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[Intervention Review]

Nebulised morphine for severe interstitial lung disease

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ABSTRACT

Background

The evidence to support the use of nebulized morphine to improve dyspnoea and exercise limitation in terminally ill patients with chronic lung disease is conflicting.

Objectives

To assess the effectiveness of nebulized morphine in reducing dyspnoea in patients with end-stage interstitial lung disease (ILD).

Search methods

We identified trials by searching the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. Searches are current to May 2011.

Selection criteria

Any RCT and adequate quality CCT in adult participants with ILD that compared nebulized morphine with a control group.

Data collection and analysis

Only one small RCT was identified. Data were extracted and described narratively.

Main results

Compared to placebo (normal saline), administration of low-dose nebulized morphine (2.5 and 5.0 mg) to six patients with ILD did not improve maximal exercise performance, and did not reduce dyspnoea during exercise. An update search identified an additional excluded study .

Authors' conclusions

The hypothesis that nebulized morphine may reduce dyspnoea in patients with interstitial lung disease has not been confirmed in the single small RCT identified.

PLAIN LANGUAGE SUMMARY

Nebulised morphine for severe interstitial lung disease

Nebulized morphine has been reported to have some beneficial effect on breathlessness and exercise limitation in terminally ill patients with chronic lung disease. Patients with end-stage interstitial lung disease might also benefit from treatment of breathlessness with

nebulized morphine. This review evaluates the effectiveness of using nebulized morphine for breathlessness reduction in patients with interstitial lung disease. Only one small randomised controlled trial was identified. This study concluded that low-dose nebulized morphine is of no benefit in the management of exercise-induced dyspnoea and exercise limitations in patients with interstitial lung disease. However, the patients included in this study were relatively mild, and definitive conclusions on the effect of nebulized morphine in the reduction of dyspnoea in end-stage interstitial lung disease requires further work.

BACKGROUND

Dyspnoea, exercise limitation, and cough are common and distressing symptoms in terminally ill patients with chronic lung disease. These symptoms result from multiple causes, are difficult to treat and are a significant precipitating factor for late-stage hospital or hospice admissions. Nebulized morphine has been reported by some to improve dyspnoea and exercise limitation (Young 1989), while others have found no significant effect (Masood 1995). The mechanism by which opioids might produce this effect is not clear (Zebraski 2000). While obstructive disease can sometimes be associated with an increase in arterial carbon dioxide, due to hypoventilation thus making use of morphine undesirable, this is seldom the case in restrictive disease. It follows that patients with end-stage interstitial lung disease could be prime candidates for treatment of dyspnoea with nebulized morphine. There are also beneficial side effects to this treatment, as patients might also experience a reduction in cough (Loos 1973) and the treatment may have some immune modulating effects (Coussons-Read 1999).

The aim of this review is to evaluate the effectiveness of using nebulized morphine for dyspnoea reduction in patients with interstitial lung disease (ILD).

OBJECTIVES

To determine the efficacy for using nebulized morphine in patients with dyspnoea due to ILD.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised double blind or single blind, placebo controlled, either parallel group or cross over studies will be selected for inclusion in this review. In the case of cross-over trials only the first treatment period will be included in the meta-analysis. Included studies will have data on at least one of the outcome variables.

Types of participants

Adult subjects with a diagnosis of interstitial lung disease who require medical treatment. The diagnosis should be based on clinical symptoms, imaging techniques (high resolution CT scanning) and ideally histology of lung specimens. Studies which included participants with severe, current other diseases, including cardiac, liver and renal disease were excluded.

Types of interventions

Inhalation of nebulized morphine

Types of outcome measures

1. Dyspnoea scores
2. Health status (health related quality of life scores)
3. Exercise capacity
4. Lung function - including fixed expiratory volume in one second (FEV1), vital capacity (VC), TLC, DLCO
5. Cough counts/scores
6. Blood-gas values
7. Adverse and haematologic effects
8. Mortality data

Search methods for identification of studies

Trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE. All databases have been searched from their inception up to May 2011. The search strategies are described in Appendix 1, Appendix 2 and Appendix 3.

In addition, we hand searched abstracts from meetings of the American and British Thoracic Societies, and the European Respiratory Society. We checked bibliographies to identify relevant cross-references. We also contacted drug companies for relevant trial data.

Data collection and analysis

Selection of studies

We reviewed all potential citations to identify relevant studies. Two reviewers independently assessed full text versions of the studies to determine if they met the inclusion criteria; any disagreement was resolved by discussion. We assessed studies that met the entry criteria for study quality.

Data extraction and management

Data for trials were extracted independently by two reviewers and entered into the Cochrane Collaboration software program (Review Manager). Standard errors were converted to standard deviations. We contacted authors and drug companies in an attempt to obtain missing and raw data.

Assessment of risk of bias in included studies

Trial quality were assessed using the Cochrane approach to concealment of allocation and Jadad 1996.

Data synthesis

If there had been sufficient data we would have carried out the following comparisons in statistical analysis:

1. Nebulised morphine versus placebo
2. Nebulised morphine versus systemic morphine
3. Nebulised morphine versus other interventions for dyspnoea reduction

We would have expressed results of the analyses for continuous outcomes as a weighted mean difference (WMD) together with 95% confidence interval (CI) or, as a standardised mean difference (SMD) for related outcomes that cannot be aggregated into a common unit of measure. For dichotomous outcomes, we would have used the odds ratio (OR).

If significant heterogeneity was found, we would have conducted sensitivity analyses using study quality as a categorising variable. If the heterogeneity was not explained in terms of study quality the following subgroup analyses would be conducted:

1. Type of interstitial lung disease
2. Severity of ILD at baseline
3. Dosage of morphine
4. Duration of study

RESULTS

Description of studies

Results of the search

We identified 43 citations from the original searches conducted on CENTRAL, MEDLINE and EMBASE. After careful scrutiny, 36 articles were excluded because they were irrelevant (case reports, reviews, work on oral or IV morphine, basic science studies, surgical investigations, studies on irrelevant drugs and on morphine toxicity). We only identified seven potentially relevant articles. An additional search conducted in May 2009 did not identify any additional studies, while the search in May 2011 identified nine references, none of which were eligible for inclusion.

Included studies

Only one study was identified which met the inclusion criteria for this review (Harris-Eze 1995). Six patients with a mild to moderate form of ILD were included in this randomised double-blind crossover, placebo controlled study. Three participants had IPF, two had scleroderma, one had sarcoidosis. A histologically proven diagnosis was obtained for three of the participants. The participants were clinically stable (no change in medication for at least two months) and without other major causes of dyspnoea such as obstructive airways disease, malignancy, congestive cardiac failure, recent pulmonary embolism, neuromuscular or rheumatologic diseases. Although it was unclear if the included participants were hypoxaemic at rest, significant arterial oxygen desaturation after exertion was reported (SaO2 desaturation of 12 ± 6%). Forced vital capacity (FVC), FEV1, and DLCO were approximately 70%, 74%, and 51% predicted respectively. The study compared on three different occasion the effect of 2.5 and 5.0 mg nebulized morphine to a control (normal saline) administered 30 min before maximal incremental cycle ergometer tests. The outcome variables were exercise duration, maximal workload, resting, submaximal, or end-exercise measurements of oxygen uptake (VO2), carbon dioxide output (VCO2), end-tidal CO2 (PETCO2), oxygen saturation (SaO2), minute ventilation (VI), respiratory frequency (f), tidal volume (VT), heart rate (HR), and sense of dyspnoea at the end of exercise. Evaluation of cough was not addressed in this study.

Excluded studies

We excluded a further six mainly on the basis of subject selection. The most recent study (Noseda 1997) was primarily carried out in participants with COPD and lung cancer with the exception of one participant with ILD (her individual data showed that nebulized morphine had no effect). Two other papers (Young 1989; Leung 1996) had similar limitations; the majority of participants investigated had COPD with the exception of one ILD participants in Leung 1996 and two participants with ILD in Young 1989 (their individual data showed that nebulized morphine had little or no effect). Allen 2005 was a before and after study assessing breathlessness in people with ILD.

Risk of bias in included studies

In the one study identified (Harris-Eze 1995), the method of randomisation was not stated. The method of blinding was described and seems adequate. The sample size was extremely small (six patients). Although significant dyspnoea was not present at rest, participant selection seems adequate.

Effects of interventions

In the only study identified (Harris-Eze 1995), no significant differences were noted in exercise duration, maximal workload, or sense of dyspnoea at the end of exercise in the control test and the tests with either morphine 2.5 mg or morphine 5.0 mg. There were no significant differences noted in resting, submaximal, or end-exercise measurements of oxygen uptake (VO2), carbon dioxide output (VCO2), end-tidal CO2 (PETCO2), oxygen saturation (SaO2), minute ventilation (VI), respiratory frequency (f), tidal volume (VT), or heart rate (HR) in the three tests. Low-dose nebulized morphine did not alter the participants' breathing pattern or affect the relationship between dyspnoea and ventilation during exercise. No significant side effects were noted.

DISCUSSION

There has been only one randomised study evaluating the effectiveness of using nebulized morphine for dyspnoea reduction in participants with interstitial lung disease (Harris-Eze 1995) and this only looked at exercise induced and not resting dyspnoea. Although anecdotal evidence indicates that nebulized morphine reduces cough in patients with advanced lung disease (Quelch 1997), this was not addressed in the present study.

The results of this study show that compared with placebo, administration of low-dose nebulized morphine to six patients with ILD did not improve maximal exercise performance, and did not reduce dyspnoea during exercise. The main problems with this study are:

1. Small sample size (only six patients were included). This is a problem considering the wide variability of some of the end-points measured, such as the Borg scores for dyspnoea.
2. It appears that significant dyspnoea was not present at rest in the participants studied.
3. The participants included were mildly affected and NOT end-stage, where palliative measures would be needed.

On the basis of the non-randomised evidence available, nebulized morphine did appear to reduce disabling dyspnoea in patients with advanced lung disease (Allen 2005). Thus, it is possible that the lack of effect of nebulized morphine in the study by Harris-Eze 1995 could be due to a low degree of dyspnoea, which may not be sensitive enough to nebulized morphine. In COPD, nebulized morphine fails to attenuate dyspnoea during exercise (Masood 1995) whereas a study in COPD patients with disabling dyspnoea concluded that nebulized morphine significantly attenuates symptoms (Young 1989).

Reduction of important dyspnoea by nebulized morphine in patients with interstitial lung disease remains to be evaluated.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, one cannot conclude that nebulized morphine is effective in reducing dyspnoea in end-stage interstitial lung disease.

Implications for research

More trials of reasonable quality are required. These studies should assess breathlessness on validated scales, they should be conducted in people with end-stage disease and should recruit large numbers of participants.

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Harris-Eze 1995 *{published data only}*

Harris-Eze AO, Sridhar G, Clemens RE, Zintel TA, Gallagher CG, Marciniuk DD. Low-dose nebulized morphine does not improve exercise in interstitial lung disease. *American Journal of Respiratory & Critical Care Medicine* 1995;**152**(6):1940-5.

References to studies excluded from this review

Allen 2005 *{published data only}*

Allen S, Raut S, Woollard J, Vassallo M. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. *Palliative Medicine* 2005;**19**(2):128-30.

Baydur 2004 *{published data only}*

Baydur A. Nebulized morphine: a convenient and safe alternative to dyspnea relief?. *Chest* 2004;**125**(2):363-5.

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?. *Canadian Family Physician* 1999;**45**:319-20.

Farncombe 1993 *{published data only}*

Farcombe M, Chater S. Case studies outlining use of nebulized morphine for patients with end-stage chronic lung and cardiac disease. *Journal of Pain and Symptom Management* 1993;**8**(4):221-5.

Leung 1996 *{published data only}*

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.

Quelch 1997 *{published data only}*

Quelch PC, Faulkner DE, Yun JW. Nebulized opioids in the treatment of dyspnea. *Journal of Palliative Care* 1997;**13**(3):48-52.

Salzman 1997 *{published data only}*

Salzman GA. Evaluation of dyspnea. *Hospital Practice* 1997;**32**(3):195-206.

Young 1989 *{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**(5):387-90.

Additional references

Coussons-Read 1999

Coussons-Read ME, Daniels M, Gilmour MI. Morphine reduces pulmonary inflammation in response to influenza infection. *Life Sciences* 1999;**65**(11):1141-52.

Jadad 1996

Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomised controlled trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

Loos 1973

Loos M. Antitussive therapy of chronic unspecific bronchial and lung diseases. Double blind study [Antitussive Therapie chronisch-unspezifischer bronchial- und Lungenkrankheiten. Doppelblindstudie]. *Arzneimittelforschung* 1973;**23**(Suppl 2a):331-6.

Masood 1995

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

Noseda A, Carpiaux JP, Markstein C, Meyvaert A, de Maertelaer V. Disabling dyspnoea in patients with advanced disease: lack of effect of nebulized morphine. *European Respiratory Journal* 1997;**10**(5):1079-83.

Zebraski 2000

Zebraski SE, Kochenash SM, Raffa RB. Lung opioid receptors: pharmacology and possible target for nebulized morphine in dyspnea. *Life Sciences* 2000;**66**(23):2221-31.

CHARACTERISTICS OF STUDIES

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

Harris-Eze 1995

Methods	Single centre randomised double-blind placebo controlled trial.
Participants	Six participants were included in the study (Mean age was 49 +/- 16, 5 males) with a baseline FEV1 of 74% predicted, DLCO 79+/-8% predicted and 12+/-6% O2 saturation. Inclusion criteria were: confirmed diagnosis of ILD, clinical stability (no change in medication over the last two months), absence of obstructive airways, cardiac, neuromuscular, or rheumatologic disease, activity limited by dyspnea, no history of opioid abuse/opioid based medication. Exclusion criteria: Participants with evidence of pul-

Harris-Eze 1995 *(Continued)*

	monary restriction secondary to diseases of pleura/chest wall, those who had weaknesses of respiratory muscles or diseases other than ILD that could impair exercise tolerance.
Interventions	Nebulised Morphine 0.5mg, 2.5mg or placebo prior to exercise challenge
Outcomes	FEV1, HR (L/min), VCO2 (L/min), VO2 (L/min), V1 (L/min), Wmax, Borg Dyspnea score, f (L/min), VT (L)
Notes	Jadad score: 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

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

Study	Reason for exclusion
Allen 2005	Before and after study.
Baydur 2004	Review article.
Eaton 1999	Critical appraisal of Noseda 1997.
Farncombe 1993	Case series.
Leung 1996	Randomised study recruiting participants with COPD.
Quelch 1997	Case series.
Salzman 1997	Review article.
Young 1989	Randomised study recruiting participants with COPD or idiopathic pulmonary fibrosis.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Lung Diseases, Interstitial explode all trees in MeSH products
#2 (interstitial near lung* near disease*) in All Fields in all products
#3 alveolitis in All Fields in all products
#4 ((interstitial near lung*) or fibros* or pneumonitis or pneumonia or pneumopathy) in All Fields in all products
#5 (pneumonia or pneumonitis or pneumopathy) in All Fields in all products
#6 (lung* near purpura) in All Fields in all products
#7 (goodpasture* near syndrome*) in All Fields in all products
#8 granulomatosis in All Fields in all products
#9 bagassosis in All Fields in all products
#10 (berylliosis or beryllium) in All Fields in all products
#11 hemosiderosis in All Fields in all products
#12 (hamman-rich next syndrome*) in All Fields in all products
#13 (pulmonary near fibrosis) in All Fields in all products

#14 (pulmonary near fibroses) in All Fields in all products
#15 histiocytosis in All Fields in all products
#16 (pneumoconiosis or pneumokoniosis or pneumonoconiosis or pneumonokoniosis) in All Fields in all products
#17 (pulmonary near sarcoidosis) in All Fields in all products
#18 (wegener* near granuloma*) in All Fields in all products
#19 (bird* or pigeon* or farmer*) near (lung* or disease*) in All Fields in all products
#20 (asbestosis or byssinosis or siderosis or silicosis or anthracosis or anthracosilicosis or silicotuberculosis) in All Fields in all products
#21 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 MeSH descriptor Morphine explode all trees in MeSH products
#23 (morphine or dihydroxy or morphinene or duromorph or epimorph or miro or morfin or morfine or morphia or morphin or morphinium or morphium or skenan) in All Fields in all products
#24 morphine or duramorph or "ms contin" or morphia or oramorph or "sdz 202-250" or sdz202-250 in All Fields in all products
#25 (morphinans or ardinex or codeine or isocodeine or n-methylmorphine or dihydrocodeinone or hydrocodeinonebitartrate or hydrocon or hydrocodon or hydrocodone or dihydrohydroxycodeinone) in All Fields in all products
#26 (oxiconum or oxycodeinon or dihydrone or dinarkon or eucodal or hydroxycodeinon or "oxycodone hydrochloride" or oxycone or pancodine or percocet or theocodin or diacetylmorphine or diamorphine or diacetylmorphine or heroin or dihydromorphine or paramorphan or paramorfan or ethomorphine or dionine or ethylmorphine) in All Fields in all products
#27 (dihydromorphinone or hydromorphon or laudacon or dilaudid or hydromorphone or methylnaloxone or n-methylnaloxone or naloxone or numorphan or oxymorphone or thebaine) in All Fields in all products
#28 (#22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29 (#21 AND #28)

Appendix 2. MEDLINE search strategy

1. exp MORPHINE/
2. (morphine or duramorph or ms contin or morphia or oramorph or sdz 202-250 or sdz202-250).mp.
3. (Morphinans or ardinex or codeine or isocodeine or n-methylmorphine or dihydrocodeinone or hydrocodeinonebitartrate or hydrocon or hydrocodon or hydrocodone or dihydrohydroxycodeinone).mp.
4. (Oxiconum or oxycodeinon or dihydrone or dinarkon or eucodal or hydroxycodeinon or oxycodone hydrochloride or oxycone or pancodine or percocet or theocodin or diacetylmorphine or diamorphine or diacetylmorphine or heroin or Dihydromorphine or paramorphan or paramorfan or ethomorphine or dionine or ethylmorphine).mp.
5. (dihydromorphinone or hydromorphon or laudacon or dilaudid or hydromorphone or methylnaloxone or n-methylnaloxone or naloxone or Numorphan or oxymorphone or Thebaine).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Lung Diseases, Interstitial/
8. alveolitis.mp.
9. (interstitial adj3 lung$ adj3 disease$).mp.
10. (interstitial adj3 (pneumonia or pneumonitis)).mp.
11. (lung adj3 purpura).mp.
12. (goodpasture$ adj3 syndrome$).mp.
13. granulomatosis.mp.
14. bagassosis.mp.
15. (beryllium adj3 disease).mp.
16. hemosiderosis.mp.
17. hamman-rich syndrome.mp.
18. (pulmonary adj3 (fibrosis or fibroses)).mp.
19. histiocytosis langerhans-cell.mp.
20. pneumoconiosis.mp.
21. (asbestosis or berylliosis or byssinosis or siderosis or silicosis or anthracosis or anthracosilicosis or silicotuberculosis).mp.
22. (pulmonary adj3 sarcoidosis).mp.
23. (wegener$ adj3 granuloma$).mp.
24. ((bird$ or pigeon$ or hen$ or farmer$) adj3 (lung$ or disease$)).mp.
25. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 6 and 25

Appendix 3. EMBASE search strategy

1. exp Lung Diseases, Interstitial/
2. alveolitis.mp.
3. (interstitial adj3 lung$ adj3 disease$).mp.
4. (interstitial adj3 (pneumonia or pneumonitis)).mp.
5. (lung adj3 purpura).mp.
6. (goodpasture$ adj3 syndrome$).mp.

7. granulomatosis.mp.
8. bagassosis.mp.
9. (beryllium adj3 disease).mp.
10. hemosiderosis.mp.
11. hamman-rich syndrome.mp.
12. (pulmonary adj3 (fibrosis or fibroses)).mp.
13. histiocytosis langerhans-cell.mp.
14. pneumoconiosis.mp.
15. (asbestosis or berylliosis or byssinosis or siderosis or silicosis or anthracosis or anthracosilicosis or silicotuberculosis).mp.
16. (pulmonary adj3 sarcoidosis).mp.
17. (wegener$ adj3 granuloma$).mp.
18. ((bird$ or pigeon$ or hen$ or farmer$) adj3 (lung$ or disease$)).mp.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp MORPHINE/
21. (Morphine or Dihydroxy or Morphinene or Duromorph or Epimorph or Miro or Morfin or Morfine or Morphia or Morphin or Morphinium or Morphium or Skenan).mp.
22. (morphine or duramorph or ms contin or morphia or oramorph or sdz 202-250 or sdz202-250).mp.
23. (Morphinans or ardinex or codeine or isocodeine or n-methylmorphine or dihydrocodeinone or hydrocodeinonebitartrate or hydrocon or hydrocodon or hydrocodone or dihydrohydroxycodeinone).mp.
24. (Oxiconum or oxycodeinon or dihydrone or dinarkon or eucodal or hydroxycodeinon or oxycodone hydrochloride or oxycone or pancodine or percocet or theocodin or diacetylmorphine or diamorphine or diacetylmorphine or heroin or Dihydromorphine or paramorphan or paramorfan or ethomorphine or dionine or ethylmorphine).mp.
25. (dihydromorphinone or hydromorphon or laudacon or dilaudid or hydromorphone or methylnaloxone or n-methylnaloxone or naloxone or Numorphan or oxymorphone or Thebaine).mp.
26. 20 or 21 or 22 or 23 or 24 or 25
27. 19 and 26

WHAT'S NEW

Date	Event	Description
5 May 2011	New search has been performed	Literatur search run, no new eligible studies identified.

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 3, 2002

Date	Event	Description
15 May 2009	New search has been performed	Literature search re-run; no new studies found.
11 August 2008	Amended	Converted to new review format.
1 May 2008	New search has been performed	Update searches ran, no new studies identified.
15 April 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AS initially developed the protocol. RP and AS examined the search results and assumed primary authorship. RP developed the results and discussion sections. EHW offered editorial support and guidance throughout the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development Programme, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [*administration & dosage]; Chronic Disease; Dyspnea [*drug therapy] [etiology]; Exercise Tolerance [drug effects]; Lung Diseases, Interstitial [complications] [*drug therapy]; Morphine [*administration & dosage]; Nebulizers and Vaporizers

MeSH check words

Humans