved the use of oxygen either during an exercise test or to drive the nebulisers in the case of inhaled opioids. It was felt that since, in the opinion of the Steering Group, it was unlikely that there was synergism between opioids and oxygen, as long as oxygen was given in both the drug and the placebo arm, these studies could be included.

As stated above, studies eligible for inclusion in the review used opioid drugs given by any route. It was decided to divide the studies into oral/parenteral and nebulised, and to analyse these two groups both together and separately. This was on the basis that there may be a local effect of nebulised opioids in the lung.

Types of outcome measures

The focus of this review was how patients experienced breathlessness and how that sensation could be relieved. The sensation of breathlessness does not correlate well with more objective, surrogate measures such as ventilation or arterial blood gases. Measurement therefore relies on subjective measures, for example, visual analogue scales or Borg scores which are visual analogue scales anchored by verbal descriptions of the gravity of the breathlessness. Since we were most interested in how patients felt, we decided to make the main outcome measure a subjective measure of breathlessness. A visual analogue score of breathlessness or similar measure, including a Borg score or an oxygen cost diagram was, therefore, the primary outcome measure (Borg 1982; Mahler 1992; Noseda 1992; Noseda 1994; McGavin 1978; Stark 1981; Stark 1982).

In studies which included an exercise test, the breathlessness measure which related to the exercise test was used in the analysis. At rest studies involved a 'one-off' dose of drug followed by breathlessness assessment. In studies which involved longer term administration of treatment and control, either a breathlessness measure from an exercise test at the end of each treatment period was used, or if an exercise test was not carried out, a measure of breathlessness relating to the whole treatment period was used. Daily diary

cards were not analysed because these data were too heterogeneous to be analysed statistically.
A wide range of other outcome measures was reported, but the majority of these were of more limited clinical significance. The principal secondary outcome measure for studies using exercise tests was, therefore, exercise capacity, assessed by either exercise duration, distance walked, or maximum power output, depending on which of these measures were reported.
Data were also collected on arterial blood gases or oxygen saturation, as these measures are of interest when assessing the risks of using opioid drugs, in particular the risk of respiratory depression. Where adverse effects were recorded, these data were noted.

Primary outcomes

The primary outcome measures used were subjective measures of breathlessness:
- Borg and modified Borg tests* (Borg 1982)
- verbal categorical scales of breathlessness*
- visual analogue scales of breathlessness*

Secondary outcomes

Secondary outcome measures used were:
- exercise tolerance* expressed as workload, distance walked, or exercise duration
- arterial blood gases
- pulse oximetry
- adverse effects of opioid drugs
- quality of life measures*(Guyatt 1987)

Only measures marked with an asterisk (*) were subjected to meta-analysis.

Search methods for identification of studies

The following electronic databases were searched:

- Medline on Silver Platter from 1966 to 4/1999
- Embase on Silver Platter from 1980 to 5/1999
- Cancercd on Silver Platter from 1988 to 5/1999
- CINAHL on Silver Platter from 1982 to 5/1999
- Cochrane Library Controlled Trials Register, and Database of Systematic Reviews,
- Dissertation Abstracts on Silver Platter
- SIGLE

The basic strategy was to combine two searches, one for opioids and one for breathlessness, using the Boolean operator 'AND'. Searches combined MeSH terms and a free text search.

Hand searching

Chapters from standard textbooks on palliative care were searched for reference lists. Reference lists of identified studies were searched as were the reference lists of all review articles found.

Personal contact

Contact was made with all the European palliative care organisations and other groups working in the field to access relevant research material and unpublished data. A letter was sent to European palliative care organisations asking them to circulate an enclosed notice describing the review to their members and asking for data. All members of the Association of Palliative Medicine were also sent this letter which was in addition published in the journal 'Palliative Medicine'. The information was also disseminated through the Science Committee of the Association of Palliative Medicine.
The authors of all identified relevant studies were contacted asking if they were aware of any further published or unpublished data, as were other established experts in the field.
Personal contacts were made by members of the Steering Group with other groups working in the fields of cardiology and respiratory physiology in order to collect additional material which might be eligible for inclusion.

Data collection and analysis

All records from each of the databases were imported to the bibliographic package, Reference Manager (Version 8), and merged into one core database.
Numbers of studies identified:
Medline 3078 references
Embase 1872 references
Cancercd 62 references
Cinahl 17 references
Cochrane Library 945 references
A total of 4691 references was imported into Reference Manager (Version 8). The titles and abstracts of each article were studied and relevant studies (including review articles) selected according to whether they met the inclusion criteria. The full text of these articles was obtained.
Each article was read independently by two review authors and, using the inclusion criteria specified, was assessed for inclusion in the review. Where differences arose they were resolved by consensus and, when necessary, in consultation with a third review author. Reasons for excluding studies were noted.

Data collection

A data collection form was designed for the review. The following data items were collected independently by the two review authors:
- publication details
- patient population
- randomisation/allocation concealment
- details of blinding measures
- description of intervention
- results

A checklist was used to assess study validity based on the Oxford Quality scale (Jadad 1996).

Differences in quality assessment were resolved by referring back to the original article. If necessary, a third party was consulted. Where necessary, information was sought from the authors of the primary studies for clarification or for missing information.

Studies were classified as 'double-blind' if they were described as such in the text. The form of double-blinding was assessed as appropriate either if it was stated that the participants could not tell the difference between the study drug and placebo, or if the placebo was described to be in the same format as the study drug, for example, if the same volume of a liquid substance were given. If injections were given but the volumes were not stated, this was taken to be adequate double-blinding. In general, if volumes were not stated but if drug and placebo were given by the same route, then this was taken to be adequate double-blinding. (For example, using nebulised solutions or injected drugs, it was assumed that if both placebo and active drug were given by the same route, the patients would be unlikely to recognise a difference in volumes.)

Analysis

A. Difficulties in analysis of results from different forms of exercise testing

There are difficulties involved in comparing results from different forms of exercise testing. Ideally, in order to confirm efficacy of a treatment for breathlessness, results should be obtained from all types of exercise test but in practice this may not be done.

There is some controversy as to whether it is possible to analyse breathlessness results from a six minute walk test which is a sub-maximal form of exercise testing with results from maximal exercise tests. Because of this controversy, a sensitivity analysis was carried out excluding studies which measured breathlessness only at the end of a six minute walk test.

Another barrier to pooling results from this group of studies concerned the method of presentation of results from the exercise tests. It can be argued that it is not useful to compare breathlessness scores at maximal exercise. For a patient whose exercise tolerance is limited by breathlessness, a visual analogue score of dyspnoea at maximal exercise is likely to be the highest possible score whatever the intervention. In addition, if exercise tolerance is affected by opioid ingestion, this will confuse the results if dyspnoea scores are compared at maximal exercise or if, as sometimes occurs, the 'highest' dyspnoea score is reported. The measures of breathlessness, therefore, that were used in the review were those made at a fixed point during exercise or after a fixed length of exercise.

In studies carried out at rest, when several breathlessness scores were recorded, the score measured nearest to one hour after administration of the drug was used in the analysis.

Attempts were made to obtain additional data from the authors of the studies where results were not presented in the original papers in a useable form. Four authors were contacted and two responded providing further useful data. Attempts were also made to find missing data when inadequate data, for example, means without standard deviations, were presented. Where these data were not forthcoming, these studies have been excluded from the meta-analysis.

B. Meta-analysis

Meta-analysis was performed for the primary and secondary outcomes when appropriate and possible, and taking into consideration the issues outlined above. Results from both periods of cross-over trials were used unless there was reason to believe carryover of effects from one period to another posed a serious problem. Breathlessness and exercise tolerance outcomes were considered as continuous outcomes. For breathlessness outcomes, change from before to after administration of the drug was used in preference to post-administration measurements. Standardised mean differences were used for breathlessness and exercise tolerance since comparable outcomes were measured on different scales. The standardised mean difference can be converted to units in a visual analogue scale or a Borg score by multiplying by the standard deviation for a particular study.

Where more than one dose of the study drug was used, an average of all doses was used in meta-analyses.

C. Statistical details

Within-study comparisons were based on paired t-tests. Reports of cross-over trials often do not report appropriate data for entry in a meta-analysis. When insufficient information was available, appropriate standard errors were estimated using methods described by Follman 1992. Correlations between repeat outcomes on the same patient were estimated when possible from P-values or from any available raw data. When correlations could not be estimated, they were imputed for each outcome using the lowest estimate among other studies. Correlations between change-from-baseline measures were assumed to be zero. Sensitivity analyses were undertaken to investigate the robustness of results to imputed quantities.

Standardised mean differences were calculated as the mean of the within-patient differences between opioid and placebo outcomes, divided by the between patient standard deviation of the outcome, whether this be post treatment measurements or change-from-baseline measurements. An approximate variance for the standardised mean difference was taken as 2 * (1-rho) / n where rho is the estimated or imputed correlation between repeated outcome measurements and n is the number of patients in the trial.

D. Heterogeneity and subgroup analyses

Clinical heterogeneity was examined prior to performing meta-analyses but did not preclude the combination of results. Random effects meta-analyses were undertaken in preference to fixed effect analyses in order to encompass residual variation between studies into the confidence interval for a pooled effect. Random effects meta-regression (using Metareg in STATA) was used to compare subgroups.

The following subgroup analyses were specified *a priori* and were carried out:

1. studies using nebulised opioids. Nebulised opioids may affect breathlessness by a direct effect on intra-pulmonary opioid receptors in addition to a possible systemic effect.

2. studies involving chronic obstructive pulmonary disease (COPD) patients.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Nine studies using oral or parenteral opioids and nine studies using nebulised opioids which fulfilled the inclusion criteria were identified. All were cross-over studies.

One study (Light 1989) was excluded because it was not considered to have been adequately double-blinded. On the day that morphine was given the participants had an arterial line inserted and were told that they needed to remain in the hospital for four hours before going home, although they were not told that this was the morphine day. Clearly the technicians were not blinded and it is arguable that the participants may have deduced that this was the day that they received the active drug.

Fourteen of the studies involved primarily or exclusively patients with chronic obstructive pulmonary disease. Two studies included only cancer patients (Bruera 1993; Davis 1996 neb). One study using oral opioids involved patients with cardiac failure (Chua 1997) and one other study was composed of patients with interstitial lung disease (Harris-Eze 95 neb).

With the exception of Davis' study published in 1996 (Davis 1996 neb) which included 76 patients, numbers of subjects in the studies were small, ranging from six to 18 patients completing the studies. The majority of the studies were carried out on an out-patient basis. The exceptions to this were the studies (Bruera 1993; Noseda 1997 neb) which included patients who were more acutely unwell, usually palliative care patients who were also those who were studied at rest because they were too unwell to carry out exercise tests.

Most of the studies incorporated some sort of exercise testing; three studies (Bruera 1993; Davis 1996 neb; Noseda 1997 neb) were carried out at rest alone. A variety of different exercise tests were used. They were divided into maximal and sub-maximal tests and included incremental treadmill tests, incremental cycle ergometer tests, non-incremental or endurance treadmill tests, an endurance cycle test and six minute walk tests.

There was considerable variety in the reporting of the breathlessness measure for the exercise tests which led to some difficulties in the analysis. This meant that not all the studies could be included in the meta-analysis. Several of the studies did not report breathlessness at a fixed point during exercise and were therefore excluded from the analysis (Beauford 1993 neb; Masood 1995 neb). Some studies did not include sufficient data, not reporting, for example, standard deviations or reporting in such a way that the relevant numbers could not be extrapolated (Davis 1994 neb; Jankelson 1997 neb; Masood 1995 neb).

Five studies involving patients with chronic obstructive pulmonary disease (COPD) included the administration of beta-2 agonists before the exercise tests (Woodcock 1981; Eiser 1991b; Light 1996; Beauford 1993 neb; Masood 1995 neb). Two studies involved the use of oxygen inhalation during the exercise tests (Young 1989 neb; Leung 1996 neb). In both cases these measures were applied during the use of drug and placebo and were not thought to bias the study results.

Most of the studies were carried out as a series of single exercise tests or as studies at rest taking place over a fixed period during one day or on consecutive days. Four studies (Woodcock 1982; Johnson 1983; Eiser 1991a; Poole 1998) involved more chronic administration of drug or placebo, continuing for study periods of between one week and six weeks.

In most cases, when prolonged administration of drugs was involved, a single exercise test was carried out at the end of each study period and a breathlessness measure as well as an exercise tolerance score was recorded arising from the test. In some studies patients were asked to rate their breathlessness over the intervention period. In one study (Poole 1998) the Chronic Respiratory Disease Questionnaire (CRQ) Dyspnoea subscale (Guyatt 1987) was used to compare breathlessness on opioids and placebo. Usually, daily breathlessness scores were recorded by the patients. In one study (Johnson 1983) the patients recorded pedometer distance over the study period of a week.

The opioids used in the studies were oral dihydrocodeine, oral diamorphine, immediate release oral morphine, slow release oral morphine, subcutaneous morphine, intravenous morphine and nebulised morphine. The dose of dihydrocodeine was 1 mg/kg in a one-off dose, and ranged from 15 mg three times a day as required, to 60 mg three times a day regularly when it was given for a continuous period. The dose of diamorphine ranged from 2.5 to 5 mg four times a day in one study and was 7.5 mg as a single dose in one other study. Oral morphine was used in a dose of 30 mg stat and subcutaneous morphine was used in an average dose of 34 mg with a standard error of 12 mg. (In this study (Bruera 1993), patients were not opioid naive, in contrast to the majority of the other studies.) Intravenous morphine was given in a dose ranging from 1 mg to 2.5 mg as a single dose. There was a wide range of different doses of nebulised morphine used, from 1 mg to 50 mg.

Risk of bias in included studies

Studies were quality scored using the Oxford Quality scale (Jadad 1996). This scale assesses methods of randomisation and blinding. Sixteen of the 18 studies scored four of a possible maximum five on this scale. The reason for sub-maximal scoring was that exact details of the methods of randomisation were not described in any of the studies.

Effects of interventions

Meta-analyses using standardised mean differences as described in the methods section are presented in an additional table. Included are fixed and random effects meta-analyses for:
i) all studies
ii) non-nebulised studies
iii) nebulised studies and,
iv) studies of patients with chronic obstructive pulmonary disease; along with some sensitivity analyses. We present random effects results and other findings here followed by results of sensitivity analyses.

A. Meta-analyses for all studies

1. Breathlessness outcome

This review shows a strong effect of treatment for breathlessness (12 studies: SMD = -0.31; 95 % confidence interval -0.50 to -0.13, P = 0.0008). There was statistically significant heterogeneity between the results of the trials for breathlessness (P = 0.05) but the direction of effect was consistent. The measure used in the meta-analysis was the standardised mean difference (SMD). This figure can be converted to units in a visual analogue scale or a Borg score by multiplying by the standard deviation for a particular study. For example, using data from Johnson 83 (Johnson 1983), the pooled result of -0.40 in the main meta-analysis for non-nebulised studies can be expressed as a change of 0.40 x 2.11 in the ten point visual analogue scale used in this study. This is the equivalent of roughly 0.8 of a point on the ten point visual analogue scale. Please see Table 1 in 'additional tables'.

Table 1. Main breathlessness results

Meta-analysis	Number of studies	Pooled SMD (95% CI)	p-val for pooled SMD	Heterogeneity test
All studies	12	-0.31 (-0.50, -0.13)	0.0008	Q = 19.4 (p = 0.054)
Nebulised studies	3	-0.11 (-0.32, 0.10)	0.3103	Q = 0.1 (p=0.952)
Non-nebulised studies	9	-0.40 (-0.63, -0.17)	0.0006	Q = 13.86 (p = 0.086)
COPD studies	9	-0.26 (-0.44, 0.08)	0.0042	Q = 10.47 (p = 0.234)

2. Exercise tolerance outcome

For the exercise tolerance outcome, an effect of treatment is indicated, although statistical significance is not achieved (12 studies: SMD=0.20; 95 % confidence interval -0.03 to 0.42, p = 0.09.) There was highly significant heterogeneity among results for exercise tolerance (P < 0.001); this and the lack of a significant treatment effect were partly due to the influence of a single study (Poole 1998) that found a significant effect in favour of placebo. Please see Table 2 in 'additional tables'.

Table 2. Main exercise tolerance results

Meta-analysis	Number of studies	Pooled SMD (95% CI)	p-val for pooled SMD	Heterogeneity test
All studies	12	0.20 (-0.03, 0.42)	0.0914	Q = 42.54 (p = <0.0001)
Nebulised studies	4	0.06 (-0.58, 0.70)	0.855	Q = 15.01 (p = 0.002)
Non-nebulised studies	8	0.22 (-0.03, 0.47)	0.0818	Q = 25.96 (p = 0.001)
COPD studies	10	0.19 (-0.05, 0.43)	0.1194	Q = 30.58 (p = <0.0001)

B. Nebulised and non-nebulised studies

1. For the breathlessness results, meta-regression comparing the non-nebulised and nebulised studies showed a significantly stronger effect for the non-nebulised studies (P = 0.02). Results for the separate subgroups are included in the tables. For the nebulised studies alone, the pooled result did not reach statistical significance.

2. For the exercise tolerance outcome, a stronger effect was observed in non-nebulised studies, but neither the subgroups separately nor the difference between them was statistically significant. There was only one nebulised study that showed a statistically significant effect of opioid over placebo on exercise tolerance (Young 1989 neb) and, in this study, the results were skewed by the performance of one patient who did extremely well on opioids (Beauford 1993 neb). If the results of this patient are excluded, the study result ceases to be statistically significant.

C. Further qualitative results

1. For the breathlessness outcome, five of the nebulised studies were not included in the meta-analysis either because they did not present adequate information on outcomes, or because breathlessness scores were not recorded at a fixed point during exercise. In the Harris-Eze 95 neb study, Borg scores were presented at the end of exercise, in Beauford 1993 neb they were presented at maximal exercise, and in Jankelson 1997 neb the highest Borg scores were presented. In the other papers (Davis 1994 neb; Masood 1995 neb) insufficient information on breathlessness was presented for analysis. In all of these studies which were not included in the meta-analysis, no significant effect of nebulised opioid was found by the original study authors.

2. For the exercise tolerance outcome, three studies were excluded from the meta-analysis (Davis 1994 neb; Masood 1995 neb; Jankelson 1997 neb) because insufficient information was presented. In none of these trials was a significant effect of opioids over placebo seen on exercise tolerance.

3. Quality of life measures were reported in only one study (Poole 1998) which used the Chronic Respiratory Disease Questionnaire (CRQ) (Guyatt 1987). There was no difference between morphine and placebo in the total score for the CRQ.

D. Studies of patients with Chronic Obstructive Pulmonary Disease (COPD)

Sub-group analysis of the COPD studies alone did not show a significantly different result from the main analysis that included all studies.

E. Adverse effects

Eleven studies contained information on blood gases or oxygen saturation after the intervention with opioids. One study (Woodcock 1982) reported a significant increase in arterial pCO2 on dihydrocodeine 30 mg three times a day and 60 mg three times a day but in no case did it rise above 40 mm Hg and oxygen partial pressure did not fall significantly. It is unclear whether this is of clinical significance. Other studies showed no significant changes in blood gases or oxygen saturation.

Adverse effects of opioid drugs are well recognised and in these studies were fairly marked in patients continuing on opioids for protracted periods. Studies using oral opioids in opioid naïve patients had most problems with adverse effects. The most common adverse effects experienced were nausea, vomiting and constipation. Some patients experienced problems with dizziness and drowsiness, and several patients in the longer studies had withdrawal symptoms on stopping the drugs.

Three patients died during the Noseda 1997 neb study: this was not felt by the authors to be related to any of the study interventions. All the patients in this study had very advanced disease and the deaths may well have been expected. In this same study, three patients had minor side effects involving a bitter taste in the mouth with 20 mg nebulised morphine, cough on 20 mg nebulised morphine and a pricking sensation in the throat which was experienced both with morphine and saline. In the other studies using nebulised morphine there were no significant problems with side effects of opioids.

F. Sensitivity analyses

The following sensitivity analyses were carried out to assess the robustness of our findings:

(i) fixed effect meta-analyses (which do not incorporate heterogeneity between studies)

(ii) analyses that ignore the nature of the studies as crossover trials. This amounts to treating the opioid periods and the placebo periods as two distinct arms as in a parallel group trial (i.e. double counting the patients) or, equivalently, to assuming correlations of 0 between repeat measurements on any particular patient.

(iii) exclusion of the Eiser studies (Eiser 1991a; Eiser 1991b) for the breathlessness outcome on the grounds that these studies used a six minute walk test and not a maximal form of exercise test.

Fixed effect meta-analyses consistently produced similar point estimates but narrower confidence intervals. These did not alter any conclusions for breathlessness outcomes but all analyses for exercise tolerance were statistically significant under a fixed effect model, indicating that some beneficial effect on this outcome is present somewhere. Meta-analytic results were similar when the crossover nature of the trials was ignored. In these sensitivity analyses, estimates from individual trials had considerably wider confidence intervals. Whereas this might be expected to widen the confidence intervals for the pooled estimate, in fact the resulting decrease in the estimated degree of heterogeneity kept the intervals to a similar width. Excluding the two Eiser studies (Eiser 1991a; Eiser 1991b) did not significantly affect the results.

Please see Table 3 and Table 4 in 'additional tables'.

Table 3. Sensitivity analyses: Breathlessness

Meta-analysis	Number of studies	Pooled SMD (95% CI)	p-val for pooled SMD	Heterogeneity test
All studies, fixed effect analysis	12	-0.31 (-0.43, -0.20)	<0.0001	Q = 19.44 (p = 0.054)
All studies, random effects, ignoring crossover design	12	-0.29 (-0.49, -0.09)	0.0044	Q = 8.38 (p = 0.679)
All studies, fixed effect, ignoring crossover design	12	-0.29 (-0.49, -0.09)	0.0044	Q = 8.38 (p=0.679)
Excluding Eiser A and Eiser B, random effects	10	-0.38 (-0.55, -0.20)	<0.0001	Q = 13.31 (p = 0.149)

Table 4. Sensitivity analyses: Exercise tolerance

Meta-analysis	Number of studies	Pooled SMD (95% CI)	p-val for pooled SMD	Heterogeneity test
All studies: fixed effect analysis	12	0.25 (0.16, 0.35)	<0.0001	Q = 42.54 (p<0.0001)
All studies, random effects, ignoring crossover design	12	0.17 (-0.16, 0.50)	0.3257	Q = 19.31 (p = 0.056)
All studies, fixed effect, ignoring crossover design	12	0.17 (-0.07, 0.42)	0.1725	Q = 19.31 (p = 0.056)

DISCUSSION

This review shows statistically strong evidence for a small and probably clinically significant effect of oral and parenteral opioids in the treatment of breathlessness. There is no evidence at this level that nebulised opioids are more effective than placebo in relieving breathlessness. Patients may benefit from the use of nebulised opioids but they probably do not receive additional benefit from nebulised morphine over nebulised saline.

The measure used in the meta-analysis was the standardised mean difference (SMD). This figure can be converted to units in a visual analogue scale or a Borg score by multiplying by the standard deviation for a particular study. For example, as mentioned above, using data from the Johnson 1983 study, the pooled result of -0.40 in the main meta-analysis for non-nebulised studies can be expressed as a change of roughly 0.8 on a ten point visual analogue scale. This may appear a relatively small difference but if a patient can clearly point to an improvement in breathlessness even if it is small, then this is worthwhile.

The strength of this evidence is limited by the fact that all but one of the studies identified in this review are small with numbers between six and eighteen subjects. The exception to this is Davis' study published in 1996 (Davis 1996 neb) which includes seventy-

six subjects.

The conclusions concerning nebulised studies may be influenced by the fact that there is a lack of consistency in the evidence, in that the nebulisers used in the various studies were not standardised. Different particle size and different distances from nebuliser to mouth piece mean that different amounts of drug would reach the lung. It is not always clear whether mouthpieces or masks were used which may also affect the efficacy of the nebulised drug. In addition, varying amounts of the drug may have been swallowed by the patients.

The conclusions drawn from this review apply only to the doses used in the included studies. In the case of nebulised opioids, a wide range of doses was used but one can speculate, however, that if bigger doses had been used it is possible that an effect may have been seen. However, if this were case, it could be explained by systemic absorption of the drug.

Of the non-nebulised studies, Poole 1998 stands out in finding, for the exercise tolerance outcome, a significant effect in favour of placebo. This study was the only one to use a slow release form of opioid and it continued for the longest time period.

A variety of different outcome measures was used in the breathlessness studies. Even within one measure, for example the Borg score or visual analogue score, the outcome is reported differently, namely often not at a fixed point in relation to exercise. This does cause difficulty in interpretation and it is recommended that future studies aim to standardise these outcome measures.

The majority of the studies were carried out on COPD patients although the largest study involved cancer patients. Clearly cancer patients are more heterogeneous than COPD patients: one might argue that there is a limit to the extent that one can extrapolate from COPD to cancer patients. However, the sub-group analysis looking at only COPD patients did not show significantly different results from the main analysis.

Although opioids have been shown to be effective, there may be problems that can limit their use. Studies which involved the use of opioids for protracted periods encountered side effects which were fairly troublesome, most commonly nausea, vomiting and constipation. Withdrawal from opioids also caused some problems. All of these adverse effects are well recognised and easily treated, and clearly they need to be weighed up against the possible benefits of using these drugs. In contrast, patients did not appear to experience significant problems using nebulised opioids although this is to accept the authors' assertion in the Noseda 1997 neb study that the patients who died did so for reasons unrelated to the study medication.

It is striking that only one of the identified studies included data on quality of life. This is an important omission as the patients in these studies are all symptomatic, and quality of life data are particularly relevant in these circumstances.

AUTHORS' CONCLUSIONS

Implications for practice

- There is evidence in favour of continuing to use oral or parenteral opioid drugs to treat breathlessness

- There is no evidence to support the use of nebulised opioids for the treatment of breathlessness and it is hard to justify their continued use in this manner at present

- There is currently a lack of consistent evidence in support of the use of opioids to improve exercise tolerance.

Implications for research

Total numbers of patients in the studies included in this review are small and further research is needed and justified by the positive effect shown so far.

Points to be addressed by future research should include:

- different drugs and effective dosing schedules. Many of the studies in the review are over ten years old and use drugs which are less commonly prescribed today such as dihydrocodeine. Morphine, for example, is now more commonly used and future studies should focus, in addition, on this drug

- standardisation of outcome measures and the recording and reporting of outcome measures so that, for example, breathlessness scores are recorded at a fixed point

- quality of life measures

- use of standardised nebuliser regimens.

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REFERENCES

References to studies included in this review

Beauford 1993 neb *{published data only}*
Beauford W, Saylor TT, Stansbury DW, Avalos K, Light RW. Effects of nebulized morphine sulfate on the exercise tolerance of the ventilatory limited COPD patient. *Chest* 1993;**104**(1):175–8.

Bruera 1993 *{published data only}*
Bruera E, MacEachern T, Ripamonti C, Hanson J. Subcutaneous morphine for dyspnea in cancer patients. *Ann Intern Med* 1993; **119**:906–7.

Chua 1997 *{published data only}*
Chua TP, Harrington D, Ponikowski P, Webb PK, Poole WP, Coats AJ. Effects of dihydrocodeine on chemosensitivity and exercise tolerance in patients with chronic heart failure. *J Am Coll Cardiol* 1997;**29**(1):147–52.

Davis 1994 neb *{published and unpublished data}*
Davis C, Hodder C, Love S, Shah R, Slevin M, Wedzicha J. Effect of nebulised morphine and morphine 6-glucuronide on exercise endurance in patients with chronic obstructive pulmonary disease. *Thorax* 1994;**49**:393.

Davis 1996 neb *{published and unpublished data}*
Davis C, Penn K, A'Hern R, Daniels J, Slevin M. Single dose randomised controlled trial of nebulised morphine in patients with cancer related breathlessness. *Pall Med* 1996;**10**:64–5.

Eiser 1991a *{published data only}*
Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer" syndrome. *Euro Respir J* 1991;**4**(8):926–31.

Eiser 1991b *{published data only}*
Eiser N, Denman WT, West C, Luce P. Oral diamorphine: lack of effect on dyspnoea and exercise tolerance in the "pink puffer" syndrome. *Euro Respir J* 1991;**4**(8):926–31.

Harris-Eze 95 neb *{published data only}*
Harris-Eze A, Sridhar G, Clemens RE, Zintel TA, Gallagher CG, Marciniuk DD. Low-dose nebulized morphine does not improve exercise in interstitial lung disease. *Am J Respir Crit Care Med* 1995; **152**:1940–5.

Jankelson 1997 neb *{published data only}*
Jankelson D, Hosseini K, Mather LE, Seale JP, Young IH. Lack of effect of high doses of inhaled morphine on exercise endurance in chronic obstructive pulmonary disease. *Eur Respir J* 1997;**10**(10): 2270–4.

Johnson 1983 *{published data only}*
Johnson MA, Woodcock AA, Geddes DM. Dihydrocodeine for breathlessness in "pink puffers". *Br Med J Clin Res Ed* 1983;**286** (6366):675–7.

Leung 1996 neb *{published and unpublished data}*
Leung R, Hill P, Burdon J. Effect of inhaled morphine on the development of breathlessness during exercise in patients with chronic lung disease. *Thorax* 1996;**51**(6):596–600.

Light 1996 *{published data only}*
Light RW, Stansbury DW, Webster JS. Effect of 30 mg of morphine alone or with promethazine or prochlorperazine on the exercise capacity of patients with COPD. *Chest* 1996;**109**(4):975–81.

Masood 1995 neb *{published data only}*
Masood AR, Reed JW, Thomas SH. Lack of effect of inhaled morphine on exercise-induced breathlessness in chronic obstructive pulmonary disease. *Thorax* 1995;**50**(6):629–34.

Noseda 1997 neb *{published data only}*
Noseda A, Carpiaux JP, Markstein C, Meyvaert A, de Maertelaer V. Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *Eur Respir J* 1997;**10**(5):1079–83.

Poole 1998 *{published data only}*
Poole PJ, Veale AG, Black PN. The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; **157**(6 Pt 1):1877–80.

Woodcock 1981 *{published data only}*
Woodcock AA, Gross ER, Gellert A, Shah S, Johnson M, Geddes DM. Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N Engl J Med* 1981;**305**(27):1611–6.

Woodcock 1982 *{published data only}*
Woodcock AA, Johnson MA, Geddes DM. Breathlessness, alcohol and opiates. *New Eng J Med* 1982;**306**:1363–4.

Young 1989 neb *{published data only}*
Young IH, Daviskas E, Keena VA. Effect of low dose nebulised morphine on exercise endurance in patients with chronic lung disease. *Thorax* 1989;**44**:387–90.

References to studies excluded from this review

Allard 1999 *{published data only}*
Allard P, Lamontagne C, Bernard P, Tremblay C. How effective are supplementary doses of opioids for dyspnea in terminally ill cancer patients? A randomized continuous sequential clinical trial. *J Pain and Symptom Management* 1999;**17**:256–65.

Giron 1991 *{published data only}*
Giron AE, Stansbury DW, Fischer CE, Light RW. Lack of effect of dextromethorphan on breathlessness and exercise performance in

patients with chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1991;**4**(5):532–5.

Light 1989 ***{published data only}***
Light RW, Muro JR, Sato RI, Stansbury DW, Fischer CE, Brown SE. Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1989;**139**(1):126–33.

Navigante 1997 ***{published data only}***
Navigante A, Sauri A, Palazzo F, Coppola M, De CO, Kirchuk R, Espinosa L, Cabalar M. Compared and randomized prospective trial between oxygenotherapy vs morphine chlorhydrate + midazolam by subcutaneous route in patients with advanced cancer and dyspnea. *Prensa Med Argent* 1997;**84**:474–6.

Penas Bataller 1996 ***{published data only}***
Penas Bataller R, Garcia GM, Fernandez GI. Prospective analysis of the efficacy of morphine in aerosol for the treatment of dyspnea in patients with terminal phase cancer. *Neoplasia* 1996;**13**:4–6.

Peterson 1996 ***{published data only}***
Peterson GM, Young RS, Dunne PF, Galloway JG, Parks TE. Pilot study of nebulised morphine for dyspnoea in palliative care patients. *Aust J Hosp Pharm* 1996;**26**(5):545–7.

Rice 1987 ***{published data only}***
Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE. Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. *Br J Dis Chest* 1987;**81**(3):287–92.

Sackner 1984 ***{published data only}***
Sackner MA. Effects of hydrocodone bitartrate on breathing pattern of patients with chronic obstructive pulmonary disease. *Mt Sinai J Med (NY)* 1984;**51**:222–6.

Schonhofer 1998 ***{published data only}***
Schonhofer B, Kohler D. Value of orally administered retard morphine for therapy of severe pulmonary emphysema of the pink-puffer type. A pilot study [Stellenwert von oral appliziertem retardiertem morphin zur therapie des schwergradigen lungenemphysems vom pink–puffer–typ. Eine pilotstudie]. *Dtsch Med Wochenschr* 1998;**123**:1433–8.

References to studies awaiting assessment

Eaton 1999 ***{published data only}***
Eaton B, Hall J, MacDonald S. Does nebulized morphine offer symptom relief to patients with disabling dyspnea during end-stage disease?. *Can-Fam-Physician* 1999;**Feb**:45319–20.

Enck 1999 ***{published data only}***
Enck RE. The role of nebulized morphine in managing dyspnea. *American Journal of Hospice and Palliative Care* 1999;**16**(1):373–4.

Mazzocato 1999 ***{published data only}***
Mazzocato C, Buclin T, Rapin CH. The effects of morphine on dyspnea and ventilatory function in elderly patients with advanced cancer: a randomized double-blind controlled trial. *Annals of Oncology* 1999;**10**:1511–4.

Quigley 2002 ***{published data only}***
Quigley C, Joel S, Patel N, Baksh A, Slevin M. A Phase I/II study of nebulized morphine-6-glucoronide in patients with cancer-related breathlessness. *Journal of pain and symptom management* 2002;**23**(1):7–9.

Additional references

Adcock 1991
Adcock JJ. Peripheral opioid receptors and the cough reflex. *Respir Med* 1991;**85**:43–6.

Bellofiore 1990
Bellofiore S, Di Maria GU, Privitera S, Sapienza S, Milic Emili J, Mistretta A. Endogenous opioids modulate the increase in ventilatory output and dyspnoea during severe acute bronchoconstriction. *Am Rev Respir Dis* 1990;**142**:812–6.

Belvisi 1988
Belvisi MG, Chung KF, Jackson DM, Barnes PJ. Opioid modulation of non-cholinergic neural bronchoconstriction in guinea-pig in vivo. *Br J Pharmacol* 1988;**95**:413–8.

Borg 1982
Borg GAV. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;**14**:377–81.

Bostwick 1987
Bostwick DG, Null WE, Holmes D, Weber E, Barchas JD, Bensch KG. Expression of opioid peptides in tumours. *N Eng J Med* 1987; **317**:1439–43.

Cabot 1994
Cabot PJ, Dodd PR, Cramond T, Smith MT. Characterisation of non-conventional opioid binding sites in rat and human lung. *Eur J Pharmacol* 1994;**268**:247–55.

Cohen 1991
Cohen MH, Anderson AJ, Krasnow SH, Spagnolo SV, Citron ML, Payne M, Fossieck BE. Continuous intravenous infusion of morphine for severe dyspnoea. *South Med J* 1991;**84**:229–34.

Eckenhoff 1960
Eckenhoff JE, Oech SR. The effects of narcotics and antagonists upon respiration and circulation in man. *Clin Pharmacol Ther* 1960;**1**:701–8.

Fishbein 1989
Fishbein D, Kearon C, Killian KJ. An approach to dyspnoea in cancer patients. *J Pain Symptom Management* 1989;**4**:76–81.

Follman 1992
Follman D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 1992;**45**:769–73.

Guyatt 1987
Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung diseases. *Thorax* 1987;**42**:773–8.

Jadad 1996
Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials; is blinding necessary. *Controlled Clinical Trials* 1996;**17**:1–12.

Krasnow 1994
Krasnow SH, Wadleigh RG, Cohen MH, Bruera E, Fainsinger RL. Morphine for dyspnoea in patients with cancer [2]. *Ann Intern Med* 1994;**120**(8):692–3.

Mahler 1992
Mahler DA. The measurement of dyspnoea during exercise in patients with lung disease. *Chest* 1992;**101**:242–7.

McGavin 1978
McGavin CR, Artvinli M, Naoe H, McHardy GJR. Dyspnoea, disability, and distance walked: comparison of estimates of exercise performance in respiratory disease. *BMJ* 1978;**2**:241–3.

McQueen 1983
McQueen DS. Opioid interactions with respiratory and circulatory systems. *Br Med Bull* 1983;**39**:77–82.

Neudeck 1998
Neudeck BL, Smith KM. Nebulized morphine for the treatment of dyspnoea in cancer patients. *J PharmTechnol* 1998;**14**(2):53–7.

Noseda 1992
Noseda A, Schmerber J, Prigogine T, Yernault JC. Perceived effect on shortness of breath of an acute inhalation of saline or terbutaline: variability and sensitivity of a visual analogue scale in patients with asthma or COPD. *Eur Respir J* 1992;**5**:1043–53.

Noseda 1994
Noseda A, Yernault JC. Quantifying dyspnoea [[Quantifier la dyspnee]]. *La Presse Medicale* 1994;**23**:1527–33.

Reuben 1986
Reuben DB, Mor V. Dyspnoea in terminally ill cancer patients. *Chest* 1986;**89**:234–6.

Ripamonti 1998
Ripamonti C, Fulfaro F, Bruera E. Dyspnoea in patients with advanced cancer: incidence, causes and treatments. *Cancer Treatment Reviews* 1998;**24**:69–80.

Robin 1986
Robin ED, Burke CM. Single-patient randomized clinical trial. Opiates for intractable dyspnoea. *Chest* 1986;**90**:888–92.

Rogers 1989
Rogers DF, Barnes PJ. Opioid inhibition of neurally mediated mucus secretion in human bronchi. *Lancet* 1989;**1**(8644):930–2.

Santiago 1977
Santiago TV, Pugliesi AC, Edelman NH. Control of breathing during methadone addiction. *Am J Med* 1977;**62**:347–54.

Santiago 1979
Santiago TV, Johnson J, Riley DJ, Edelman NH. Effects of morphine on ventilatory response to exercise. *J Appl Physiol* 1979; **47**:112–8.

Stark 1981
Stark RD, Gambles SA, Lewis JA. Methods to assess breathlessness in healthy subjects; a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide. *Clin Sci* 1981;**61**:429–39.

Stark 1982
Stark RD, Gambles SA, Chatterjee SS. An exercise test to assess clinical dyspnoea: estimation of reproducibility and sensitivity. *Br J Dis Chest* 1982;**76**:269–78.

Stark 1983a
Stark RD, Morton PB, Sharman P, Percival PG, Lewis JA. Effects of codeine on the respiratory responses to exercise in healthy subjects. *Br J Clin Pharmacol* 1983;**15**:355–9.

Tooms 1993
Tooms A, McKenzie A, Grey H. Communication to the editor: nebulised morphine. *Lancet* 1993;**342**:1123–4.

Wanke 1993
Wanke T, Lahrmann H, Formanek D, Zwick B, Merle M, Zwick H. The effect of opioids on inspiratory muscle fatigue during inspiratory resistive loading. *Clin Physiol* 1993;**13**:349–60.

Weil 1975
Weil JV, McCullough RE, Cline JS, Sodal IE. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. *N Eng J Med* 1975;**292**:1103–6.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Beauford 1993 neb

Methods	Cross-over study Exercise study Incremental cycle ergometer Nebulised opioid
Participants	COPD 8 patients 7 men, 1 woman Mean age 60.8, sd 9.1 FEV1 0.9 sd 0.26 FVC 2.62 sd 0.83 Exclusion criteria: PaCO2>45mmHg, long-term O2, cardiac disease, narcotic abuse,other significant disease affecting exercise performance, tranquilisers, mood-altering drugs, hypnotics, or opioids in previous week, hx of alcoholism.
Interventions	Morphine 1mg neb or Morphine 4mg neb or Morphine 10mg neb or Placebo approx. 45 mins before exercise tests Tests on four separate days
Outcomes	Borg score* Workload FEV1 FVC Exercise duration* Visual vigilance Motor speed test Bond visual analogue scale VO2 VCO2 VE VT
Notes	Beta agonists given before testing Data presented at Emax only Nebulised particle size 0.93-1.42 mcm Authors report no significant effect of nebulised morphine on exercise tolerance compared with placebo QS = 3

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Bruera 1993

Methods	Cross-over study At rest study Single dose study
Participants	Cancer 10 patients In-patients On continuous O2 Normal cognitive function On regular subcutaneous morphine for pain Stable morphine dose for five days
Interventions	Morphine sc- mean dose 32mg sd 12mg - 50% higher than regular dose- vs placebo 24hour wash-out period
Outcomes	VAS for dyspnoea* O2 satn RR
Notes	VAS at 60 minutes following injection used in results Authors concluded treatment is safe and effective. QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chua 1997

Methods	Cross-over study Exercise study Incremental treadmill test (modifed Bruce protocol)
Participants	Chronic heart failure 12 male patients Mean age 65.5 se 1.5, range 58-75 LVEF 21.3% se 3% range 8-39% NYHA fuctional class 2 and 3 No chest pain or inducible ischaemia during previous exercise testing No history pulmonary disease Stable No oedema All patients on diuretics and ACE inhibitors
Interventions	Dihydrocodeine 1mg/kg vs placebo Tests took place on separate days

Chua 1997 (*Continued*)

Outcomes	Modified Borg score (dyspnoea)* Pulse Systolic BP End-tidal CO2 concn % PaO2 satn Modified Borg score (fatigue) Hypoxic chemosensitivity Hypercapnic chemosensitivity Peak O2 consumption VE-VCO2 slope Exercise duration (s)* R
Notes	Borg score analysed at 6 mins QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Davis 1994 neb

Methods	Cross-over study Exercise study 6MW Endurance cycle test Nebulised opioid
Participants	COPD 18 patients Median age 66 (42-75) Mean FEV1 0.93 sd 0.23 Mean FVC 2.53 sd 0.57 Mean paO2 9.5 sd1.08 kPa Mean paCO2 5.8 sd 1.0 kPa stable, Exclusion criteria: infective exacerbation in past 2 weeks, pulmonary hypertension, angina or arrhythmias, on opioids or variable dose of steriods.
Interventions	Morphine 12.5 mg or Morphine 6 glucouronide 4mg or Placebo Tests at least one week apart
Outcomes	6MW* Endurance cycle tests at 60% VO2 max VE VO2

Davis 1994 neb (*Continued*)

	paO2 paCO2 VAS breathlessness Borg scale
Notes	Additional information from authors Authors report no significant effect of morphine alone QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Davis 1996 neb

Methods	Cross-over study At rest study Nebulised opioid
Participants	Cancer 79 patients 34 men, 45 women Median age 60, range 20-81
Interventions	Morphine single nebulised dose, range 5-50mg or placebo Interventions made on separate days
Outcomes	VAS score for breathlessness* Modified Borg score VAS scores for nausea and drowsiness
Notes	Data analysed using first arm only (76 patients), and using both arms (66 patients). Additional information from authors Authors concluded no significant difference in response to nebulised morphine and normal saline QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Eiser 1991a

Methods	Cross-over 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 chest infection,1 itching on diamorphine, 1 constipation on diamorphine, 1 headache due to cerebral metastases)
Participants	COPD 14 patients 8 men; 6 women Mean age 65 'Severe', 'stable' disease Mean FEV1 32% predicted Mean paO2 9.0 range 7.1-10.9kPa Mean paCO2 5.1 range 3.4-6.5kPa
Interventions	Diamorphine 2.5 mg qds, or diamorphine 5mg qds or placebo
Outcomes	Daily diary cards with 10cm VAS for dyspnoea, feeling of well-being, drowsiness, number of bronchodilator puffs At end of each 2 week period: FEV1 PaO2 PaCO2 A-aPO2 (alveolar-arterial oxygen tension difference) 6MW* VAS dyspnoea for 6MW* Time on treadmill VAS dysnoea for treadmill O2 satn % O2 satn rest-exercise% End-tidal PCO2 Morphine levels
Notes	**unclear whether incremental or 'lowest speed available' Authors detected no significant effect of opioid compared with placebo Dyspnoea assessed 'at completion of each type of exercise' QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Eiser 1991b

Methods	Cross-over study Exercise study 6MW 2 drop-outs 1 pt developed chest pain between 2 test days 1 pt suffered deterioration in blood gases- unclear whether had received medication or placebo when this occurred
Participants	COPD 10 patients 6 men, 4 women Mean age 65 Similar to Eiser A
Interventions	7.5 mg diamorphine or placebo given twice, with four hour interval, 50 minutes before 6MW Tests two weeks apart
Outcomes	6MW distance* VAS for dyspnoea* FEV1 A-aPO2 VC PaO2 PaCO2 Morphine levels 20 minutes after drug
Notes	Salbutamol and ipratropium bromide by spacer given to all patients c 1 hour before exercise test VAS reported at end of 6MW Trialists report no significant effect of opioid compared with placebo QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Harris-Eze 95 neb

Methods	Cross-over study Exercise study Incremental cycle ergometer Nebulised opioid
Participants	ILD 6 patients 5 male, 1 female Mean age 49 years, sd 16 FEV1 2.54 sd 0.69

Harris-Eze 95 neb (*Continued*)

	Stable:no change in medication over 2 months No history opioid abuse No opioid drugs for 1 month
Interventions	Morphine 2.5 mg or Morphine 5mg or placebo 15 minutes before exercise test Median particle diam 3.7mcm At least three days between tests
Outcomes	Modified Borg Scale-mean value at end exercise Exercise duration* Heart rate Maximal workload ECG SaO2 O2 uptake (VO2) CO2 output (VCO2) End-tidal CO2 Minute ventilation (VI) Respiratory frequency Tidal volume
Notes	Data presented at Emax only Authors report no significant effect of nebulised morphine compared with placebo QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jankelson 1997 neb

Methods	Cross-over study Exercise study 6MW test Nebulised opioid
Participants	COPD 16 patients 11 male, 5 female Mean age 69 range 61-85 Mean FEV1 0.93 Mean FVC 2.21 Mean PaO2 9.6 kPa Mean PaCO2 5.4 kPa One patient on continuous O2

Jankelson 1997 neb (*Continued*)

Interventions	Morphine 20mg or Morphine 40mg or placebo immediately before and 1 hour before exercise test Particle mass median diameter 3mcm Tests separated by one or two days
Outcomes	Modified Borg score 6MW* SaO2 Heart rate Plasma morphine levels
Notes	Highest Borg score only reported Authors report no significant effect of opioid compared with placebo QS = 4

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Johnson 1983

Methods	Cross-over study Two consecutive one week periods followed by exercise test Incremental treadmill test 1 drop-out: developed chest infection and right heart failure on dihydrocodeine
Participants	COPD 19 patients 15 men 3 women Mean age 64.9 sd 9.1 Mean wt 66.6kg FEV1 830 sd 260 ml FVC 2080 sd 790ml PaO2 9.3 sd 0.8 kPa PaCO2 4.8 sd 0.5 kPa At least Grade 3 breathlessness (MRC scale) Stable No recent hospital admissions No sedative drugs FEV1 < or = 1.2l paCO2< or = 5.3 Continued usual bronchodilators and steroids
Interventions	Dihydrocodeine 15mg or placebo over 2 consecutive one week periods. Drug to be taken 30 minutes before exercise up to three times daily Tests at end of each week period

Johnson 1983 (*Continued*)

Outcomes	Pedometer distance for one week Daily VAS for breathlessness PEFR FEV1 FVC Incremental treadmill test: Distance walked * VAS for breathlessness at 75% distance walked on placebo day*
Notes	QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Leung 1996 neb

Methods	Cross-over study Exercise study Incremental cycle ergometer Nebulised opioid
Participants	COPD (1 pt ILD) 10 patients 6 male 4 female Mean age 62 range 51-71 Mean FEV1= 1.12
Interventions	Morphine 5mg in 5mls or placebo 15 minutes before exercise test 100% O2 inhaled during exercise test Tests on separate days
Outcomes	Modified Borg score* Maximum power output* VE max Heart rate
Notes	Additional data from authors Authors reported no significant effect of opioid compared with placebo QS = 4

Risk of bias

Item	Authors' judgement	Description

Leung 1996 neb (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Light 1996

Methods	Cross-over study Exercise study Incremental cycle ergometer
Participants	COPD 7 male patients Age 66.4 sd 3.25 FEV1 0.99 sd 0.3 FEV1/FVC 0.35 sd .07 Exercise limited by breathlessness Stable disease Exclusion criteria: PaCO2 >45 mmHg, FEV1>1.39l, long-term O2, cardiac disease, history of narcotic abuse, other sigificant disease affecting exercise performance, use of tranquilisers, hypnotics, mood altering drugs or opioids in week prior to study, alcoholism in past 5 years
Interventions	Morphine 30mg or placebo once po 60 minutes before exercise test Tests on separate days
Outcomes	Modified Borg score each minute of exercise* Workload Exercise duration* VO2 VCO2 VE PETO2 PETCO2 R Heart rate SaO2
Notes	Beta agonist given before assessment QS = 4

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Masood 1995 neb

Methods	Cross-over study Exercise study Incremental cycle ergometer Nebulised and iv opioid
Participants	COPD 12 men ADLs limited by breathlessness FEV1<1.51 Stable Exclusion criteria: exacerbations needing antibiotics, change in oral steroid dose or hospital admission within two months, overt cardiac disease, contra-indication to exercise testing, pCO2 >7.0, use of opioids, benzodiazepines or other sedative agent within one month.
Interventions	Morphine 10mg neb or morphine 25 mg neb or morphine 1mg iv or morphine 2.5 mg iv or placebo neb or placebo iv 15 minutes before exercise tests Each test separated by at least 48 hours Median particle diam 3.1-4.9 mcm
Outcomes	Heart rate Respiratory rate VO2 RER SaO2 VAS for breathlessness Exercise duration Plasma morphine levels Ventilation
Notes	Nebulised Beta 2 agonist given before exercise tests Only changes in exercise duration and breathlessness at peak exercise reported Authors conclude no significant effect of opioid compared with placebo on exercise tolerance or breathlessness QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Noseda 1997 neb

Methods	Cross-over study At rest study Nebulised opioid 3 drop outs :3 patients died over the study period, during the night: the authors did not consider their deaths to be related to the treatment
Participants	12 COPD, 3 malignant disease, 1 heart failure, 1 idiopathic pulmonary fibrosis All hospital in-patients Mean age 69 sd 11 Distressing dyspnoea not relieved by conventional medical therapy Mean FEV1 0.92 sd 0.18 Normal cognitive function
Interventions	Morphine 10mg + O2 or morphine 20mg + O2, or morphine 10mg or placebo + O2 O2 at 2l/min Tests took place over consecutive days
Outcomes	VAS for breathlessness* SaO2% RR
Notes	Results using morphine alone not analysed Authors report no benefit of morphine compared with placebo QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Poole 1998

Methods	Cross-over study 2 six week treatment periods followed by exercise tests 2 week wash-out period 6MW test 2 drop-outs
Participants	COPD 16 patients 11 men, 5 women mean age 70.7, se 1.6 FEV1 0.6,se0.4 mean pO2 9.8 mean pCO2 5.3 Exclusion criteria: CCF, paCO2>5.4, FEV1>1.49, alcoholism, psychiatric disorder, on opiates, change in drugs in past month or hospitalised in past 2 months

Poole 1998 (*Continued*)

Interventions	MST 10-20mg od-bd or placebo Average dose 25 mg over 24 hours Tests at end of treatment periods
Outcomes	Chronic Respiratory Disease Questionnaire 6MW* SaO2 Spirometry Breathlessness scores on Likert scale before and at the end of six minute' walk* Side effects
Notes	Authors concluded no significant improvement after opioid QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Woodcock 1981

Methods	Cross-over study Exercise study Incremental treadmill test
Participants	COPD 12 patients 10 men, 2 women Mean age 62 'Stable' No recent hospital admissions At least Grade 3 breathlessness (MRC scale) Normal or low pCO2 FEV1 0.73 sd 0.31 paO2 72.6 sd 6.86 paCO2 35.3 sd 2.4 No 'other serious conditions' All ex-smokers-stopped at least 6 months before study Weight mean 59.1kg (7.8)
Interventions	Dihydrocodeine 1mg/kg given once, po, 45 minutes before treadmill test (incremental speed to exhaustion) or alcohol or caffeine Placebo Tests on consecutive days

Woodcock 1981 (*Continued*)

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 O2 consumption FVC FEV1
Notes	Salbutamol 200mcg, inh, 30 minutes before study QS = 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Woodcock 1982

Methods	Cross-over study 3 consecutive two week periods followed by exercise tests 6MW test 5 drop-outs due to nausea and vomiting on dihydrocodeine
Participants	COPD 16 patients FEV1 0.75 sd 0.27 FVC 2.76 sd1.03 paO2 71.0 sd 4 mmHg paCO2 33.5 sd 3.2 mmHg At least Grade 3 breathlessness (MRC scale)
Interventions	Dihydrocodeine 30mg tds,or 60mg tds, or placebo, for 2 weeks Tests carried out at the end of each treatment period
Outcomes	FEV1 FVC paO2 paCO2 Ventilation at rest Ventilation during exercise O2 consumption O2 cost diagram* 6MW distance*
Notes	Abstract only O2 cost diagram reported at end of study period QS = 3

Woodcock 1982 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Young 1989 neb

Methods	Cross-over study Exercise study Cycle endurance test Nebulised opioid
Participants	COPD(9) or idiopathic pulmonary fibrosis (2) Mean age 58.4 (39-74) Exercise tolerance limited by dyspnoea FEV1 0.4-1.41 VC 1.1-4.01
Interventions	Morphine 5mg or placebo neb 15 mins before exercise test Tests on separate days 100% O2 inhaled during exercise test Median particle size 2.3mcm
Outcomes	Cycle ergometer exercise test at 80% of pre-determined Emax: endurance time ventilation during last minute of exercise FEV1 FVC
Notes	Dyspnoea not used as outcome measure, although patients selected because exercise was limited by dyspnoea. 18 patients initially studied and 7 excluded on run-in day because exercise limited by other factors: excluded from authors' and from this analysis Mean endurance time increased by 64 seconds: one patient had increase of 400 seconds. If that patient excluded, mean increase would have been c 25 seconds and not statistically significant. Concludes that morphine had significant effect on exercise endurance time vs placebo QS = 4

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Emax - Maximal exercise
ILD - Interstitial lung disease

6MW - 6 minute walk
VAS - Visual analogue score
A-aPO2 - Alveolar-arterial oxygen tension difference
BP - Blood pressure
LVEF - Left ventricular ejection fraction
NYHA - New York Heart Association
Pt - patient
RR - Respiratory rate
R - Respiratory exchange ratio
SC - Subcutaneously
SD - Standard deviation
SE - Standard error
s - seconds
Satn - Saturation
*Analysed in review
COPD - Chronic obstructive pulmonary disease
MRC - Medical Research Council

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

Study	Reason for exclusion
Allard 1999	Double-blind, randomised study comparing two doses of opioid in terminal cancer patients. Not placebo controlled.
Giron 1991	Cross-over, placebo-controlled study of dextromorphan on exercise performance of COPD patients. Single-blind study. Not randomised. ? dextromorphan classified as opioid.
Light 1989	Randomised, cross-over, placebo-controlled study of oral morphine on exercise tolerance of COPD patients. Inadequate blinding. Patients had arterial line inserted on day they received morphine . Patients not allowed to drive home on day they received morphine. Patients in two groups not treated the same.
Navigante 1997	Prospective, randomised study comparing oxygen treatment with subcutaneous morphine and midazolam in patients with advanced cancer. Not blinded. Not placebo-controlled.
Penas Bataller 1996	Prospective cross-over study of nebulised morphine in advanced cancer patients. Not randomised. Not blinded.
Peterson 1996	Cross-over study of nebulised morphine in palliative care patients. Not randomised. Not blinded. Not placebo-controlled.

(*Continued*)

Rice 1987	Double-blind, randomised, cross-over study of codeine 30 mg qds compared with promethazine 25 mg qds during one month period in COPD patients. Not placebo-controlled.
Sackner 1984	Study of oral hydrocodone in COPD patients. Open, uncontrolled study.
Schonhofer 1998	Study of slow release oral morphine in COPD patients. Not randomised. Not blinded. Not placebo-controlled.

DATA AND ANALYSES

Comparison 1. Opioids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breathlessness			Other data	No numeric data
2 Exercise tolerance			Other data	No numeric data

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

Breathlessness

Study	Sample size	Outcome measure	Mean on opioid	Mean on placebo	Pooled SD	Mean difference (MD)	Crude/ Correct SE(MD)	Correlation	Corr. derived from	SMD (95% c.i.)
Bruera 1993	10	Change from baseline	-14	4	23.5	-18	10.5 / 10.5	0	asumption	-0.77 (-1.65, 0.11)
Chua 1997	12	Post treatment	2.91	3.6	0.82	-0.69	0.33 / 0.18	0.71	paired t-test	-0.85 (-1.28, -0.42)
Davis 1996 neb	70	Change from baseline	-9.58	-7.66	20.89	-1.91	3.53 / 3.3	0.13	data	-0.09 (-0.41, 0.22)
Eiser 1991a	10	Post treatment	7.0	6.5	2.3	0.5	1.03 / 0.58	0.68	imputed (Davis 1996)	0.22 (-0.27, 0.71
Eiser 1991b	8	Post treatment	6.2	6.1	1.98	0.1	0.99 / 0.71	0.49	data	0.05 (-0.66, 0.76)
Johnson 1983	18	Post treatment	6.7	7.6	2.11	-0.9	0.7 / 0.23	0.91	paired t-test and data	-0.43 (-0.62, -0.23)
Leung 1996 neb	10	Change from baseline	-0.72	-0.45	1.05	-0.28	0.47 / 0.53	-0.29	data	-0.26 (-1.26, 0.74)
Light 1996	7	Change from baseline	-0.14	0.14	0.49	-0.28	0.26 / 0.26	0	assumption	-0.57 (-0.61. 0.47)

Breathlessness (*Continued*)

Noseda 1997 neb	14	Post treatment	37.2	40.3	27.1	-3.1	10.3 / 4.07	0.84	data	-0.11 (-0.40, 0.18)
Poole 1998	14	Change from baseline	-2.5	-0.44	4.38	-2.06	1.66 / 1.35	0.38	paired t-test	-0.47 (-1.06, 0.12)
Woodcock 1981	12	Change from baseline	-1.39	-0.16	1.61	-1.23	0.66 / 0.66	0	assumption	-0.77 (-1.57, 0.03)
Woodcock 1982	11	Post treatment	-45.1	-42.5	9.25	-2.6	3.95 / 2.23	0.68	imputed (Davis 1996)	-0.28 (-0.75, 0.19)

Analysis 1.2. Comparison 1 Opioids versus placebo, Outcome 2 Exercise tolerance.

Exercise tolerance

Study	**Sample size**	**Outcome measure**	**Mean on opioid**	**Mean on placebo**	**Pooled SD**	**Mean difference (MD)**	**Crude/ Correct SE(MD)**	**Correlation**	**Corr. derived from**	**SMD (95% c.i.)**
Beauford 1993 neb	8	Change from baseline	0	-0.1	0.58	0.1	0.29 / 0.29	0	assumption	0.17 (-0.81, 1.15)
Chua 1997	12	Post treatment	512	455	93.5	57	38.2 / 12.9	0.89	paired t-test	0.61 (0.34, 0.88)
Eiser 1991a	10	Post treatment	223.5	216	118.1	7.5	52.8 / 22.5	0.82	imputed (Woodcock 1981)	0.06 (-0.31, 0.44)
Eiser 1991b	8	Post treatment	272	263	141.4	9	70.7 / 14.5	0.96	data	0.06 (-0.14, 0.26)
Harris-Eze 95 neb	5	Post treatment	425	437	36.9	-12	21.3 / 9.1	0.82	imputed (Woodcock 1981)	-0.32 (-0.81, 0.16)

Exercise tolerance (*Continued*)

Johnson 1983	18	Post treatment	249	213	133.1	36	44.4 / 15.4	0.88	paired t-test	0.27 (0.05. 0.49)
Leung 1996 neb	10	Change from baseline	2	7	11	-5	4.9 / 5.2	-0.13	data	-0.45 (-1.39, 0.48)
Light 1996	7	Change from baseline	0.2	0.07	0.65	0.13	0.35 / 0.35	0	assumption	0.20 (-0.85, 1.25)
Poole 1998	14	Change from baseline	-35.1	21.6	66.6	-56.7	25.2 / 24.9	0.02	paired t-test	-0.85 (-1.58, -0.12)
Woodcock 1981	12	Change from baseline	53	4	39.2	49	16.0 / 16.0	0	assumption	1.25 (0.45, 2.05)
Woodcock 1982	11	Post treatment	387	368	103.2	19	44.0 / 18.7	0.82	imputed (Woodcock 1981)	0.18 (-0.17, 0.54)

WHAT'S NEW

Last assessed as up-to-date: 25 April 2001.

Date	Event	Description
8 February 2011	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2000

Review first published: Issue 4, 2001

Date	Event	Description
9 November 2009	Amended	Contact details updated.
12 November 2008	Amended	Contact details updated
16 July 2008	Amended	Converted to new review format.

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Data entry to Revman: ALJ and JPTH

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DECLARATIONS OF INTEREST

None known.

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External sources

- No sources of support supplied

INDEX TERMS

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*Palliative Care; *Terminally Ill; Apnea [*drug therapy; etiology]; Narcotics [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans