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ABSTRACT

Background

Breathlessness is one of the most common symptoms experienced in the advanced stages of malignant and non-malignant disease. Benzodiazepines are widely used for the relief of breathlessness in advanced diseases and are regularly recommended in the literature. However, the evidence for their use for this symptom is unclear.

Objectives

To determine the efficacy of benzodiazepines for the relief of breathlessness in patients with advanced disease.

Search strategy

We searched 14 electronic databases up to September 2009. We checked the reference lists of all relevant studies, key textbooks, reviews, and websites. We contacted investigators and specialists in palliative care for unpublished data.

Selection criteria

We included randomised controlled trials (RCTs) and controlled clinical trials (CCTs) assessing the effect of benzodiazepines in relieving breathlessness in patients with advanced stages of cancer, chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF), motor neurone disease (MND), and idiopathic pulmonary fibrosis (IPF).

Data collection and analysis

Two review authors independently assessed identified titles and abstracts. Three independent review authors performed assessment of all potentially relevant studies (full text), data extraction, and assessment of methodological quality. We carried out meta-analysis where appropriate.

Main results

Seven studies were identified, including 200 analysed participants with advanced cancer and COPD. Analysis of all seven studies (including a meta-analysis of six out of seven studies) did not show a beneficial effect of benzodiazepines for the relief of breathlessness in patients with advanced cancer and COPD. Furthermore, no significant effect could be observed in the prevention of breakthrough dyspnoea in cancer patients. Sensitivity analysis demonstrated no significant differences regarding type of benzodiazepine, dose, route and frequency of delivery, duration of treatment, or type of control.
Authors’ conclusions

There is no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness in patients with advanced cancer and COPD. There is a slight but non-significant trend towards a beneficial effect but the overall effect size is small. Benzodiazepines caused more drowsiness as an adverse effect compared to placebo, but less compared to morphine. These results justify considering benzodiazepines as a second or third-line treatment within an individual therapeutic trial, when opioids and non-pharmacological measures have failed to control breathlessness. Although a few good quality studies were included in this review, there is still a further need for well-conducted and adequately powered studies.

PLAIN LANGUAGE SUMMARY

Benzodiazepines for the relief of breathlessness in advanced diseases in adults

Breathlessness is a common and distressing symptom in advanced cancer and other diseases at the end of life. It is still very difficult to treat breathlessness sufficiently. Benzodiazepines, a group of sedating drugs that are mainly used for sleep disturbance and anxiety, are widely used for the relief of breathlessness. This systematic review aimed to determine whether benzodiazepines relieve breathlessness in adults with advanced disease. In summary, this review concludes, on the basis of seven included studies, that there is no evidence for a beneficial effect of benzodiazepines in the relief of breathlessness in adults with advanced disease. The review supports the use of benzodiazepines only if other first-line treatments, such as opioids and non-drug treatments, have failed. However, there is still an urgent need for more studies in this field to find better ways to relieve this burdensome symptom in patients with advanced diseases.

BACKGROUND

Description of the condition

The American Thoracic Society defined breathlessness as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses” (ATS 1999). This multidimensional concept of breathlessness as ‘total breathlessness’ is comparable with the concepts of ‘total pain’ or ‘total suffering’ (Booth 2006). The term ‘breathlessness’ is used interchangeably with dyspnoea, shortness of breath, breathing difficulty, and laboured breathing.

Breathlessness is one of the most common symptoms in the last year of life (Higginson 2004). In advanced diseases it is highly prevalent in chronic obstructive pulmonary disease (COPD, 90% to 95%), chronic heart failure (CHE, 60% to 88%), and cancer (10% to 70%) (Solano 2006). It is a distressing symptom for the patient but also for the carers (Nordgren 2003). The frequency and severity of breathlessness increases during the course of the disease until death (Muers 1993). Furthermore, breathlessness may be related to anxiety and depression (Neumann 2006), thus treatment of anxiety and depression may reduce this symptom. However, the contribution, the causal relationship, and the direction of influence is still unclear (Booth 2008).

Breathlessness is caused by different diseases, such as primary and secondary cancer, COPD, CHE, motor neurone disease (MND), and cryptogenic fibrosing alveolitis/idiopathic pulmonary fibrosis (IPF). The advanced stage of each disease has to be defined separately because of the different disease trajectories. The pathophysiology of breathlessness depends mainly on the underlying cause. It includes, for example, airway obstruction, reduction of lung or gas exchange capacity, muscle weakness, degeneration of neurons, or reduction of blood diffusing capacity. The pathological pathway is complex and beyond a sole reduction of P0₂ (partial pressure of oxygen) or increase of PCO₂ (partial pressure of carbon dioxide) (Manning 1995). The medulla in the brain stem, the motor and sensory cortex, peripheral and central chemoreceptors, and mechanoreceptors in the airways and chest wall are the main sites of action responsible for the perception of breathlessness (Booth 2008). There are different explanations of how different parts interact and induce the sensation of breathlessness, such as corollary discharge, afferent-reafferent dissociation, and receptor reaction.
The corollary discharge describes the hypothesis that a sensory 'copy' of the motor output is sent from the motor cortex to the sensory cortex and imparts a conscious awareness of respiratory effort, and is the most widely accepted hypothesis (Beach 2006). After treatment of the underlying cause, symptom management of breathlessness includes non-pharmacological and pharmacological interventions. A recent Cochrane Review on non-pharmacological interventions for the relief of breathlessness in advanced disease showed effectiveness of neuro-electrical muscle stimulation, chest wall vibration, walking aids, and breathing training (Bausewein 2008). A recent review on the use of oxygen highlights that there is a statistically and clinically significant benefit for both ambulatory and long-term oxygen in COPD, but no consistent evidence for the use in cancer (Cranston 2008).

Opioids are the first choice in the pharmacological management of refractory breathlessness. A Cochrane Review showed evidence for the use of oral and parenteral application of opioids, but there is currently no evidence for nebulised opioids (Jennings 2001). However, most of the studies were underpowered and there is a need for further well-designed studies to investigate the effectiveness in different diseases, applications, and doses. Besides opioids, there are other drugs for the palliation of breathlessness, such as steroids (for lymphangitis carcinomatosa), inhaled local anaesthetics or more sedating drugs, such as benzodiazepines, phenothiazines, buspirone, or chlorpromazine, with variable evidence in symptom control (Davis 2005).

**Description of the intervention**

Benzodiazepines are frequently used in the management of breathlessness in advanced diseases and are regularly recommended in textbooks for palliative medicine or clinical guidelines (Booth 2006; Bruera 2006). The most common drugs are diazepam, midazolam, alprazolam, and lorazepam. However, there are more than 40 different benzodiazepines (Hardman 2005). Benzodiazepines belong to the group of hypnotics and sedatives. Their core chemical structure is a fusion of the benzene and the diazepine ring with various modifications which are responsible for the different compounds of the drug. The interaction of benzodiazepines with specific subunits of GABA (gamma-aminobutyric acid) receptors is responsible for their mechanism of action. The central and main effects of benzodiazepines are sedative-hypnotic, muscle-relaxant, anxiolytic, and anticonvulsant. Side effects include impairment of mental and motor function, light-headedness, and nausea (Hardman 2005). Physical dependence is a huge problem in long-term use of benzodiazepines. There is no effect on respiration (e.g., depression of respiration) in normal doses, and only a slight depression of ventilation in higher doses (Hardman 2005). The main therapeutic uses are insomnia, anxiety disorders, acute epilepsy, alcohol withdrawal, and anaesthetic premedication (Hardman 2005). The group of non-benzodiazepines (e.g., zolpidem) act on the same receptors with similar effects, but have a different chemical structure. They are not included in this review as they do not belong to the benzodiazepine group.

**Why it is important to do this review**

Despite the frequent use of benzodiazepines for the relief of breathlessness in palliative care, the evidence for their efficacy is still unclear. No systematic review on this specific topic has been published so far.

**OBJECTIVES**

The primary objective of this review was to determine the efficacy of benzodiazepines for the relief of breathlessness in patients with advanced disease.

Secondary objectives were to determine the efficacy of different benzodiazepines, different doses of benzodiazepines, different routes of application, adverse effects of benzodiazepines, and the efficacy in different disease groups.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

- Randomised controlled trials (RCTs). We defined 'randomised' as studies which were described by the authors as 'randomised' anywhere in the manuscript.
- Controlled clinical trials (CCTs).

While writing the protocol we expected a limited number of studies and therefore decided also to include controlled trials, giving special consideration to the higher risk of bias in these trials in the analysis.

**Types of participants**

Adult participants described as suffering from either breathlessness, dyspnoea, shortness of breath, difficult breathing, or laboured breathing due to advanced malignant and non-malignant diseases. The advanced stages of diseases included the following:

- cancer: advanced local or metastatic disease;
- COPD: stage III (severe) or IV (very severe) according to the GOLD classification (Global Initiative for Obstructive Lung Disease) - this includes patients with airflow limitation of FEV1

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Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)

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< 50%, FEV<sub>1</sub>/FVC < 0.7 (FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity) and symptoms such as more severe breathlessness, reduced exercise capacity, and repeated exacerbations (GOLD 2007);

- CHF: stage III or IV of the NYHA classification (New York Heart Association) including symptoms such as breathlessness or palpitation and an increasing limitation of exercise capacity and discomfort at rest;
  - MND: all participants suffering from breathlessness;
  - IPF: all participants suffering from breathlessness as the most prominent and disabling symptom.

We excluded studies including participants with acute or chronic asthma, pneumonia, or other potentially curable diseases. Participants included in the studies could be in any care setting (e.g. hospital or home care).

We included studies evaluating participants on oxygen as long as oxygen was used in both the intervention and the control arm.

**Types of interventions**
The use of benzodiazepines (at any dose, any frequency (also single dose), any duration, and through any route) for the relief of breathlessness compared with placebo or active control. We included all drugs which belong to the pharmacological group of benzodiazepines (Hardman 2005).

**Types of outcome measures**

**Primary outcomes**
Primary outcomes included subjective measurements of breathlessness on validated and reliable scales such as:

- uni-dimensional scales (e.g. visual analogue scales (VAS), numeric rating scales (NRS), categorical scales, modified Borg scales); or
- multidimensional scales (e.g. St. George’s Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ)).

We included studies that measured breathlessness as a primary or secondary outcome, and also studies evaluating breathlessness at rest or on exercise.

**Secondary outcomes**
Secondary outcomes included:

- measurement of anxiety;
- measurement of depression;
- adverse effects of benzodiazepines;
- functional exercise capacity (e.g. walking tests);
- measurement of quality of life; and
- attrition.

**Search methods for identification of studies**

**Electronic searches**
We identified studies from a search of the following 14 databases:

- the Cochrane Pain, Palliative and Supportive Care Trials Register (12 September 2009);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2009, Issue 3) (12 September 2009);
- the Cochrane Database of Systematic Reviews (CDSR) in The Cochrane Library (12 September 2009);
- Database of Abstracts of Reviews of Effectiveness (DARE) (12 September 2009);
- MEDLINE (1950 to 12 September 2009);
- EMBASE (1980 to 12 September 2009);
- CINAHL (1980 to 12 September 2009);
- PsycINFO (1806 to 12 September 2009);
- ACP (American College of Physicians) Journal Club (12 September 2009);
- HTA Health Technology Assessment (12 September 2009);
- NHSEED NHS Economic Evaluation Database (12 September 2009);
- Database of Halley Stewart Library (St. Christopher’s Hospice) (12 September 2009);
- International Pharmaceutical Abstracts (1970 to 12 September 2009); and

**Search strategy**
During the development of the search strategy we realised that the criteria ‘diseases’ and ‘advanced stage of disease’ would narrow our search with the consequence of missing potentially relevant studies. Therefore we chose a wider search strategy. The decision on inclusion or exclusion of studies regarding disease and disease stage was made when screening the retrieved studies in more detail. Please see Appendix 1 for the MEDLINE search strategy in OVID and Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7 and Appendix 8 for all other search strategies developed for this review.

**Searching other resources**

**Handsearching**
We checked the reference lists of all relevant studies, key textbooks, and key websites for further relevant studies. We checked the reference lists of several reviews on the subject (Abernethy 2008; Allen 1984; Altose 1985; Bausewein 2008; Booth 2008; Davis 1997; De Conno 1991; Lanken 2008; Manning 2000; Ripamonti 1999; Rocker 2007; Runo 2001; Thomas 2002; Tobin 1990; Viola 2008; Williams 2006).

We handsearched the reference lists of the following 16 textbooks: Goodman and Gilman’s The Pharmacological Basis of Therapeutics; Oxford Textbook of Palliative Medicine; Textbook of Palliative Medicine; Textbook of Palliative Nursing; Palliative Medicine; Management of Advanced Disease; Palliative Care Formulary 3; Oxford Handbook of Palliative Care; Palliative Medicine - a case based manual; Principles and Practice of Palliative Care and Supportive Oncology; Dyspnoea in Adverse Disease; Dyspnoea; Heart Failure and Palliative Care; Supportive Care in Respiratory Disease; Textbook of Respiratory Medicine; and Palliative Care in Neurology.

In addition, we searched seven websites to identify relevant data:
- www.benzo.org.uk
- www.book.palliative.info
- www.caresearch.com.au
- www.cks.library.nhs.uk
- www.controlled-trials.com
- www.palliativedrugs.com
- and www.patient.co.uk.

**Personal contact**

We contacted the following authors of main studies and investigators who are known to be carrying out research in this area for further studies and unpublished data: Amy Abernethy; Sam Ahmedzai; Eduardo Bruera; Leandro Cerchietti; Jessica Corner; David Currow; Carol Davies; Deborah Dudgeon; Wesley Ely; Tim Harrison; Michio Hosaka; Miriam Johnson; Alfredo Navigante; Andrew Wilcock; and Ashley Woodcock. We asked all members of the Association of Palliative Medicine (APM; UK) for additional studies or unpublished data in a circular letter. All users of the bulletin board of www.palliativedrugs.com received a similar letter asking for additional studies or unpublished data.

**Language**

There was no language restriction in the selection of studies.

**Data collection and analysis**

**Selection of studies**

Two review authors (SS, CB) independently assessed the relevant titles and abstracts identified. Disagreement was resolved by consensus and with a third review author (IJH). Three independent review authors (SS, CB, SB) assessed the full text of all potentially relevant studies. Disagreement at this stage was resolved again by consensus and with a fourth review author (IJH).

**Assessment of methodological quality of included studies**

Three independent review authors (SS, CB, SB) assessed all selected studies for methodological quality. We used two measures of methodological quality. First, we assessed the quality of studies using the Review Manager (RevMan) ‘Risk of bias’ table following guidance from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008; RevMan 2008). Second, we also graded the quality of studies according to the ‘Edwards Method Score’ (Edwards 2000; Edwards 2003). This checklist of methodological quality contains 11 items which assess the primary research quality of the studies and its published description. The following items were assessed and scored zero, one, or two for adequacy: definition of aims; sample formation; description of inclusion and exclusion criteria; description of participant characteristics; power calculation; objectivity of outcome measures used; adequacy of follow up; adequacy of analysis (intention-to-treat (ITT)); adjustment for baseline differences between groups; appropriate unit of allocation to groups; and randomisation method. We then constructed a total method score and rated the overall quality of the studies as follows: low (12 and under), medium (13 to 14), high (15 and over) (Edwards, personal communication). We integrated the results of the quality assessment in data analysis, as well as in meta-analysis (cumulative meta-analysis only in high quality studies).

**Data extraction**

Three review authors (SS, CB, SB) independently extracted data from each appropriate study. An extraction form for collection of relevant data was specifically designed consisting of:

**Study ID and publication details**, including:
- study aim.

**Study design and methods**, including:
- randomisation procedure;
- allocation concealment;
- details of blinding;
- number and time of follow ups;
- handling of missing data; and
- details of analysis.

**Patient characteristics**, including:
- demographics;
- diagnosis;
- performance status;
- number and description of participants in the intervention and control groups; and
- setting.

**Intervention**, including:
- the drug and its characteristics (e.g. half-life);
- route of administration;
• dose;
• frequency of application;
• duration of therapy; and
• description of placebo.

Primary outcomes, including:
• measurement of breathlessness; and
• change in level of breathlessness.

Secondary outcomes, including:
• adverse effects of benzodiazepines;
• functional exercise capacity;
• dose modification;
• number and reason of withdrawals/attrition;
• measurement of anxiety;
• measurement of depression;
• measurement of quality of life; and
• arterial blood gas measurements.

Additional information, including:
• patient comments on intervention.

We contacted authors of studies to provide unpublished data for the meta-analysis where required.

Data analysis
We combined studies using RevMan (Version 5.0) (RevMan 2008). We tried to obtain all relevant data from each paper. When means and standard deviations (SD) were missing we did not impute or estimate them for meta-analysis, because none of the suggested imputations in the Cochrane Handbook were reliable (after consultation with the statistician of the Cochrane Review Group) (Higgins 2008). We therefore contacted the authors to get additional data (means and SD). If they could not provide means or SD, we asked for the original data and calculated means and SD from these data. Data were only retrieved from graphs if exact numbers could be determined. With this procedure, we were able to retrieve all relevant data.

Meta-analysis
We performed a meta-analysis including all appropriate studies. We excluded studies from the meta-analysis if the methodological quality of the study was low (Edwards Method Score 12 and lower). We used primary and secondary outcomes in the meta-analysis when appropriate and possible. The primary outcome measures (breathlessness) were either in the form of continuous or ordinal data. We treated all ordinal data as continuous data because the scales used were long enough (following the recommendation of the Cochrane Handbook, Higgins 2008). In the meta-analysis we treated studies with cross-over design in the same way as studies with a parallel design if there was no indication of a carry-over effect (following the advice of the Cochrane Handbook and after discussion with the statistician of the Cochrane Review Group) (Higgins 2008). We judged the potential existence of a carry-over effect on a theoretical basis after analysis of the study (e.g. drug persistency in the body into the next period). We estimated the effect by comparing the post-treatment measurements of the intervention and the control groups. We calculated the standardised mean differences (SMD) for continuous data with a 95% confidence interval (CI) to show the size of the effect of interventions. Because of the diversity of measurement tools for breathlessness, we used SMD to measure the intervention effect in standardised units. A negative SMD was defined as a beneficial effect of the intervention. We calculated the risk ratio (RR) for dichotomous data to estimate the relative risk. We used risk difference (RD) when there was no event in one of the groups (e.g. for adverse effects or attrition), because the estimation of RR is not possible in this case. For all data we considered a P value of < 0.05 as statistically significant. We used a random-effects model because clinical heterogeneity was present (differences in diagnostic groups, types of benzodiazepines, doses, duration of treatment, route of delivery).

We used the fixed-effect model only for the presentation of single studies or for studies with adequate homogeneity. We undertook sensitivity analysis to look for influences of different variables (e.g. participants, interventions, outcomes, and study design). We also performed sensitivity analysis taking into account methodological quality and the robustness of results.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search
One review author (SS) searched the literature in June 2008 and updated the search in September 2009 (no additional studies were found for the update). We identified a total of 1309 references through the search of 14 databases. We excluded 207 duplicates. We studied the titles and abstracts of each of the 1102 articles and selected relevant articles if they met the inclusion criteria. At this stage, we excluded 1071 articles and sorted them into the following exclusion groups: different disease (241 articles), different drug (223), reviews (242), anaesthesia related study (111), psychology related study (61), pharmacokinetic study (45), different design (38), palliative/terminal sedation (37), non-pharmacological interventions (14), and other (e.g. children) (59). We retrieved 31 articles for more detailed evaluation. We furthermore identified 48 additional references from the reference lists of the original
31 articles identified by handsearching and the auxiliary function ‘Related Articles’ in Science Direct (www.sciencedirect.com). The search of 59 reviews, 16 textbooks and seven websites did not add any new articles. Altogether we studied 79 articles in more detail after obtaining the full text. Of these 79 articles five studies met our inclusion criteria and were included in the review. We excluded 74 articles (see below). In addition, after sending a letter to all members of the Association of Palliative Medicine (APM, UK) and after personal contact with several investigators (see above), we were able to identify three new and unpublished studies. We received data from two out of the three unpublished studies. The author of the third unpublished study (Stege (unpublished)) offered to send the data after acceptance of the paper for publication (no information received on submission of this Cochrane Review). Finally, we included the data from seven studies in the analysis.

Included studies

Eimer 1985 (see also the ‘Characteristics of included studies’ table): a double-blind, placebo-controlled, cross-over RCT tested clorazepate in five non-anxious participants with severe COPD in a hospital setting to determine whether a benefit could be achieved in relieving breathlessness. The study started with three arms (7.5 mg/day and 22.5 mg/day oral clorazepate compared to placebo), but the high-dose arm (22.5 mg) was excluded from analysis after 3/5 dropped out due to intolerable adverse effects. The duration of treatment was two weeks with a one-week wash-out period. Breathlessness was assessed weekly with a Breathlessness Grade from 1 (little breathlessness) to 6 (extreme breathlessness). Secondary outcomes were anxiety, depression, adverse effects, a 12-minute walking test, and attrition.

Harrison (unpublished) (see also the ‘Characteristics of included studies’ table): the effectiveness of lorazepam in the relief of breathlessness was tested in a randomised, double-blind, placebo-controlled, cross-over study with 26 participants with advanced cancer in an in- and outpatient setting (single-centre). Seventeen participants completed the study and were included in the analysis. Lorazepam 0.5 mg twice daily orally was tested over five days with a two-day wash-out period. A visual analogue scale (VAS) (0 to 100) was used to measure breathlessness as primary outcome (responding to three questions: 1. Breathlessness in general over the last 24 hours (summary); 2. Breathlessness at its best over the last 24 hours; and 3. Breathlessness at its worst over the last 24 hours). Secondary outcomes were anxiety and depression (measured on the Hospital Anxiety and Depression Scale (HADS)), and adverse effects after the treatment.

Man 1986 (see also the ‘Characteristics of included studies’ table): a double-blind, placebo-controlled, cross-over RCT was conducted in 29 participants with advanced but clinically stable COPD in an outpatient setting, to assess the efficacy and safety of alprazolam in relieving breathlessness. Twenty-four participants were included in the analysis and five participants dropped out. The effect of alprazolam 1.0 mg/day orally was compared to placebo before and after one week of treatment (with a one-week wash-out period after cross-over). Breathlessness was measured either by Grade of Dyspnoea with 5 (breathlessness at rest) to 2 (able to keep up with people of similar age on level, but not on hills and stairs) to 1 (other than 2 to 5), as well as with a Dyspnoea Scoring (VAS 0 to 10) at rest and during exercise (cycle ergometer). Adverse effects, attrition, and a 12-minute walking test were measured as additional outcomes.

Navigante 2006 (see also the ‘Characteristics of included studies’ table): a single-blind RCT with a parallel design was undertaken to assess the role of midazolam in the alleviation of severe breathlessness during the last week of life of 101 participants with advanced cancer. The investigators conducted a three-arm trial in a hospital setting comparing morphine only (10 mg/day), midazolam only (20 mg/day), and the combination of morphine + midazolam (10 + 20 mg/day), with a treatment duration of 48 hours and subcutaneous (sc) administration. The dose was adjusted if the participant was not morphine naive (+25% on top of DsEDM (daily subcutaneous equivalent dose of morphine)). Rescue medication was provided with 5 mg midazolam in the morphine group and 2.5 mg morphine in the midazolam and midazolam + morphine group. Breathlessness was the primary outcome assessed in four different ways: 1. Breathlessness intensity with the modified Borg scale (0 to 10) before the intervention and 24 hours and 48 hours after intervention; 2. Percentage of participants with breathlessness relief (yes/no) after 24 hours and 48 hours and no breathlessness relief after 48 hours; 3. Numbers of breakthrough dyspnoea (= numbers of rescue medication) per patient after 24 hours and 48 hours; and 4. Percentage of participants with breakthrough dyspnoea after 24 hours and 48 hours. Other outcomes used were adverse effects (total of clinical relevance and different adverse effects in grading 1 to 3), anxiety, and attrition.

Navigante (unpublished) (see also the ‘Characteristics of included studies’ table): a single-blind RCT with a parallel design was undertaken with 63 participants with advanced cancer in a single-centre outpatient clinic to assess the efficacy of oral midazolam to relieve breathlessness in comparison to oral morphine (two participants dropped out after randomisation). This is an unpublished study and only the method and result section of the paper in preparation was available (additional data were sent after we contacted the author). At the day of baseline assessment a ‘Fast Titration Phase’ (FTP) was used to find the effective dose (effect of at least 50% reduction of breathlessness) and started with midazolam 2 mg every four hours (excluding sleeping time) and morphine 3 mg every four hours (excluding sleeping time) with incremental steps of 25% of the preceding dose every 30 minutes. The duration of treatment was five days with daily assessment. Breathlessness intensity was measured using a Numerical Rating Scale (NRS, 0 to 10). The assessment included the number of participants with one or more breakthrough episodes of dyspnoea (BTD) during the previous day, the descriptor which the participant used for breath-
lessness, and the number of adverse effects (AE). Dose reduction, therapeutic failure, and additional procedures (such as antibiotics) were reported. Shivaram 1989 (see also the ‘Characteristics of included studies’ table): a double-blind, randomised, placebo-controlled, cross-over study was conducted in 12 participants with advanced COPD with anxiety (non-psychiatric stage) in an unknown setting (probably hospital) to assess the effect of alprazolam to relieve breathlessness. Four participants dropped out and were excluded, leaving eight participants for analysis. The effect of oral alprazolam 0.75 mg/day was compared to placebo at baseline and after two weeks of treatment (with two days wash-out). Breathlessness was measured on a modified Borg Scale (0 to 10). No other outcomes except adverse effects were assessed. Woodcock 1981 (see also the ‘Characteristics of included studies’ table): a double-blind, placebo-controlled, cross-over RCT was undertaken in 18 participants with severe COPD comparing the effect of oral diazepam (25 mg/day) and promethazine (125 mg/day) on breathlessness. After drop-out of three participants, 15 participants were included in the analysis. Breathlessness was the main outcome assessed as daily dyspnoea by VAS (0 to 10) and dyspnoea grade 5 (breathlessness at rest) to 2 (able to keep up with people of similar age on level, but not on hills and stairs) to 1 (other than 2 to 5), after each intervention in an outpatient setting with a two-week treatment duration (no wash-out period). Adverse effects, dose modification, anxiety, depression, a 12-minute walking test, treadmill, and ergometer measurement were assessed.

Study design

All studies were RCTs (Eimer 1985; Harrison (unpublished); Man 1986; Navigante 2006; Navigante (unpublished); Shivaram 1989; Woodcock 1981). Besides Navigante 2006 and Navigante (unpublished), who used a single-blind, parallel and morphine-controlled design, all other studies were double-blind, cross-over, and placebo-controlled (Eimer 1985; Harrison (unpublished); Man 1986; Shivaram 1989; Woodcock 1981).

Sample size

In general, the sample size was small (between five and 29 participants), except for two studies (Navigante 2006 with 101 participants and Navigante (unpublished) with 63 participants). One study (Eimer 1985) finished data collection without drop-outs. Four studies (Man 1986; Harrison (unpublished); Shivaram 1989; Woodcock 1981) had three to nine drop-outs (drop-out/N: 5/29, 9/26, 4/12, 3/18), which were always excluded from analysis. Three studies (Harrison (unpublished); Navigante (unpublished); Shivaram 1989) provided a power calculation, but only two of them reached an appropriate number of participants (Navigante (unpublished); Shivaram 1989). None of the studies presented an intention-to-treat analysis. In total, 200 participants were analysed, including 33 participants of the third intervention arm of the parallel designed study from Navigante 2006.

Participants

Participants with cancer were analysed in three studies (Harrison (unpublished); Navigante 2006; Navigante (unpublished)) and four studies analysed participants with advanced COPD (Eimer 1985; Man 1986; Shivaram 1989; Woodcock 1981).

Outcomes

Breathlessness was measured mainly on a VAS/NRS (Harrison (unpublished); Navigante (unpublished); Man 1986; Woodcock 1981), a modified Borg scale (Navigante 2006; Shivaram 1989) or a Dyspnoea Grade one to six scale (Eimer 1985) or one to five scale (Man 1986; Woodcock 1981). The majority measured breathlessness at rest (Eimer 1985; Harrison (unpublished); Navigante 2006; Navigante (unpublished); Shivaram 1989); only three studies additionally assessed breathlessness on exercise (Eimer 1985; Man 1986; Woodcock 1981). Other outcomes were: anxiety (Harrison (unpublished); Navigante 2006; Woodcock 1981), depression (Harrison (unpublished); Woodcock 1981), adverse effects (all), walking tests (Eimer 1985; Man 1986; Woodcock 1981), and atrition (all).

Intervention

Two studies tested alprazolam, one with 1.0 mg/day (Man 1986) and one with 0.75 mg/day (Shivaram 1989). Diazepam was used in one study with 25 mg/day (Woodcock 1981 - within a three-arm design with 125 mg/day promethazine compared to placebo). Navigante 2006 applied midazolam 20 mg/day only and in combination with morphine 10 mg/day compared to morphine 10 mg/day only within a three-arm design. Navigante (unpublished) studied midazolam 8 mg/day versus morphine 12 mg/day (both starting doses). Harrison (unpublished) examined lorazepam 1 mg/day. Eimer 1985 used clorazepate in two different doses: 7.5 mg and 22.5 mg per day (compared to placebo). However, due to intolerable adverse effects the 22.5 mg arm was excluded from analysis. The treatment durations range between 48 hours (Navigante 2006) and two weeks (Eimer 1985; Shivaram 1989; Woodcock 1981).

Excluded studies

We excluded 74 out of 79 studies because they did not meet the inclusion criteria (29 ‘no subjective measurement of breathlessness’; 20 ‘reviews’; 15 ‘different drugs’; six ‘different disease/healthy subject’; three ‘combination of drugs’; and one ‘different study design’) (see ‘Characteristics of excluded studies’). We excluded a substantial number of studies because of a lack of subjective measurement of breathlessness, mainly older studies from the 1970s.
and 1980s which studied benzodiazepines in relation to spirometry, functional tests, or blood tests. Among them is the most cited paper in this area (Mitchell-Heggs 1980), which we had to exclude because of a lack of subjective measurement of breathlessness. Although the authors mentioned breathlessness as an outcome, no subjective measure could be determined, either in the text, tables, or graphs. Other reasons for excluding this study were the lack of systematic or standardised design and absence of control group. Three excluded studies (Lichterfeld 1967; Navigante 1997; Navigante 2003) used benzodiazepines only in combination with other drugs, thus a separate assessment of the drug effect was not possible. Three excluded studies (Jones 1985; Stark 1981a; Stark 1981b) assessed breathlessness in healthy patients (comparing diazepam, promethazine, and placebo). One study compared diazepam versus flupenthixol in patients with psychosomatic disorders (breathlessness was only one of 12 associated symptoms but was not the primary outcome) (Jokinen 1984). Although we expected a substantial number of observational studies, the case report from Greene 1989 was the only non-controlled study which we had to exclude. We excluded the study Hosaka 1996 because four of the 22 patients did not meet our inclusion criteria regarding the underlying disease (asthma, tuberculosis) and also the level of airways obstruction was above our inclusion criteria (mean FEV₁ 63% and FEV₁/FVC 1.06), indicating that the disease stage was not as advanced as required for this review. This non-randomised, placebo-controlled, double-blind, cross-over trial studied the use of diazepam 10 to 12 mg/day over four weeks in 22 patients with chronic respiratory insufficiency (mainly COPD and fibrosis) who received home oxygen therapy. It was published in Japanese (abstract in English). A significant improvement was shown in breathlessness at rest in the diazepam group and a non-significant worsening in the placebo group but the levels of breathlessness at baseline were different between the groups.

Risk of bias in included studies

See also the 'Characteristics of included studies' table and the corresponding 'Risk of bias' tables. Six studies (Harrison (unpublished); Man 1986; Navigante 2006; Navigante (unpublished); Shivaram 1989; Woodcock 1981) showed high quality on the 'Edwards Method Score' (Edwards 2000) (see also 'Risk of bias' tables in section 'Characteristics of included studies', with a summary in Figure 1). Only one study (Eimer 1985) had a high risk of bias due to lack of presented data and information (see Figure 1), and inappropriate presentation of data in figures. This study was therefore not included in the meta-analysis.
Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

<table>
<thead>
<tr>
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<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Harrison (unpublished)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Man 1986</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Navigante (unpublished)</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)  
Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
It has to be taken into account that Harrison (unpublished) and Navigante (unpublished) contain unpublished data. The judgment of methodological quality using the 'Risk of bias' table, the Grade of Evidence, and the Edwards Methods Score was therefore not always appropriate and must be interpreted with caution.

**Allocation**

All studies were RCTs. Four studies (Man 1986; Navigante (unpublished); Shivaram 1989; Woodcock 1981) did not mention the denominator population which was screened for participation. There was a substantial gender imbalance due to more males than females participating in most studies (exact total numbers are not countable because of a different presentation of data for gender of randomised or analysed participants); only Navigante 2006 included more females than males. One study did not mention the gender distribution at all (Navigante (unpublished)).

**Blinding**

Two studies were single-blinded (Navigante 2006; Navigante (unpublished)), one study did not define blinding appropriately, but was stated to be double-blind (Eimer 1985) and the rest used a double-blind design.

**Incomplete outcome data**

Four out of six studies with drop-outs excluded them from the analysis (Harrison (unpublished); Man 1986; Shivaram 1989; Woodcock 1981); the other two studies did not mention the handling of drop-outs clearly (Navigante 2006; Navigante (unpublished)). None of the studies mentioned missing data or the handling of missing data.

**Selective reporting**

Woodcock 1981 stated that there was no effect of diazepam in the relief of breathlessness. However, a beneficial effect could be seen for diazepam although it was not statistically significant (P = 0.06).

**Other potential sources of bias**

Five studies were published in indexed, peer-reviewed journals (Eimer 1985; Man 1986; Navigante 2006; Shivaram 1989; Woodcock 1981). Two studies were unpublished. The author of one unpublished study sent us all the original data (Harrison (unpublished)), whereas the second author sent only the methods and results sections (Navigante (unpublished)). Both authors were very helpful and supportive. One study did not mention a wash-out period between intervention and control phases (cross-over design) (Woodcock 1981). However, sensitivity analysis showed no difference regarding the results compared to studies including a wash-out period. Navigante 2006 used the comparative drug (midazolam - morphine) for rescue medication. Since this combination of midazolam and morphine could have been used in all three treatment arms, a confident comparison or distinction between midazolam and morphine only was not possible. Navigante (unpublished) allowed additional treatments related to breathlessness besides the ones used during the intervention and the control in the study (e.g. antibiotics, aspiration of pleural effusion, radiotherapy). Although the percentage of patients receiving these procedures was presented for each group, it was not possible to distinguish which group received which treatment.

**Effects of interventions**

Seven studies (seven RCTs; five cross-over and two parallel designs; four COPD and three cancer studies) were included in the review with a total number of 200 participants included in the analysis (COPD N = 52; cancer N = 148). The main findings of each of the studies are summarised below, starting with the effect of benzodiazepines in patients with COPD, with cancer, and for breakthrough dyspnoea (BTD) (please also see the 'Characteristics of included studies' table). We carried out the meta-analysis separately for placebo-controlled (Harrison (unpublished); Man 1986; Shivaram 1989; Woodcock 1981) and morphine-controlled studies (Navigante 2006; Navigante (unpublished)).

**Benzodiazepines for breathlessness in chronic obstructive pulmonary disease (COPD)**

**Eimer 1985**

Five participants with advanced COPD were examined in a randomised, cross-over trial. Breathlessness was measured at rest and after a 12-minute walking test, after two weeks of treatment with clorazepate 7.5 mg/day compared to placebo. All participants completed the study. The change scores from baseline to post-intervention showed no significant difference between the intervention and the control group. The results were only presented in a figure without exact data, which was difficult to interpret.

**Man 1986**

Twenty-nine participants with advanced COPD were randomised in a cross-over design to alprazolam 1.0 mg/day or placebo over one week, respectively, but only 24 participants completed the study (five drop-outs were excluded from analysis). There was no significant effect of alprazolam versus placebo compared to baseline in the relief of breathlessness at rest and on exercise. Furthermore, no difference between the intervention and the control group was observed after treatment.

**Shivaram 1989**

Twelve participants with advanced COPD were randomised (cross-over), of which only eight participants completed the study (four drop-outs were excluded from analysis). Alprazolam 0.75 mg/day did not show an improvement of breathlessness at rest compared to baseline after two weeks but placebo did (not significant). Furthermore, no difference was observed after treatment between the intervention and the control group.

**Woodcock 1981**

Eighteen participants with advanced COPD were randomised in a cross-over design to examine the effect of diazepam 25 mg/day in the relief of breathlessness compared to placebo and promethazine...
125 mg/day (third arm). After three drop-outs 15 participants completed the study and were included in the analysis. Diazepam produced a non-significant effect in the relief of breathlessness at rest compared to placebo after two weeks. There was also no difference in breathlessness on exercise compared to placebo.

**Meta-analysis and summary (see Data and analyses 2.1)**

We included three out of four cross-over studies (see 'Risk of bias in included studies') with 47 COPD participants (94 observations) in the meta-analysis (Man 1986; Shivaram 1989; Woodcock 1981), comparing post-treatment measures between intervention and control group. No significant effect of alprazolam or diazepam was observed with a SMD estimated as -0.16 (95% CI -0.73 to 0.40) (see Figure 2). The overall heterogeneity of effects was moderate ($I^2 = 42\%$).

**Figure 2. Forest plot of comparison: 2 Disease, outcome: 2.1 COPD.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Man 1986</td>
<td>3</td>
<td>0.8</td>
<td>24</td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>3.63</td>
<td>1.92</td>
<td>8</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>3.33</td>
<td>1.11</td>
<td>15</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Tau^2 = 0.11; Chi^2 = 3.48, df = 2 ($P = 0.18$); $I^2 = 42%$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect $Z = 0.56 (P = 0.57)$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, the analysis (four studies) and meta-analysis (three studies) with 52/47 participants showed no significant effect of three different benzodiazepines (clorazepate, diazepam, alprazolam) in the relief of breathlessness in patients with advanced COPD. One study (Woodcock 1981) showed a slight but non-significant advantage of diazepam compared to placebo (Figure 3).

**Figure 3. Forest plot of comparison: 3 Intervention, outcome: 3.2 Benzodiazepines - diazepam.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>3.33</td>
<td>1.11</td>
<td>15</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect $Z = 1.90 (P = 0.06)$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Benzodiazepines for breathlessness in cancer**

**Harrison (unpublished)**

Twenty-six participants with advanced cancer were randomised (cross-over), but only 17 participants completed the study and were included in the analysis. Lorazepam 1.0 mg/day had no significant effect on breathlessness at rest compared to baseline and to placebo after five days of treatment. This result was similar to the same extent for the overall level of breathlessness, breathlessness at its best and at its worst.

**Navigante 2006**

One hundred and one participants with terminal cancer were randomised in a three-arm study with a parallel design in order to compare midazolam 20 mg/day, morphine 10 mg/day, and midazolam 20 mg/day + morphine 10 mg/day after 24 and 48 hours of treatment, respectively (plus rescue doses). Thirty-one participants died during the study after receiving the treatment (no difference between the study groups). Every treatment arm showed a signifi-
icant reduction of breathlessness compared to baseline, but without any difference when comparing the three arms after 48 hours. After 24 hours, morphine only and the combination of both drugs were slightly better than midazolam only. The highest percentage of participants (92%) who experienced a relief of breathlessness was shown in the midazolam + morphine group after 24 hours, the lowest percentage in the midazolam only group (46%) (Figure 4). The midazolam group showed the highest percentage of participants (26%) with persistent and uncontrolled breathlessness after 48 hours, the midazolam + morphine group the lowest.

After 24 hours, morphine only and the combination of both drugs were slightly better than midazolam only. The highest percentage of participants (92%) who experienced a relief of breathlessness was shown in the midazolam + morphine group after 24 hours, the lowest percentage in the midazolam only group (46%) (Figure 4). The midazolam group showed the highest percentage of participants (26%) with persistent and uncontrolled breathlessness after 48 hours, the midazolam + morphine group the lowest.

**Figure 4. Forest plot of comparison: 4 Primary outcome, outcome: 4.2 Breathlessness - no relief (morphine-controlled).**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>M-H, Random, 95% CI</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Navigante 2006 (1)</td>
<td>14</td>
<td>26</td>
<td>1.74 [0.91, 3.32]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>26</td>
<td>29</td>
<td>1.74 [0.91, 3.32]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>14</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 1.66 (P = 0.10)

(1) Assessment after 48 hours.

For meta-analysis the assessment after 48 hours was used unless stated otherwise.

Navigante (unpublished)

Sixty-three participants with advanced cancer were randomised in a parallel design to compare midazolam 8 mg/day and morphine 12 mg/day (control) over five days (starting doses with titration phase and rescue doses). Sixty-one participants completed the study with one drop-out in each group (31 participants in the midazolam group and 30 participants in the morphine group). For the morphine group, data from only 29 participants were available at day five. Both treatments showed a significant reduction in breathlessness after two, three, four, and five days compared to baseline. Midazolam reduced breathlessness significantly better than morphine when comparing the end points after all treatment days. Twenty-one participants treated with midazolam reached a 50% reduction of breathlessness after the starting dose compared to only 11 participants in the morphine group (P = 0.023). Therapeutic failure was observed in 20% of participants in the morphine group compared to none in the midazolam group. A dose reduction was necessary in one participant in the midazolam group and in two participants in the morphine group due to excessive somnolence.

For meta-analysis the assessment after five days was used unless stated otherwise.

**Meta-analysis and summary (see Data and analyses 2.2, 2.3)**

All three studies with cancer patients could be included in the meta-analysis but were analysed separately for placebo-controlled and morphine-controlled studies. The placebo-controlled study found no significant effect with a SMD of -0.06 (95% CI -0.73 to 0.62) (see Figure 5) (Harrison (unpublished)). In addition, pooling of the two morphine-controlled studies showed no significant effect with a SMD of -0.68 (95% CI -2.21 to 0.84) (see Figure 6) (Navigante 2006; Navigante (unpublished)). One study demonstrated a significant effect of midazolam compared to morphine (Navigante (unpublished)), but this result was contrary to a similar study of the same research group where the morphine group showed a slightly better improvement of breathlessness than the midazolam group (Navigante 2006). When comparing midazolam with midazolam + morphine (Figure 7, third study arm in Navigante 2006), no difference could be shown.
Overall, no significant effect could be shown. Because of the high level of heterogeneity regarding the designs of the three studies (control group, study design, stage of disease, benzodiazepine, dose, and route of application) the meta-analysis of all three studies should be interpreted with caution. There are conflicting results in the comparison of midazolam to morphine based on two studies from the same research group.

**Benzodiazepines for the prevention of breakthrough dyspnoea in cancer**

Navigante 2006

The proportion of participants with breakthrough dyspnoea (BTD) was lower in the midazolam + morphine group (21.2/24.0%) than in both groups with morphine and midazolam after 24 and 48 hours, and highest in the midazolam group (36.4/38.5%). The median of BTD episodes per patient after 24 and 48 hours was higher in the morphine only group (two episodes) than in the midazolam only and midazolam + morphine group (one episode), respectively.

Navigante (unpublished)

The proportion of participants with BTD was lower in the midazolam group compared to the morphine group and reached a significant level of P = 0.035 at three days, P = 0.034 at four days, and P < 0.001 at five days of treatment. The proportion of participants with BTD in the midazolam group was lowest after five days of treatment with a significant level of P < 0.001 compared to baseline (42.0% to 80.6%). In contrast, the proportion of participants with BTD in the morphine group was lowest after the second day (66.7%) and increased up to five days (75.8%).
reduction in the morphine group at no time reached a significant
level of P < 0.05 compared to baseline (75.8% to 83.3% after five
days, P = 0.476).

Meta-analysis and summary (see Data and analyses 4.3, 4.4)
Both studies that examined BTD could be included in the meta-
analyses (Navigante 2006; Navigante (unpublished)) looking at
116/108 participants with cancer (after 24/48 hours) and compar-
ing midazolam with morphine. For the second study (Navigante
(unpublished)), we calculated the effect after 48 hours using the
measurement at the third day when asked for BTD on the day
before (that is 48 hours). Overall, no significant effect could be
shown after 48 hours with a risk ratio of 0.76 (95% CI 0.53 to
1.09) (see Figure 8).

Figure 8. Forest plot of comparison: 4 Primary outcome, outcome: 4.2 Breathlessness - breakthrough
(BTD) after 48 hours.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished) (1)</td>
<td>16</td>
<td>21</td>
<td>30</td>
<td>80.5%</td>
<td>0.69 [0.45, 1.07]</td>
<td></td>
</tr>
<tr>
<td>Navigante 2006 (2)</td>
<td>10</td>
<td>23</td>
<td>11</td>
<td>81.2%</td>
<td>0.83 [0.59, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>54</td>
<td>108</td>
<td>100.0%</td>
<td>0.76 [0.53, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.68; df = 1 (P = 0.42); P = 99%</td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.19 (P = 0.14)</td>
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</table>

(1) Assessment at day three asking for breathlessness after 48 hours.
(2) Assessment after 48 hours.
Although one study demonstrated a significant positive effect with midazolam after three, four, and five days (Navigante (unpublished)), the previous study from the same research group observed no difference between midazolam and morphine in preventing BTD.

**Overall - benzodiazepines in breathlessness**

**Meta-analysis and summary** (see Data and analyses 1.1, 1.2)

One study (Eimer 1985) was excluded from the meta-analysis due to a lack of methodological quality and lack of data (see 'Risk of bias in included studies'). Therefore, we included six studies in the overall meta-analysis but analysed placebo-controlled and morphine-controlled studies separately. Pooling of the placebo-controlled studies showed no significant effect with a SMD of -0.13 (95% CI -0.52 to 0.25) (Harrison (unpublished); Man 1986; Shivaram 1989; Woodcock 1981) (see Figure 9; Figure 10). The meta-analysis of all placebo-controlled studies included 128 observations equating to 64 participants. Pooling of the morphine-controlled studies with 107 participants also showed no significant effect with a SMD of -0.68 (95% CI -2.21 to 0.84) (Navigante 2006; Navigante (unpublished)) (see Figure 11; Figure 10). Overall, there is no significant beneficial effect of benzodiazepines in the relief of breathlessness at rest. The results have to be interpreted with caution because of some heterogeneity between the six included studies regarding different components (e.g. disease group, control group, benzodiazepine, among others).

**Figure 9.** Forest plot of comparison: 1 Overall, outcome: 1.1 Placebo-controlled/cross-over design.

**Figure 10.** Forest plot of comparison: 4 Primary outcome, outcome: 4.1 Breathlessness - no relief (placebo-controlled).
In the sensitivity analysis, a comparison to baseline of studies which presented baseline and after treatment measures demonstrated a positive trend for benzodiazepines but did not reach statistical significance (data not shown). However, changes from baseline have a higher risk of confounders (e.g., regression to the mean) compared to after treatment measures and should be avoided (Higgins 2008). Only two studies looked at breathlessness on exercise (Man 1986; Woodcock 1981) but could not be included in the meta-analysis because of a lack of appropriate data (data presented only in graphs).

In summary, all but one study showed no beneficial effect of benzodiazepines (Eimer 1985; Harrison (unpublished); Man 1986; Navigante 2006; Shivaram 1989). Only one study showed a significant effect of midazolam compared to morphine (Navigante (unpublished)), but as mentioned above this result was in contrast to a previous study (Navigante 2006). One study demonstrated a beneficial effect of diazepam but was not statistically significant (Woodcock 1981).

### Secondary outcomes

#### Anxiety

Four out of seven studies measured anxiety with different scales (Eimer 1985; Harrison (unpublished); Navigante 2006; Woodcock 1981). Benzodiazepines did not reduce anxiety, either in change from baseline or compared to the control group after treatment.

#### Depression

Three studies examining depression did not find any significant difference between the intervention and the placebo group (Eimer 1985; Harrison (unpublished); Woodcock 1981).

#### Adverse effects (see Data and analyses 5.1 to 5.5)

All studies reported the occurrence of adverse effects. Two studies did not observe any adverse effects (Eimer 1985; Shivaram 1989). Harrison (unpublished) described three adverse effects in the intervention group which lead to withdrawal compared to one case in the placebo group. Man 1986 and Woodcock 1981 observed significantly more adverse effects (mainly drowsiness) in the benzodiazepine group compared to placebo. Navigante 2006 reported more adverse effects (mainly somnolence) in the morphine group (19/45) compared to midazolam (15/45). Surprisingly, the fewest adverse effects were reported for the combination group (11/45; third arm with midazolam + morphine). The authors defined an adverse effect as clinically relevant with Grade 2 to 4 (Grade 1 mild, 2 moderate, 3 severe, 4 life-threatening - but observed no Grade 4) and examined the highest number in the morphine group (10/16) compared to midazolam (3/16) and midazolam + morphine (3/16). These results were confirmed in the following study (Navigante (unpublished)), which found significantly more adverse effects (mainly somnolence) in the morphine group compared to the midazolam group (see Figure 12; Figure 13).
Regarding adverse effects, a beneficial but not significant effect could be observed in the control group when studies used placebo as a control (Figure 14). Studies comparing midazolam with morphine showed a significant favourable effect for midazolam (Figure 12). Drowsiness and somnolence were mainly reported with a significant difference between intervention and control group when placebo was used as a control (benzodiazepines caused more drowsiness or somnolence) (see Figure 15; Figure 16).

Figure 14. Forest plot of comparison: 5 Secondary outcomes, outcome: 5.1 Adverse effects (placebo-controlled).

Figure 15. Forest plot of comparison: 5 Secondary outcomes, outcome: 5.4 Adverse effects - drowsiness and somnolence only (placebo-controlled).
Exercise tolerance

Only three out of seven studies looked at breathlessness on exercise. Eimer 1985 used a 12-minute walking distance test and Man 1986 a 12-minute walking distance test and bicycle exercise. They did not find any difference between benzodiazepines and placebo regarding exercise tolerance. However, Woodcock 1981 demonstrated a significant impairment in walking distance after 12 minutes in the intervention group compared to placebo, and a non-significant decline in time to exhaustion on treadmill and workload on bicycle ergometer.

Quality of life

None of the included studies studied quality of life.

Attrition (see Data and analyses 5.6 to 5.9)

Regarding attrition, there was no difference between the intervention and control groups, either for the placebo-controlled studies or for the morphine-controlled studies (see Figure 17; Figure 18). Only one study (Shivaram 1989) reported results in favour of the intervention group with four drop-outs in the placebo group mainly due to increasing breathlessness and drowsiness. One study had no attrition, either in the intervention or in the control group (Eimer 1985). One study (Man 1986) reported five drop-outs, but only one drop-out was assigned to the placebo group (unknown adverse effect). The other four drop-outs were missing appointments without assignment to one group. The Harrison (unpublished) study showed twice as many drop-outs in the placebo group (six) as in the intervention group (three). Woodcock 1981 counted twice as many drop-outs but vice versa (intervention: two, placebo: one). The reason for attrition was mainly drowsiness and occurred in the intervention group in both studies. Both drop-outs in Navigante (unpublished) were missing follow ups. Navigante 2006 had a very high attrition rate and all drop-outs were due to death (31 deaths in all three study arms with 101 participants), but without a difference when comparing the three arms. Looking at deaths in all studies, no difference between intervention and control group could be found, either for the placebo-controlled studies or for the morphine-controlled studies (Figure 19; Figure 20).
Figure 18. Forest plot of comparison: 5 Secondary outcomes, outcome: 5.7 Attrition (morphine-controlled).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigation (unpublished) (1)</td>
<td>1</td>
<td>2</td>
<td>10</td>
<td>1 31</td>
</tr>
<tr>
<td>Navigation 2006 (2)</td>
<td>10</td>
<td>33</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>65</td>
<td>66</td>
<td>100.0%</td>
<td>-0.00 [-0.08, 0.08]</td>
</tr>
</tbody>
</table>

Total events: 111

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.99), I² = 0%
Test for overall effect: Z = 0.06 (P = 0.95)

(1) Assessment after five days.
(2) Assessment after 40 hours.

Figure 19. Forest plot of comparison: 5 Secondary outcomes, outcome: 5.8 Deaths (placebo-controlled).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigation (unpublished)</td>
<td>0</td>
<td>13</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>Man 1989</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Shivaram 1999</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>60</td>
<td>60</td>
<td>100.0%</td>
<td>-0.01 [-0.03, 0.00]</td>
</tr>
</tbody>
</table>

Total events: 121

Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 3 (P = 0.43), I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

(1) Assessment after five days.
(2) Assessment after 40 hours.

Figure 20. Forest plot of comparison: 5 Secondary outcomes, outcome: 5.9 Deaths (morphine-controlled).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
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</tr>
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<tr>
<td>Navigation (unpublished) (1)</td>
<td>0</td>
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<td>31</td>
</tr>
<tr>
<td>Navigation 2006 (2)</td>
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<td>33</td>
<td>11</td>
<td>35</td>
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<tr>
<td>Total (95% CI)</td>
<td>65</td>
<td>66</td>
<td>100.0%</td>
<td>-0.00 [-0.08, 0.08]</td>
</tr>
</tbody>
</table>

Total events: 121

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.44), I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)

(1) Assessment after five days.
(2) Assessment after 40 hours.

Others

Blood gases

Only one study reported a slightly but almost significant difference (P = 0.05) in blood gases between alprazolam and placebo (PaO₂ at rest higher and PaCO₂ after exercise lower with placebo) (Man 1986). All other studies which measured oxygen saturation, PaO₂, or PaCO₂ found no significant change from baseline or between intervention and control group (Eimer 1985; Navigante 2006; Navigante (unpublished); Shivaram 1989; Woodcock 1981).

Spirometric tests

Only one study found a slight but almost significant difference (P = 0.05) in spirometric tests with higher levels for FEV₁, TLC (total lung capacity), and FRC (functional residual capacity) in the placebo group (Man 1986). Three other studies measured the functional lung capacity, but did not find any significant change from baseline or between intervention and control group (Eimer 1985; Shivaram 1989; Woodcock 1981).

DISCUSSION

Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Benzodiazepines are widely used drugs in the treatment of breathlessness but very few studies have evaluated their effectiveness. This systematic review concludes, on the basis of seven RCTs including 200 participants, that there is no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness at rest in patients with advanced cancer or chronic obstructive pulmonary disease (COPD). However, this conclusion is based on a small number of studies with a limited number of participants, heterogeneity among included studies, and some inconsistency across the studies. Furthermore, no significant effect could be observed in the prevention of breakthrough dyspnoea in cancer patients. Sensitivity analysis demonstrated no significant differences regarding the type of benzodiazepine, dose, route and frequency of delivery, duration of treatment, or type of control.

The study from Navigante (unpublished) is the only RCT that showed a significant beneficial effect, although it used morphine as a control. This result is surprising, as morphine has been shown to be effective in the relief of breathlessness (Jennings 2001). Furthermore, a study from the same research group (Navigante 2006) demonstrated, in patients with terminal cancer two years earlier, a contrary result with an advantage of morphine over midazolam and best results for the combination of the two drugs. However, the results of the earlier study (Navigante 2006) must be interpreted with caution as there were some methodological difficulties: the authors studied patients with terminal cancer and observed a very high attrition rate due to death (31/101); they allowed rescue medication during the study, therefore all three treatment arms might have included both drugs and a valid differentiation of the effect was not possible without uncertainty. Further studies are needed to examine the comparison between morphine and midazolam and to verify the results of Navigante (unpublished).

Breakthrough dyspnoea (BTD) was only studied in cancer patients and in preventing BTD (no evaluation of the effect in the relief of breakthrough dyspnoea) (Navigante 2006; Navigante (unpublished)). The extent of the beneficial preventative effect of midazolam compared to morphine was larger after 48 hours than after 24 hours, but non-significant at both times (see Figure 8; Figure 21). RCTs assessing the treatment (not prevention) of breakthrough dyspnoea are still missing.
Most studies observed adverse effects. Drowsiness and somnolence were mainly reported with a significantly higher occurrence in the benzodiazepine group, when a placebo was the control. In contrary to the other studies, Shivaram 1989 reported only attrition in the placebo group, caused by increasing breathlessness and drowsiness. These three cases were excluded from analysis. It could be argued that the occurrence of increasing breathlessness only in the placebo group favours the intervention group in the relief of breathlessness and this might have changed their conclusion. Shivaram 1989 argued that this could be a suggestive effect, as participants were told that the treatment might cause increasing breathlessness. However, as only 12 participants were included, it is not possible to judge if this is a random effect.

There was no difference between the intervention and control groups in respect of attrition and deaths, either for the placebo-controlled studies or for the morphine-controlled studies. However, the reporting of drop-outs in cross-over studies was not always sufficient to assess when the drop-out occurred (first or second period of the study), in order to calculate the attrition (Eimer 1985; Harrison (unpublished); Man 1986; Shivaram 1989; Woodcock 1981). Given the small numbers of drop-outs, the potential miscalculation was likely to be small for the present cross-over studies. However, attrition must still be interpreted with caution. Navigante 2006 observed a high attrition rate due to deaths (31/101) without any difference between the three study arms. As mentioned before, all three treatment arms allowed a combination of midazolam and morphine, therefore the high death rate could not be attributed to a single drug. The authors argued that most of the deaths were caused by the underlying advanced disease. This seems to be likely, because they studied patients with terminal cancer and a life expectancy of less than a week. However, a relation between treatment and death could not be entirely excluded because of the relatively high doses of midazolam. Different types of benzodiazepines were tested as well as different doses, long and short-acting drugs, different durations of treatment and modes of administration. However, no differences could be found when conducting sensitivity analysis regarding all these criteria (see Figure 22; Figure 3; Figure 23; Figure 24; Figure 25; Figure 26; Figure 27; Figure 28; Figure 7; Figure 29). Furthermore, different comparators were used: four studies used placebo (Harrison (unpublished); Man 1986; Shivaram 1989; Woodcock 1981) and two studies morphine as a control treatment (Navigante 2006; Navigante (unpublished)). Therefore, we conducted separate meta-analyses for each group with the same control treatment.

Figure 22. Forest plot of comparison: 3 Intervention, outcome: 3.1 Benzodiazepines - alprazolam.
The measurement tools for examining breathlessness in all but one study were validated and frequently used (Eimer 1985).

Overall, this review analysed 200 participants in seven studies, including 33 participants of the third intervention arm of the parallel designed study from Navigante 2006. However, the number of participants in each single study was small (between five to 35 in each comparison group). We intended to evaluate the effect of benzodiazepines in five different disease groups (cancer, COPD, chronic heart failure, motor neurone disease, idiopathic pulmonary fibrosis) but could only identify studies in COPD and cancer. Studies in the other patient groups are also needed.

Six out of seven studies were judged to be of high quality on the Edwards Methods Score (15 or more on the scale) (Edwards 2003). To minimise the risk of bias we excluded one study from the meta-analysis due to lack of quality (Eimer 1985). However, the single-blinding process in two studies (Navigante 2006; Navigante (unpublished)) and the exclusion of drop-outs from analysis increased the risk of bias of all studies. The Edwards Methods Score has previously been used successfully for judging the quality of non-pharmacological interventions (e.g. communication sessions and treatments of breathlessness) (Bausewein 2008; Edwards 2003). Our experience of using the Edwards Methods Score to assess the quality of a pharmacological intervention in this review was good and the tool seemed appropriate with good

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**Figure 27.** Forest plot of comparison: 3 Intervention, outcome: 3.7 Benzodiazepines - short duration of treatment (≤ 24 hours).

<table>
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<th>Experimental Mean</th>
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<th>Total</th>
<th>Control Mean</th>
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<th>Total</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
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<tr>
<td>Navigante (unpublished)</td>
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<td>2.45</td>
<td>31</td>
<td>6.4</td>
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<td>30</td>
<td>-0.78 [-1.16, -0.40]</td>
<td>-</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>4.1</td>
<td>2.21</td>
<td>26</td>
<td>3.9</td>
<td>2.21</td>
<td>29</td>
<td>0.22 [-0.26, 0.71]</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>57</strong></td>
<td></td>
<td></td>
<td><strong>59</strong></td>
<td></td>
<td></td>
<td><strong>-0.36 [-0.74, 0.01]</strong></td>
<td><strong>-</strong></td>
</tr>
</tbody>
</table>

Favours experimental | Favours control

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**Figure 28.** Forest plot of comparison: 3 Intervention, outcome: 3.8 Benzodiazepines - long duration of treatment (5 to 14 days).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
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<th>Std. Mean Difference IV, Fixed, 95% CI</th>
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<td>25.08</td>
<td>17</td>
<td>45.94</td>
<td>25.74</td>
<td>17</td>
<td>0.37 [-0.37, 1.09]</td>
<td>-</td>
</tr>
<tr>
<td>Man 1998</td>
<td>3.0</td>
<td>0.28</td>
<td>24</td>
<td>3.0</td>
<td>0.28</td>
<td>24</td>
<td>0.00 [-0.69, 0.69]</td>
<td>-</td>
</tr>
<tr>
<td>Ghuram 1998</td>
<td>3.63</td>
<td>1.92</td>
<td>8</td>
<td>5.16</td>
<td>2.67</td>
<td>8</td>
<td>0.54 [-0.95, 1.65]</td>
<td>-</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>2.35</td>
<td>1.18</td>
<td>15</td>
<td>4.37</td>
<td>0.88</td>
<td>15</td>
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<td>-</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>84</strong></td>
<td></td>
<td></td>
<td><strong>84</strong></td>
<td></td>
<td></td>
<td><strong>-0.13 [-0.48, 0.22]</strong></td>
<td><strong>-</strong></td>
</tr>
</tbody>
</table>

Favours experimental | Favours control

---

**Figure 29.** Forest plot of comparison: 3 Intervention, outcome: 3.12 Benzodiazepines - promethazine-controlled.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
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<th>Std. Mean Difference IV, Fixed, 95% CI</th>
<th>Std. Mean Difference IV, Fixed, 95% CI</th>
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<tr>
<td>Woodcock 1981</td>
<td>3.33</td>
<td>0.62</td>
<td>33</td>
<td>3.33</td>
<td>0.62</td>
<td>33</td>
<td>0.00 [-0.72, 0.72]</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
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<td></td>
<td></td>
<td><strong>15</strong></td>
<td></td>
<td></td>
<td><strong>0.00 [-0.72, 0.72]</strong></td>
<td><strong>-</strong></td>
</tr>
</tbody>
</table>

Favours experimental | Favours control

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face-validity.

Three excluded studies assessed breathlessness in healthy participants and could not find a beneficial effect of diazepam (Jones 1985; Stark 1981a; Stark 1981b). The trial from Hosaka 1996 was the only study excluded because of the non-advanced disease stage (patients with chronic respiratory insufficiency but lung function tests above our inclusion criteria). This study was also the only non-RCT study but with a high risk of bias. A significant improvement in the relief of breathlessness was seen in the intervention group in change from baseline. However, baseline data between intervention and control group were different. Some other methodological problems in this study (no wash-out phase, breathlessness not primary outcome, sample of participants included a few patients with potentially curable disease) necessitate careful interpretation of results. Apart from this trial, no study was identified which looked at patients with a non-advanced disease stage. Furthermore, we included only RCTs to reduce the risk of bias but expected some uncontrolled trials in this area. Surprisingly, we could only find one uncontrolled study (Greene 1989). This case study reported a beneficial effect of alprazolam in one patient.

We combined cross-over trials and studies with a parallel design in the meta-analysis and treated the cross-over studies as parallel design. We did this after a critical analysis of all studies, review of the literature (Higgins 2008; Elbourne 2002), discussion with a statistician, and the following judgements:

1. the cross-over design was suitable for the targeted research questions;
2. none of the cross-over studies showed evidence of a carry-over effect;
3. drop-outs were excluded from analysis;
4. there was no evidence for a period effect. This approach can produce a unit-of-analysis error.

However, this error leads to a conservative analysis and underweighs the cross-over studies (Higgins 2008). Most cross-over studies did not show an effect of benzodiazepines in the relief of breathlessness. Therefore, this conservative analysis supports our conclusion. In addition, sensitivity analysis showed no difference when analysing the cross-over studies separately (Figure 9; Figure 11).

Two studies presented only median scores for post-treatment measures because of skewed data (Navigante 2006; Navigante (unpublished)). To include these studies in the meta-analysis the mean and standard deviation (SD) was needed. Instead of calculating the mean and SD from the median and range, we followed the advice of the statistician of the Cochrane Review Group and obtained the mean and SD from the raw data provided by the author. With this approach we were able to include these studies in the meta-analysis.

Although we used a broad search strategy we could have missed some unpublished data, such as PhD or Masters theses. However, we identified two unpublished studies through circular mails and personal contact with authors (Harrison (unpublished); Navigante (unpublished)). There is one more study which has not yet been published but we could not obtain the data for our review (Stege (unpublished)).

After little research activity in this field, with a few studies in the 1980s and no studies during the 1990s, the set-up of four trials during the last five years might give some hope for further studies, which are urgently needed.

**Authors’ conclusions**

**Implications for practice**

- There is no evidence for a beneficial effect of benzodiazepines in the relief of breathlessness in patients with advanced cancer and COPD. There is a slight, non-significant trend towards a beneficial effect but the overall effect size is small. Benzodiazepines caused more drowsiness as an adverse effect compared to placebo but less compared to morphine. These results justify considering benzodiazepines as second or third-line treatment within an individual therapeutic trial, when opioids and non-pharmacological measures have failed to control breathlessness. Although a few good quality studies were included in this review, there is still a further need for well-conducted and adequately powered studies in this field.

- There is currently not enough evidence to support the use of benzodiazepines in the prevention of breakthrough dyspnoea in patients with cancer. There are no data from controlled trials for the treatment of breakthrough dyspnoea with benzodiazepines.

- There are no differences regarding the type of benzodiazepine, dose, mode and frequency of administration, and duration of treatment.

**Implications for research**

Although a few good quality studies were included in this review there is still further need for more well-conducted and larger studies in this field. Further research should pay attention to the following issues.

- Larger studies with more participants to reach a statistically sound conclusion are required.

- Studies in chronic heart failure (CHF), motor neurone disease (MND), idiopathic pulmonary fibrosis (IPF), and other life-threatening diseases with breathlessness (e.g. advanced renal failure) are urgently needed.

- Treatment of breakthrough dyspnoea (BTD) has not yet been studied in controlled trials.

- Benzodiazepines in the relief of breathlessness with panic attacks might be worth studying.
ACKNOWLEDGEMENTS

We are grateful to John Plummer (statistician of the Cochrane Review Group) for his very helpful comments and discussions regarding statistical methods and analysis. We are also grateful to Dr Yoshih Shizusawa who helped with the extraction of data from the Japanese paper. Many thanks to Dr Fliss Murtagh for comments on an earlier draft of this review.

The following peer referees contributed feedback to initial drafts of this review: Fiona Cramp, Ollie Minton, and Paul Perkins.

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Anonymous 1980a [published data only]

Anonymous 1980b [published data only]

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Argyropoulou 1993 [published data only]

Bar-Or 1982 [published data only]

Beaupre 1988 [published data only]

Borson 1992 [published data only]

Bottomley 1990 [published data only]

Catchlove 1971 [published data only]

Catchlove 1971a [published data only]

Clark 1971 [published data only]

Anonymous 1980b [published data only]

Appel 1989 [published data only]

Argyropoulou 1993 [published data only]

Bar-Or 1982 [published data only]

Beaupre 1988 [published data only]

Borson 1992 [published data only]

Bottomley 1990 [published data only]

Catchlove 1971 [published data only]
Cohn 1992  [published data only]

De Sousa 1988  [published data only]

Denaun 1974  [published data only]

Dolly 1982  [published data only]

Dowson 2004  [published data only]

Forster 1983  [published data only]

Gaddie 1972  [published data only]

Geddes 1976  [published data only]

Greene 1980  [published data only]

Guilleminault 1993  [published data only]

Guz 1980  [published data only]

Heinonen 1972  [published data only]

Hoeijer 1994  [published data only]

Hofarfar 2006  [published data only]

Hosaka 1996  [published data only]

Huttemann 1971  [published data only]

Johanson 1993  [published data only]

Jokinen 1984  [published data only]

Jolly 1996  [published data only]

Jones 1985  [published data only]

Kann 1968  [published data only]

Kronenberg 1975  [published data only]

Lakshminarayanan 1976  [published data only]

Lareau 1999  [published data only]

Laros 1982  [published data only]

Lichterfeld 1967  [published data only]

Light 1996  [published data only]
Light RW, Stanbury 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.

Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)
Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)

Marin 1987  {published data only}

McIver 1994  {published data only}

Mitchell-Heggs 1980  {published data only}

Mitchell-Heggs 1980a  {published data only}

Murciano 1990  {published data only}
Murciano D, Aubier M, Palacios S, Pariente R. Comparison of zolpidem (Z), triazolam (T), and flunitrazepam (F) effects on arterial blood gases and control of breathing in patients with severe chronic obstructive pulmonary disease (COPD) (abstract). Chest 1990;97:515–525.

Murciano 1993  {published data only}

Navigante 1997  {published data only}

Navigante 2003  {published data only}

Nordt 1997  {published data only}

O’Neill 1985  {published data only}

Rao 1973  {published data only}

Rapport 1991  {published data only}

Rice 1986  {published data only}

Rice 1987  {published data only}

Rose 2002  {published data only}

Rudolf 1978  {published data only}

Runo 2001  {published data only}

Schulze-Werninghaus 2007  {published data only}

Sen 1983  {published data only}

Singh 1993  {published data only}

Stark 1981a  {published data only}

Stark 1981b  {published data only}
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. *Clinical Science* 1981;61:429–39.

**Stark 1983** [published data only]

**Stark 1988** [published data only]

**Steen 1993** [published data only]

**Timms 1988** [published data only]

**Walsh 1993** [published data only]

**Wanrooij 2005** [published data only]

**Wiedemann 1995** [published data only]

**Wilson 1954** [published data only]

**Woodcock 1981a** [published data only]

**Woodcock 1981b** [published data only]

**Stege (unpublished)** [unpublished data only]

**Additional references**

**Abernethy 2008**

**Allen 1984**

**Altose 1985**

**ATS 1999**

**Bausewein 2008**

**Beach 2006**

**Booth 2006**

**Booth 2008**

**Bruera 2008**

**Cranston 2008**

**Davis 1997**

**Davis 2005**

**De Conno 1991**

**Edwards 2000**

**Edwards 2003**
Edwards A, Unigwe S, Elwyn G, Hood K. Personalised risk communication for informed decision making about entering

Elbourne 2002

GOLD 2007

Hardman 2005

Higgins 2008

Higginson 2004

Jennings 2001

Lanken 2008

Manning 1995

Manning 2000

Muers 1993

Neumann 2006

Nordgren 2003

RevMan

Ripamonti 1999

Rocker 2007

Runo 2001

Solano 2006

Thomas 2002

Tobin 1990

Viola 2008

Williams 2006

* Indicates the major publication for the study.
### Characteristics of included studies  [ordered by study ID]

#### Eimer 1985

| Methods | Design: RCT, cross-over, placebo-controlled  
|         | Blinding: double  
|         | Methodological quality: 10/22 (Edwards Methods Score)  
| Participants | Disease: COPD  
|              | Number (randomised): N = 5  
|              | Setting: hospital  
|              | Age (years, mean): not stated (only range: 51 to 68)  
|              | Sex (male/female): 4/1  
|              | Patient pool: 56  
|              | Randomised: 5; study completed: 5  
|              | Withdrawals/drop-outs: 0 (intervention 2 (clorazepate 22.5 mg) with 3 drop-outs - whole intervention excluded from analysis)  
|              | Reason for drop-out (intervention 2): intolerable adverse effects (not mentioned which AE)  
|              | Baseline parameters: FEV1 less than 50%  
|              | SpO2 (mmHg): 65.36; SpCO2 (mmHg): 41.58  
| Interventions | Drug (dose): 1. clorazepate 7.5 mg at bedtime; (2. clorazepate 22.5 mg at bedtime) 3. placebo  
|              | Delivery: oral  
|              | Duration of treatment: 2 weeks  
| Outcomes | Breathlessness grade (1 to 6)  
|          | Results: no significant difference between clorazepate and placebo regarding dyspnoea and walking test (no numbers are given - dyspnoea change only in graphs)  
|          | Adverse effects: none within the 5 patients in intervention 1 and placebo  
|          | SpO2 and SpCO2: no significant change  
| Notes | AUTHOR CONCLUSION: this study failed to demonstrate that placebo or clorazepate consistently relieved breathlessness in non-anxious patients with severe COPD  

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Method not mentioned (&quot;Patients were assigned in a randomised double-blind manner&quot;)</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Unclear</td>
<td>Double-blind stated in the abstract, but not further mentioned</td>
</tr>
</tbody>
</table>
Incomplete outcome data addressed? | Unclear | Not mentioned
--- | --- | ---
Free of selective reporting? | No | Data on anxiety, depression etc. were assessed but not reported
Free of other bias? | No | - Inclusion criteria "severe COPD" not explained (although the results of COPD functions did meet our inclusion criteria)
- No literature/validity regarding dyspnoea grading
- Lack of patient demographics (only gender and range of age)
- Imbalance in male/female (4/1)
- No reasons for exclusion after screening
- Not clearly mentioned that "treatment" means "7.5 mg clorazepate" (conclusion only after a statement, that 22.5 mg-group was excluded because of loss)
- Presentation of results, especially dyspnoea quite difficult and poor
- Only data in a graph presenting "improvement" or "worse" compared to baseline after first and second week of intervention or placebo
- Numbers are only approximate, because it is difficult to read them in the graph

### Harrison (unpublished)

| Methods | Design: RCT, cross-over, placebo-controlled  
| Blinding: double-blind  
| Methodological quality: 18/22 (Edwards Methods Score) |
| Participants | Disease: advanced cancer (12/17 lung cancer)  
| Number (randomised): N = 26  
| Setting: outpatient and inpatient  
| Age (years, SD): 67.2 (8.3)  
| Sex (male/female): 16/1  
| Patient pool: 54  
| Randomised: 26; study completed: 17  
| Withdrawals/drop-outs: 9 (4 drowsiness, 1 deterioration, 1 dysphagia, 2 death, 1 unclear) (excluded from analysis) |
Harrison (unpublished)  *(Continued)*

| Interventions | Drug (dose): lorazepam (0.5 mg twice daily = 1 mg per day)  
Delivery: oral  
Duration of treatment: 5 days (2 days wash-out) |
|----------------|-----------------------------------------------------------------|
| Outcomes | Dyspnoea VAS 0-100 (“How much trouble has your breathing caused you over the last 24 hours?”)  
Results (mean): baseline - after 5 days intervention: 1. (lorazepam) 49.18 to 44.49; 2. (placebo) 48.06 to 45.94  
Adverse effects (number of AE/number with withdrawal): 1. (lorazepam): 5/3; 2 (placebo): 4/1  
No change or differences in anxiety and depression (HADS) |
| Notes | AUTHOR CONCLUSION: there were no differences between lorazepam and placebo in relieving breathlessness |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>“...was randomly determined by computer prior to the study commencement”</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>“A randomisation list was kept by the pharmacy.”</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Study was blinded</td>
</tr>
</tbody>
</table>
| Incomplete outcome data addressed? | Yes | All data were presented  
The study author sent the raw data in addition |
| Free of selective reporting? | Yes | Study protocol is available |
| Free of other bias? | Yes | Yes, study appeared to be free of other bias |

**Man 1986**

| Methods | Design: RCT, cross-over, placebo-controlled  
Blinding: double  
Methodological quality: 16/22 (Edwards Methods Score) |
|----------------|-----------------------------------------------------------------|
| Participants | Disease: COPD  
Number (randomised): N = 29  
Setting: outpatient  
Age (years, mean): 65.4  
Sex (male/female): 16/8 (complete) |
Patient pool: not stated
Randomised: 29; study completed: 24
Withdrawals/drop-outs: 5 (excluded from analysis)
Reason for drop-out: one adverse effect (placebo), 4 missed appointments
Baseline parameters: FEV1/FVC: 54%
SpO2 (mmHg): 73.4; SpCO2 (mmHg): 32.8

### Interventions
Drug (dose): alprazolam 1.0 mg/day (0.5 mg twice daily)
Control: placebo
Delivery: oral
Duration of treatment: 1 week

### Outcomes
Dyspnoea grade at rest (1 to 5); dyspnoea scoring at rest and exercise (VAS 0 to 10)
Results (mean, baseline - after intervention): alprazolam: 3.0 to 3.0; placebo: 3.2 to 3.0
No significant change in dyspnoea scoring during rest and exercise
Adverse effects: 11 reported (7/11 drowsiness), 9/11 on alprazolam
Functional test (12-minute walking test in metres; baseline to after intervention): alprazolam: 896.5 to 880.88; placebo: 902.17 to 931.29
The resting SpO2 was significant higher with placebo and exercising SpCO2 significant lower with placebo

### Notes
AUTHOR CONCLUSION: the subjective perception of dyspnoea was the same before and after alprazolam, at rest and during exercise

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>&quot;...designed as a randomized...” Not mentioned how it was done</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>&quot;double-blind... using alprazolam and matching placebo”</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Labelled bottles with tablets (alprazolam-placebo-washout)described in detailed Probably done</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Unclear</td>
<td>Total screened patients not mentioned</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>No intention-to-treat analysis (5/29 lost were excluded from analysis), however only one with AE (placebo)</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>Broad information available, good summaries, good presentation</td>
</tr>
</tbody>
</table>
Free of other bias? | Yes | Pharmaceutical funding (company with alprazolam)- although negative results

Navigante (unpublished)

| Methods | Design: RCT, parallel, control: morphine  
| Blinding: single-blind (only patient blinded)  
| Methodological quality: 17/22 (Edwards Methods Score) |

| Participants | Disease: advanced cancer  
| Number (randomised): N = 63  
| Setting: outpatient clinic  
| Age (years, median, intervention-group 1/2): 59/55  
| Sex (male/female): not mentioned  
| Patient pool: not mentioned  
| Randomised: 63; study completed: 61*  
| Withdrawals/drop-outs: 2* (not willing to follow up) (excluded from analysis)  
*Data at day 5 for the morphine group were only available for 29 patients, therefore, all calculations at day 5 were done with 29 patients |

| Interventions | Drug (starting dose with titration phase): 1. midazolam 4 x 2 mg; 2. morphine 4 x 3 mg (+ rescue dose)  
| Delivery: oral  
| Duration of treatment: 5 days |

| Outcomes | Dyspnoea intensity: NRS 0 to 10  
| Results presented in unpublished paper: baseline (mean) to after 5 days intervention (median): 1. (midazolam)8.8 to 4; 2. (morphine) 8.7 to 6  
| Mean and CI (95%) for baseline and day 5 measures received from the authors (data skewed): 1. (midazolam)baseline: 8.84 (8.50 to 9.19), day 5: 3.23 (2.51 to 3.94); 2. (morphine) baseline: 8.74 (8.44 to 9.04), day 5: 6.00 (5.31 to 6.09))  
| Percentages of patients with one or more breakthrough dyspnoea episode (baseline to after 5 days): 1. (midazolam)80.6% to 42.0%; 2. (morphine) 83.3% to 75.8%  
| Therapeutic failure: 1. (midazolam): 0%; 2 (morphine): 20%  
| Dose reduction: 1. (midazolam): 1; 2 (morphine): 2  
| Number of patients with 50% reduction of dyspnoea after starting dose (or after second/third step): 1. (midazolam): 21* (9/2*), 2. (morphine): 11 (9/2) (*P < 0.05: compared group of patients taking midazolam and morphine)  
| Adverse effects (number of AE, clinically relevant, all 5 days): 1. (midazolam): 4; 2 (morphine): 11  
| Oxygen saturation: no change in either group |

Notes | AUTHOR CONCLUSION: the data demonstrate the beneficial effect of midazolam versus morphine in the relief of dyspnoea intensity |

Risk of bias
Navigante (unpublished)  
(Continued)

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>“random number generator in 1:1 ratio in blocks of six”</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Not mentioned how it was done</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td>Only single-blind</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>Dyspnoea relief not mentioned, but does not change outcome</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>No indication of selective reporting</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>Other therapies (causes of dyspnoea) parallel, but not distinguished in which group</td>
</tr>
</tbody>
</table>

Navigante 2006

Methods

- Design: RCT, parallel, multi-arm (3), control: morphine and morphine + midazolam
- Blinding: single-blind (only patient blinded)
- Methodological quality: 17/22 (Edwards Methods Score)

Participants

- Disease: terminal cancer (life expectancy less than a week)
- Number (randomised): N = 101
- Setting: hospital inpatient
- Age (years, mean): 57.3
- Sex (male/female): 47/54
- Patient pool: n = 146
- Randomised: 101; study completed: 70
- Withdrawals/drop-outs: 31 (all deaths) (excluded from analysis)

Interventions

- Drug (dose): 1. morphine (Mo - 10 mg/day); 2. midazolam (Mi - 20 mg/day); 3. morphine + midazolam (MM - Mo 10 mg/day + Mi 20 mg/day)
- Rescue dose: 1. Mi 5 mg; 2. Mo 2.5 mg; 3. Mo 2.5 mg (this means that all 3 treatment arms could include a combination of morphine and midazolam)
- Delivery: subcutaneous
- Duration of treatment: 48 hours

Outcomes

- Dyspnoea intensity: modified Borg Scale 0 to 10
- Results presented in the paper: baseline (mean) to after intervention (24/48 hours = median): 1. (Mo) 7.1 - 3/2; 2. (Mi) 6.9 - 4/2; 3. (MM) 6.8 - 3/2 (all results with P < 0.05 versus baseline)
- (Mean and CI (95%) for 24-hour and 48-hour measures received from the authors (data skewed): 1. (Mo) 24 hours: 3.9 (2.8 to 5.0), 48 hours: 2.8 (1.6 to 4.0); 2. (Mi) 24 hours: 4.1 (2.8 to 5.4), 48 hours: 3.1 (1.7 to 4.5); 3. (MM) 24 hours: 3.4 (2.4 to 4.4), 48 hours: 3.0 (2.0 to 4.0))
Percentages of patients with breakthrough dyspnoea (24/48 hours): 1. (Mo) 34.3/38%; 2. (Mi) 36.4/38.5%; 3. (MM) 21.2/24%

Numbers of breakthrough episodes of dyspnoea per patient (24/48 hours): 1. (Mo) 2/2; 2. (Mi) 1/1; 3. (MM) 1/1

Percentages of patients with dyspnoea relief after 24 hours: 1. (Mo) 69%*; 2. (Mi) 46%*; 3. (MM) 92% (*P < 0.05 compare to MM)

Percentages of patients with persistent, uncontrolled dyspnoea after 48h: 1. (Mo) 12.6%; 2. (Mi) 26%*; 3. (MM) 4% (*P < 0.05 compare to MM)

Adverse effects: the most frequently recorded AE was somnolence (Mo > MM > Mi)

Oxygen saturation (mean; baseline to after intervention; 24/48 hours): 1. (Mo) 72% to 72/70%; 2. (Mi) 73% to 70/70%; 3. (MM) 73% to 73/71.5%

Notes

AUTHOR CONCLUSION: the data demonstrate that the beneficial effects of morphine in controlling baseline levels of dyspnoea could be improved with the addition of midazolam to the treatment

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>“... using a random number generator in 1:1:1 ratio in blocks of nine”</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Not mentioned how it was done</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Yes</td>
<td>“Drug administrations were performed in a single-blind fashion.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“One potential limitation of our study is the single-blinded nature of the design. The treating physicians’ knowledge of which schedule of drugs the patient received could influence their need for administering rescue medications. A double-blind design can avoid this, but was considered not appropriate for our study population by the Ethics Committee at our institution. Nevertheless, the risk for underestimation of rescue needs was minimized by a double assessment of breakthrough episodes carried out by caregivers and research physicians.”</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Unclear</td>
<td>45/146 excluded with statement of reasons Attrition (deaths) mentioned clearly Missing data not stated Unclear if patients who experienced relief of dyspnoea was assessed on the whole number of patients or only on patients alive at the end of the study (30% died)</td>
</tr>
<tr>
<td>Item</td>
<td>Authors' judgement</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>Unclear which other symptoms were measured (only anxiety-dyspnoea is reported). Results of ECOG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and MMSE not reported. Dyspnoea relief (only after 24 hours) and uncontrolled dyspnoea (only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>after 48 hours)</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Using cross-over rescue medication (midazolam for the morphine group and vice versa) could</td>
</tr>
<tr>
<td></td>
<td></td>
<td>produce confusion for separate analysis</td>
</tr>
</tbody>
</table>

**Shivaram 1989**

**Methods**
- Design: RCT, cross-over, placebo-controlled
- Blinding: double
- Methodological quality: 15/22 (Edwards Methods Score)

**Participants**
- Disease: COPD
- Number (randomised): N = 12
- Setting: unclear
- Age (years, mean): 64.9
- Sex (male/female): 8/0
- Patient pool: not stated
- Randomised: 12; study completed: 8
- Withdrawals/drop-outs: 4 (excluded from analysis)
- Reason for drop-out: all on placebo (3/4 increasing dyspnoea and drowsiness, 1/4 acute exacerbation)
- Baseline parameters: FEV1/FVC: all less than 65%
  SpO2 (mmHg): 76.0; SpCO2 (mmHg): 38.0

**Interventions**
- Drug (dose): alprazolam 0.75 mg/day (0.25 mg 3 times a day)
- Control: placebo
- Delivery: oral
- Duration of treatment: 2 weeks

**Outcomes**
- Dyspnoea (modified Borg scale 0 to 10)
- Results**: baseline to after intervention: alprazolam: 3.6 to 3.6; placebo: 3.6 to 3.0
  (**not explicitly stated if mean or median, but must be mean because of decimal numbers)
- Adverse effects: none within the 8 patients.
- SpO2 and SpCO2: no significant change

**Notes**
- AUTHOR CONCLUSION: alprazolam did not alter the sensation of breathlessness

**Risk of bias**
### Shivaram 1989  (Continued)

| Adequate sequence generation? | Unclear | “Patients were started on a double-blind, randomized crossover regimen?”
|                              |         | “The patients then received either placebo or alprazolam 0.25 mg in a double-blind fashion.”
|                              |         | Not mentioned how it was done |

| Allocation concealment? | Unclear | Not mentioned how it was done |

| Blinding? All outcomes | Yes | “The medication code was known only to the hospital pharmacist.”
|                       |     | “Patients were started on a double-blind, randomized crossover regimen”
|                       |     | “The patients then received either placebo or alprazolam 0.25 mg in a double-blind fashion.” |

| Incomplete outcome data addressed? All outcomes | Unclear | Described the attrition and the reasons Excluded from analysis, but stated that they did not differ with regard to spirometric measures
|                                                 |       | Demographics only from included patients (8/12)
|                                                 |       | No predicted FEV1 and FVC mentioned |

| Free of selective reporting? | Yes | No indication for selective reporting |

| Free of other bias? | No | Only men (VA Medical Center) |

### Woodcock 1981

**Methods**
- Design: RCT, cross-over, placebo-controlled, multi-arm (3)
- Blinding: double
- Methodological quality: 15/22 (Edwards Methods Score)

**Participants**
- Disease: COPD
- Number (randomised): N = 18
- Setting: outpatient
- Age (years, mean): 60.5
- Sex (male/female): 15/3
- Patient pool: not stated
- Randomised: 18; study completed: 15
- Withdrawals/drop-outs: 3 (excluded from analysis)
- Reason for drop-out: 1 death (diazepam), 1 intolerable drowsiness (diazepam), one hypercapnia (placebo)
- Baseline parameters: FEV1: 25.3%; FEV1/FVC: 0.38
- SpO2 (kPa): 9.5 (= 71.25 mmHg); SpCO2 (kPa): 4.6 (= 34.5 mmHg)
### Interventions

| Drug (dose): | 1. diazepam 25 mg/day (diaz - 5 mg 3 times a day plus 10 mg at bedtime); 2. promethazine 125 mg/day (prom - 25 mg 3 times a day plus 50 mg at bedtime); 3. placebo (plac) |
| Delivery: | oral |
| Duration of treatment: | 2 weeks |

### Outcomes

| Dyspnoea grade (1 to 5) after each intervention and daily dyspnoea by VAS (0 to 10) at rest and after exercise (only by graph) |
| Results (mean): | dyspnoea grade: 1. 3.46 (diaz); 2. 3.29* (prom); 3. 4.00 (plac) (*P < 0.05) |
| Adverse effects (6 - reduce dosage): | all drowsiness: 5/6 diazepam; 1/6 promethazine - 5/5 drowsiness incidents (like falling down stairs) with diazepam |
| Functional test (12-minute walking test in metres): | 1. 642* (diaz); 2. 707* (prom); 3. 675 (plac) (*P < 0.05) |
| SpO2 and SpCO2: | no significant change |

### Notes

AUTHOR CONCLUSION: diazepam had no significant effect on breathlessness and noticeably reduced exercise tolerance. Promethazine reduced breathlessness and improved exercise tolerance without altering lung function. REVIEWER: however, there is a beneficial effect of diazepam, although not significant.

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>“The treatment were given in a randomized order.” Not mentioned how it was done</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Blinding? All outcomes</td>
<td>Yes</td>
<td>“Double-blind” procedure was described</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? All outcomes</td>
<td>Yes</td>
<td>Although 3/18 patients were lost and excluded from the analysis, they would underline the presented results rather than bias them</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear</td>
<td>All main outcomes are presented in detail. The effect of diazepam in the relief of breathlessness is nearly statistically significant, but was discussed as “diazepam had no effect on breathlessness”</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>Unclear</td>
<td>It is not exactly stated if a wash-out phase was used (on contacting the author: there was no wash-out)</td>
</tr>
</tbody>
</table>
Woodcock 1981  (Continued)

Results of compliance test are not mentioned
Screening method and numbers are not mentioned

AE = adverse effects; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; MM = midazolam; MO = morphine; NRS = numeric rating scale; RCT = randomised controlled trial; VAS = visual analogue scale

Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen 1984</td>
<td>Review</td>
</tr>
<tr>
<td>Anonymous 1980a</td>
<td>Review</td>
</tr>
<tr>
<td>Anonymous 1980b</td>
<td>Review</td>
</tr>
<tr>
<td>Appel 1989</td>
<td>No subjective measurement of breathlessness; different drug (flumazenil)</td>
</tr>
<tr>
<td>Argyropoulou 1993</td>
<td>Different drug (buspirone)</td>
</tr>
<tr>
<td>Bar-Or 1982</td>
<td>Review</td>
</tr>
<tr>
<td>Beaupre 1988</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Borson 1992</td>
<td>Different drug (nortriptyline)</td>
</tr>
<tr>
<td>Bottomley 1990</td>
<td>No subjective measurement of breathlessness; observational design</td>
</tr>
<tr>
<td>Catchlove 1971</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Catchlove 1971a</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Author</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Clark 1971</td>
<td>No subjective measurement of breathlessness; case series</td>
</tr>
<tr>
<td>Cohn 1992</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>De Sousa 1988</td>
<td>No subjective measurement of breathlessness; letter/observational design</td>
</tr>
<tr>
<td>Denaut 1974</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Dolly 1982</td>
<td>No subjective measurement of breathlessness; healthy subjects</td>
</tr>
<tr>
<td>Dowson 2004</td>
<td>Review</td>
</tr>
<tr>
<td>Forster 1983</td>
<td>No subjective measurement of breathlessness; healthy participants</td>
</tr>
<tr>
<td>Gaddie 1972</td>
<td>Review</td>
</tr>
<tr>
<td>Geddes 1976</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Greene 1989</td>
<td>No controlled experimental study (case report)</td>
</tr>
<tr>
<td>Guilleminault 1993</td>
<td>No subjective measurement of breathlessness; observational design</td>
</tr>
<tr>
<td>Gutz 1980</td>
<td>Review</td>
</tr>
<tr>
<td>Heinonen 1972</td>
<td>No subjective measurement of breathlessness; sedation for artificial ventilation</td>
</tr>
<tr>
<td>Hoeijer 1994</td>
<td>No subjective measurement of breathlessness; different disease (sleep apnoea)</td>
</tr>
<tr>
<td>Horfarter 2006</td>
<td>Review</td>
</tr>
<tr>
<td>Hosaka 1996</td>
<td>Non-advanced disease stage; a few patients with a different disease (asthma, tuberculosis)</td>
</tr>
<tr>
<td>Huttemann 1971</td>
<td>Different drug (laevomepromazine)</td>
</tr>
<tr>
<td>Johanson 1993</td>
<td>Review</td>
</tr>
<tr>
<td>Jokinen 1984</td>
<td>Different disease (psychosomatic disorder)</td>
</tr>
<tr>
<td>Jolly 1996</td>
<td>No subjective measurement of breathlessness; observational design</td>
</tr>
<tr>
<td>Jones 1985</td>
<td>Different disease (healthy subjects)</td>
</tr>
<tr>
<td>Kann 1968</td>
<td>Review</td>
</tr>
<tr>
<td>Kronenber 1975</td>
<td>No subjective measurement of breathlessness; observational design</td>
</tr>
<tr>
<td>Lakshminarayan 1976</td>
<td>No subjective measurement of breathlessness; healthy subjects</td>
</tr>
<tr>
<td>Reference</td>
<td>Details</td>
</tr>
<tr>
<td>-----------</td>
<td>---------</td>
</tr>
<tr>
<td>Lareau 1999</td>
<td>No drug intervention (secondary analysis)</td>
</tr>
<tr>
<td>Laros 1982</td>
<td>No subjective measurement of breathlessness; case report; no benzodiazepine</td>
</tr>
<tr>
<td>Lichterfeld 1967</td>
<td>Benzodiazepine only in combination (oxazepam + orciprenaline)</td>
</tr>
<tr>
<td>Light 1996</td>
<td>Different drug (promethazine)</td>
</tr>
<tr>
<td>Marin 1987</td>
<td>No drug intervention (retrospective study)</td>
</tr>
<tr>
<td>McIver 1994</td>
<td>Different drug (chlorpromazine)</td>
</tr>
<tr>
<td>Mitchell-Heggs 1980</td>
<td>No subjective measurement of breathlessness; no control group; no standardized or systematic design</td>
</tr>
<tr>
<td>Mitchell-Heggs 1980a</td>
<td>No drug intervention</td>
</tr>
<tr>
<td>Murciano 1990</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Murciano 1993</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Navigante 1997</td>
<td>Benzodiazepine only in combination (midazolam + morphine)</td>
</tr>
<tr>
<td>Navigante 2003</td>
<td>Benzodiazepine only in combination (midazolam + morphine)</td>
</tr>
<tr>
<td>Nordt 1997</td>
<td>Review</td>
</tr>
<tr>
<td>O’Donnell 1992</td>
<td>No drug intervention (observational study)</td>
</tr>
<tr>
<td>O’Donnell 1994</td>
<td>Review</td>
</tr>
<tr>
<td>O’Donnell 1998</td>
<td>Review</td>
</tr>
<tr>
<td>O’Neill 1985</td>
<td>Different drug (chlorpromazine)</td>
</tr>
<tr>
<td>Rao 1973</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Rapoport 1991</td>
<td>No subjective measurement of breathlessness; healthy subjects</td>
</tr>
<tr>
<td>Rice 1986</td>
<td>Review</td>
</tr>
<tr>
<td>Rice 1987</td>
<td>Different drug (promethazine)</td>
</tr>
<tr>
<td>Rose 2002</td>
<td>Review</td>
</tr>
<tr>
<td>Rudolf 1978</td>
<td>No subjective measurement of breathlessness</td>
</tr>
<tr>
<td>Runo 2001</td>
<td>Review</td>
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</table>
### Characteristics of studies awaiting assessment  
**[ordered by study ID]**

#### Stege (unpublished)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised controlled trial, placebo-controlled, double-blind, cross-over design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>COPD patients, GOLD III or IV, with subjective sleeping problems</td>
</tr>
<tr>
<td>Interventions</td>
<td>Temazepam 10 mg during 7 consecutive nights</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: transcutaneous pCO2 and pO2, oxygen saturation. Secondary: (amongst others): dyspnoea visual analogue score</td>
</tr>
</tbody>
</table>
### Notes

Collection of data is complete and the manuscript has been submitted for publication (personal contact with primary investigator)  
See ClinicalTrials.gov identifier: NCT00245661
### DATA AND ANALYSES

#### Comparison 1. Overall

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Placebo-controlled/cross-over design</td>
<td>4</td>
<td>128</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.13 [-0.52, 0.25]</td>
</tr>
<tr>
<td>2 Morphine-controlled/parallel design</td>
<td>2</td>
<td>107</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.68 [-2.21, 0.84]</td>
</tr>
</tbody>
</table>

#### Comparison 2. Disease

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 COPD</td>
<td>3</td>
<td>94</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.16 [-0.73, 0.40]</td>
</tr>
<tr>
<td>2 Cancer - placebo-controlled</td>
<td>1</td>
<td>34</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.06 [-0.73, 0.62]</td>
</tr>
<tr>
<td>3 Cancer - morphine-controlled</td>
<td>2</td>
<td>107</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.68 [-2.21, 0.84]</td>
</tr>
</tbody>
</table>

#### Comparison 3. Intervention

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Benzodiazepines - alprazolam</td>
<td>2</td>
<td>64</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>0.08 [-0.41, 0.57]</td>
</tr>
<tr>
<td>2 Benzodiazepines - diazepam</td>
<td>1</td>
<td>30</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.72 [-1.46, 0.02]</td>
</tr>
<tr>
<td>3 Benzodiazepines - midazolam</td>
<td>2</td>
<td>107</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.68 [-2.21, 0.84]</td>
</tr>
<tr>
<td>4 Benzodiazepines - ultra short-acting</td>
<td>2</td>
<td>107</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>-0.68 [-2.21, 0.84]</td>
</tr>
<tr>
<td>5 Benzodiazepines - intermediate-acting</td>
<td>3</td>
<td>98</td>
<td>Std. Mean Difference (IV, Random, 95% CI)</td>
<td>0.03 [-0.36, 0.43]</td>
</tr>
<tr>
<td>6 Benzodiazepines - long-acting</td>
<td>1</td>
<td>30</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.72 [-1.46, 0.02]</td>
</tr>
<tr>
<td>7 Benzodiazepines - short duration of treatment (≤ 24 hours)</td>
<td>2</td>
<td>116</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.36 [-0.74, 0.01]</td>
</tr>
<tr>
<td>8 Benzodiazepines - long duration of treatment (5 to 14 days)</td>
<td>4</td>
<td>128</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.13 [-0.48, 0.22]</td>
</tr>
<tr>
<td>9 Benzodiazepines - morphine-midazolam-controlled</td>
<td>1</td>
<td>46</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.03 [-0.54, 0.61]</td>
</tr>
<tr>
<td>10 Benzodiazepines - promethazine-controlled</td>
<td>1</td>
<td>30</td>
<td>Std. Mean Difference (IV, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>
### Comparison 4. Primary outcome

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Breathlessness - no relief (placebo-controlled)</td>
<td>2</td>
<td>50</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.88 [0.56, 1.39]</td>
</tr>
<tr>
<td>2 Breathlessness - no relief (morphine-controlled)</td>
<td>1</td>
<td>55</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.74 [0.91, 3.32]</td>
</tr>
<tr>
<td>3 Breathlessness - breakthrough (BTD) after 48 hours</td>
<td>2</td>
<td>108</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.76 [0.53, 1.09]</td>
</tr>
<tr>
<td>4 Breathlessness - breakthrough (BTD) after 24 hours</td>
<td>2</td>
<td>116</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>0.97 [0.71, 1.34]</td>
</tr>
</tbody>
</table>

### Comparison 5. Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Adverse effects (placebo-controlled)</td>
<td>4</td>
<td>66</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>0.44 [-0.06, 0.94]</td>
</tr>
<tr>
<td>2 Adverse effects (morphine-controlled)</td>
<td>2</td>
<td>192</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.19 [-0.33, -0.05]</td>
</tr>
<tr>
<td>3 Adverse effects - clinical relevance only (morphine-controlled)</td>
<td>2</td>
<td>54</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.49 [-0.72, -0.25]</td>
</tr>
<tr>
<td>4 Adverse effects - drowsiness and somnolence only (placebo-controlled)</td>
<td>3</td>
<td>38</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>0.74 [0.37, 1.11]</td>
</tr>
<tr>
<td>5 Adverse effects - drowsiness and somnolence only (morphine controlled)</td>
<td>2</td>
<td>122</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.07 [-0.30, 0.16]</td>
</tr>
<tr>
<td>6 Attrition (placebo-controlled)</td>
<td>3</td>
<td>112</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.11 [-0.32, 0.10]</td>
</tr>
<tr>
<td>7 Attrition (morphine-controlled)</td>
<td>2</td>
<td>131</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.06 [-0.08, 0.08]</td>
</tr>
<tr>
<td>8 Deaths (placebo-controlled)</td>
<td>4</td>
<td>120</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>-0.01 [-0.06, 0.05]</td>
</tr>
<tr>
<td>9 Deaths (morphine-controlled)</td>
<td>2</td>
<td>131</td>
<td>Risk Difference (M-H, Random, 95% CI)</td>
<td>Not estimable</td>
</tr>
</tbody>
</table>
## Analysis 1.1. Comparison 1 Overall, Outcome 1 Placebo-controlled/cross-over design.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 1 Overall

Outcome: 1 Placebo-controlled/cross-over design

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison (unpublished)</td>
<td>17</td>
<td>44.49 (25.06)</td>
<td>17</td>
<td>45.94 (25.74)</td>
<td>27.2 %</td>
</tr>
<tr>
<td>Man 1986</td>
<td>24</td>
<td>3 (0.8)</td>
<td>24</td>
<td>3 (0.8)</td>
<td>36.0 %</td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>8</td>
<td>3.63 (1.92)</td>
<td>8</td>
<td>3 (1.6)</td>
<td>13.8 %</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>15</td>
<td>3.33 (1.11)</td>
<td>15</td>
<td>4.07 (0.88)</td>
<td>23.0 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>64</td>
<td>64</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.02; \chi^2 = 3.53, df = 3 (P = 0.32); I^2 = 15\%$

Test for overall effect: $Z = 0.69 (P = 0.49)$

## Analysis 1.2. Comparison 1 Overall, Outcome 2 Morphine-controlled/parallel design.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 1 Overall

Outcome: 2 Morphine-controlled/parallel design

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>31</td>
<td>3.2 (1.93)</td>
<td>29</td>
<td>6 (1.83)</td>
<td>50.0 %</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>23</td>
<td>3.1 (3.26)</td>
<td>24</td>
<td>2.8 (2.84)</td>
<td>50.0 %</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>54</td>
<td>53</td>
<td></td>
<td></td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.13; \chi^2 = 14.17, df = 1 (P = 0.00017); I^2 = 93\%$

Test for overall effect: $Z = 0.88 (P = 0.38)$
Analysis 2.1. Comparison 2 Disease, Outcome 1 COPD.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 2 Disease
Outcome: 1 COPD

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean(SD)</td>
<td>N  Mean(SD)</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Man 1986</td>
<td>24  3 (0.8)</td>
<td>24  3 (0.8)</td>
<td>43.8 %</td>
<td>0.0 [ -0.57, 0.57 ]</td>
<td></td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>8   3.63 (1.92)</td>
<td>8   3 (1.6)</td>
<td>23.0 %</td>
<td>0.34 [ 0.05, 1.33 ]</td>
<td></td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>15  3.33 (1.11)</td>
<td>15  4.07 (0.88)</td>
<td>33.2 %</td>
<td>-0.72 [-1.46, 0.02]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>47  47</td>
<td>100.0 %</td>
<td>-0.16 [-0.73, 0.40]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.11; \) \( \chi^2 = 3.46, \) df = 2 (P = 0.18); \( I^2 = 42\% \)
Test for overall effect: \( Z = 0.56 \) (P = 0.57)

Analysis 2.2. Comparison 2 Disease, Outcome 2 Cancer - placebo-controlled.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 2 Disease
Outcome: 2 Cancer - placebo-controlled

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Mean(SD)</td>
<td>N  Mean(SD)</td>
<td>IV, Random, 95% CI</td>
<td></td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Harrison (unpublished)</td>
<td>17  44.49 (25.06)</td>
<td>17  45.94 (25.74)</td>
<td>100.0 %</td>
<td>-0.06 [-0.73, 0.62]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>17  17</td>
<td>100.0 %</td>
<td>-0.06 [-0.73, 0.62]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: \( Z = 0.16 \) (P = 0.87)
Analysis 2.3. Comparison 2 Disease, Outcome 3 Cancer - morphine-controlled.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 2 Disease

Outcome: 3 Cancer - morphine-controlled

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Navigante (unpublished)</td>
<td>31</td>
<td>3.2 (1.95)</td>
<td>29</td>
<td>6 (1.83)</td>
<td>50.0%</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>23</td>
<td>3.1 (3.26)</td>
<td>24</td>
<td>2.8 (2.84)</td>
<td>50.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>53</td>
<td>100.0%</td>
<td>-0.68 [-2.21, 0.84]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.13; \chi^2 = 14.17, df = 1 (P = 0.00017); I^2 = 93%$
Test for overall effect: $Z = 0.88 (P = 0.38)$

Analysis 3.1. Comparison 3 Intervention, Outcome 1 Benzodiazepines - alprazolam.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 1 Benzodiazepines - alprazolam

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Man 1986</td>
<td>24</td>
<td>3 (0.8)</td>
<td>24</td>
<td>3 (0.8)</td>
<td>75.3%</td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>8</td>
<td>3.63 (1.92)</td>
<td>8</td>
<td>3 (1.6)</td>
<td>24.7%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>32</td>
<td>32</td>
<td>100.0%</td>
<td>0.08 [-0.41, 0.57]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.34, df = 1 (P = 0.56); I^2 = 0.0%$
Test for overall effect: $Z = 0.33 (P = 0.74)$
### Analysis 3.2. Comparison 3 Intervention, Outcome 2 Benzodiazepines - diazepam.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 2 Benzodiazepines - diazepam

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodcock 1981</td>
<td>15 3.33 (1.11)</td>
<td>15 4.07 (0.88)</td>
<td>IV, Fixed, 95% CI</td>
<td>100.0%</td>
<td>-0.72 [-1.46, 0.02]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td>15</td>
<td>IV, Fixed, 95% CI</td>
<td>100.0%</td>
<td>-0.72 [-1.46, 0.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.90 (P = 0.058)

<table>
<thead>
<tr>
<th>Favours experimental</th>
<th>Favours control</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>-1</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

### Analysis 3.3. Comparison 3 Intervention, Outcome 3 Benzodiazepines - midazolam.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 3 Benzodiazepines - midazolam

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>31 3.2 (1.95)</td>
<td>29 6 (1.83)</td>
<td>IV, Random, 95% CI</td>
<td>50.0%</td>
<td>-1.46 [-2.03, -0.89]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>23 3.1 (3.26)</td>
<td>24 2.8 (2.84)</td>
<td>IV, Random, 95% CI</td>
<td>50.0%</td>
<td>0.10 [-0.48, 0.67]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>53</td>
<td>IV, Random, 95% CI</td>
<td>100.0%</td>
<td>-0.68 [-2.21, 0.84]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.13; \chi^2 = 14.17, df = 1 (P = 0.00017); I^2 = 93%$

Test for overall effect: Z = 0.88 (P = 0.38)
### Analysis 3.4. Comparison 3 Intervention, Outcome 4 Benzodiazepines - ultra short-acting.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 4 Benzodiazepines - ultra short-acting

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Navigante (unpublished)</td>
<td>31</td>
<td>29</td>
<td>3.2 (1.95)</td>
<td>50.0 %</td>
<td>-1.46 [-2.03, -0.89 ]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>23</td>
<td>24</td>
<td>3.1 (3.26)</td>
<td>50.0 %</td>
<td>0.10 [-0.48, 0.67 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>53</td>
<td></td>
<td>100.0 %</td>
<td>-0.68 [-2.21, 0.84 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.13; \chi^2 = 14.17, df = 1 (P = 0.00017); I^2 = 93\%$

Test for overall effect: $Z = 0.88 (P = 0.38)$

---

### Analysis 3.5. Comparison 3 Intervention, Outcome 5 Benzodiazepines - intermediate-acting.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Benzodiazepines - intermediate-acting

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Random,95% CI</td>
<td>IV,Random,95% CI</td>
</tr>
<tr>
<td>Harrison (unpublished)</td>
<td>17</td>
<td>17</td>
<td>44.49 (25.06)</td>
<td>34.8 %</td>
<td>-0.06 [-0.73, 0.62 ]</td>
</tr>
<tr>
<td>Man 1986</td>
<td>24</td>
<td>24</td>
<td>3 (0.8)</td>
<td>49.1 %</td>
<td>0.0 [ -0.57, 0.57 ]</td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>8</td>
<td>8</td>
<td>3.63 (1.92)</td>
<td>16.1 %</td>
<td>0.34 [-0.65, 1.33 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>49</td>
<td>49</td>
<td></td>
<td>100.0 %</td>
<td>0.03 [-0.36, 0.43 ]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0; \chi^2 = 0.44, df = 2 (P = 0.80); I^2 = 0.0\%$

Test for overall effect: $Z = 0.17 (P = 0.86)$
### Analysis 3.6. Comparison 3 Intervention, Outcome 6 Benzodiazepines - long-acting.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 6 Benzodiazepines - long-acting

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>NFixed,95% CI</td>
<td>NFixed,95% CI</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>15 3.33 (1.11)</td>
<td>15 4.07 (0.88)</td>
<td>100.0 %</td>
<td>-0.72</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15</td>
<td>15</td>
<td>100.0 %</td>
<td>-0.72 [-1.46, 0.02]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 1.90 (P = 0.058)

### Analysis 3.7. Comparison 3 Intervention, Outcome 7 Benzodiazepines - short duration of treatment (<24 hours).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 7 Benzodiazepines - short duration of treatment (<24 hours)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td>NFixed,95% CI</td>
<td>NFixed,95% CI</td>
</tr>
<tr>
<td>Navigante (unpublished)</td>
<td>31 4.6 (2.45)</td>
<td>30 6.4 (2.08)</td>
<td>50.7 %</td>
<td>-0.78 [-1.30, -0.26]</td>
<td></td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>26 4.1 (3.21)</td>
<td>29 3.9 (2.91)</td>
<td>49.3 %</td>
<td>0.06 [-0.46, 0.59]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>57</td>
<td>59</td>
<td>100.0 %</td>
<td>-0.36 [-0.74, 0.01]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chisq = 4.97, df = 1 (P = 0.03); I^2 =80%

Test for overall effect: Z = 1.92 (P = 0.055)
Analysis 3.8. Comparison 3 Intervention, Outcome 8 Benzodiazepines - long duration of treatment (5 to 14 days).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 8 Benzodiazepines - long duration of treatment (5 to 14 days)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Harrison (unpublished)</td>
<td>17</td>
<td>44.49 (25.06)</td>
<td>17</td>
<td>45.94 (25.74)</td>
<td>27.1 %</td>
</tr>
<tr>
<td>Man 1986</td>
<td>24</td>
<td>3 (0.8)</td>
<td>24</td>
<td>3 (0.8)</td>
<td>38.2 %</td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>8</td>
<td>3.63 (1.92)</td>
<td>8</td>
<td>3 (1.6)</td>
<td>12.5 %</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>15</td>
<td>3.33 (1.11)</td>
<td>15</td>
<td>4.07 (0.88)</td>
<td>22.2 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 64 64 100.0 % -0.13 [ -0.48, 0.22 ]

Heterogeneity: $\chi^2 = 3.53$, df = 3 ($p = 0.32$); $I^2 = 15$

Test for overall effect: $Z = 0.74$ ($p = 0.46$)

Analysis 3.9. Comparison 3 Intervention, Outcome 9 Benzodiazepines - morphine+midazolam-controlled.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 3 Intervention

Outcome: 9 Benzodiazepines - morphine+midazolam-controlled

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV, Fixed, 95% CI</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>23</td>
<td>3.1 (3.26)</td>
<td>23</td>
<td>3 (2.3)</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 23 23 100.0 % 0.03 [ -0.54, 0.61 ]

Heterogeneity: not applicable

Test for overall effect: $Z = 0.12$ ($p = 0.91$)
### Analysis 3.10. Comparison 3 Intervention, Outcome 10 Benzodiazepines - promethazine-controlled.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: Intervention

Outcome: 10 Benzodiazepines - promethazine-controlled

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>IV,Fixed, 95% CI</td>
<td></td>
<td>IV,Fixed, 95% CI</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>15 3.33 (1.11)</td>
<td>15 3.33 (0.62)</td>
<td>100.0 %</td>
<td>0.0 [ -0.72, 0.72 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>15 15</td>
<td>100.0 %</td>
<td>0.0 [ -0.72, 0.72 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)

### Analysis 4.1. Comparison 4 Primary outcome, Outcome 1 Breathlessness - no relief (placebo-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: Primary outcome

Outcome: 1 Breathlessness - no relief (placebo-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Harrison (unpublished)</td>
<td>9/17</td>
<td>11/17</td>
<td>64.0 %</td>
<td>0.82 [ 0.46, 1.45 ]</td>
<td></td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>5/8</td>
<td>5/8</td>
<td>36.0 %</td>
<td>1.00 [ 0.47, 2.14 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>25 25</td>
<td>100.0 %</td>
<td>0.88 [ 0.56, 1.39 ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 14 (Experimental), 16 (Control)
Heterogeneity: Tau$^2$ = 0.0, Chi$^2$ = 0.17, df = 1 (P = 0.68); I$^2$ =0.0%
Test for overall effect: Z = 0.55 (P = 0.58)
Analysis 4.2. Comparison 4 Primary outcome, Outcome 2 Breathlessness - no relief (morphine-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 4 Primary outcome

Outcome: 2 Breathlessness - no relief (morphine-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante 2006</td>
<td>14/26</td>
<td>9/29</td>
<td>1.74 [0.91, 3.32]</td>
<td>100.0%</td>
<td>1.74 [0.91, 3.32]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>26</td>
<td>29</td>
<td>100.0%</td>
<td>1.74 [0.91, 3.32]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 14 (Experimental), 9 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.66 (P = 0.096)

Analysis 4.3. Comparison 4 Primary outcome, Outcome 3 Breathlessness - breakthrough (BTD) after 48 hours.

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 4 Primary outcome

Outcome: 3 Breathlessness - breakthrough (BTD) after 48 hours

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>15/31</td>
<td>21/30</td>
<td>0.69 [0.45, 1.07]</td>
<td>68.5%</td>
<td>0.69 [0.45, 1.07]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>10/23</td>
<td>11/24</td>
<td>0.95 [0.50, 1.79]</td>
<td>31.5%</td>
<td>0.95 [0.50, 1.79]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>54</td>
<td>100.0%</td>
<td>0.76 [0.53, 1.09]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 25 (Experimental), 32 (Control)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.66, df = 1 (P = 0.42); I^2 = 0.0%
Test for overall effect: Z = 1.48 (P = 0.14)
**Analysis 4.4. Comparison 4 Primary outcome, Outcome 4: Breathlessness - breakthrough (BTD) after 24 hours.**

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 4 Primary outcome

Outcome: 4 Breathlessness - breakthrough (BTD) after 24 hours

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>19/31</td>
<td>20/30</td>
<td>71.7 %</td>
<td>0.92 [0.63, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>12/26</td>
<td>12/29</td>
<td>28.3 %</td>
<td>1.12 [0.61, 2.03]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>57</strong></td>
<td><strong>59</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.97 [0.71, 1.34]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 31 (Experimental), 32 (Control)

Heterogeneity: $\tau^2 = 0.0$; $\chi^2 = 0.30$, df = 1 ($P = 0.58$); $I^2 = 0.0$

Test for overall effect: $Z = 0.18$ ($P = 0.86$)

**Analysis 5.1. Comparison 5 Secondary outcomes, Outcome 1: Adverse effects (placebo-controlled).**

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 1 Adverse effects (placebo-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Difference M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Difference M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison (unpublished)</td>
<td>5/9</td>
<td>4/9</td>
<td>22.7 %</td>
<td>0.11 [-0.35, 0.57]</td>
<td></td>
</tr>
<tr>
<td>Man 1986</td>
<td>9/11</td>
<td>2/11</td>
<td>25.2 %</td>
<td>0.64 [0.31, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>0/8</td>
<td>0/8</td>
<td>26.8 %</td>
<td>0.0 [-0.21, 0.21]</td>
<td></td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>5/5</td>
<td>0/5</td>
<td>25.3 %</td>
<td>1.00 [0.69, 1.31]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>33</strong></td>
<td><strong>33</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.44 [-0.06, 0.94]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 19 (Experimental), 6 (Control)

Heterogeneity: $\tau^2 = 0.23$; $\chi^2 = 31.37$, df = 3 ($P < 0.00001$); $I^2 = 90$

Test for overall effect: $Z = 1.71$ ($P = 0.087$)
Analysis 5.2. Comparison 5 Secondary outcomes, Outcome 2 Adverse effects (morphine-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 2 Adverse effects (morphine-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>24/62</td>
<td>38/62</td>
<td>-0.23 [-0.40, -0.05]</td>
<td>65.5 %</td>
<td>-0.23 [-0.40, -0.05]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>15/34</td>
<td>19/34</td>
<td>-0.12 [-0.35, 0.12]</td>
<td>34.5 %</td>
<td>-0.12 [-0.35, 0.12]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>96</td>
<td>96</td>
<td>-0.19 [-0.33, -0.05]</td>
<td>100.0 %</td>
<td>-0.19 [-0.33, -0.05]</td>
</tr>
</tbody>
</table>

Total events: 39 (Experimental), 57 (Control)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =0.0%
Test for overall effect: Z = 2.66 (P = 0.0078)

-1 -0.5 0 0.5 1
Favours experimental Favours control

Analysis 5.3. Comparison 5 Secondary outcomes, Outcome 3 Adverse effects - clinical relevance only (morphine-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 3 Adverse effects - clinical relevance only (morphine-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>4/14</td>
<td>10/14</td>
<td>-0.43 [-0.76, -0.09]</td>
<td>48.4 %</td>
<td>-0.43 [-0.76, -0.09]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>3/13</td>
<td>10/13</td>
<td>-0.54 [-0.86, -0.21]</td>
<td>51.6 %</td>
<td>-0.54 [-0.86, -0.21]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>27</td>
<td>27</td>
<td>-0.49 [-0.72, -0.25]</td>
<td>100.0 %</td>
<td>-0.49 [-0.72, -0.25]</td>
</tr>
</tbody>
</table>

Total events: 7 (Experimental), 20 (Control)
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.21, df = 1 (P = 0.64); I^2 =0.0%
Test for overall effect: Z = 4.09 (P = 0.000044)
Analysis 5.4. Comparison 5 Secondary outcomes, Outcome 4 Adverse effects - drowsiness and somnolence only (placebo-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 4 Adverse effects - drowsiness and somnolence only (placebo-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harrison (unpublished)</td>
<td>4/6</td>
<td>2/6</td>
<td>24.9 %</td>
<td>0.33</td>
<td>[-0.20, 0.87]</td>
</tr>
<tr>
<td>Man 1986</td>
<td>7/8</td>
<td>1/8</td>
<td>37.2 %</td>
<td>0.75</td>
<td>[0.43, 1.07]</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>5/5</td>
<td>0/5</td>
<td>37.9 %</td>
<td>1.00</td>
<td>[0.69, 1.31]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>19</strong></td>
<td><strong>19</strong></td>
<td>100.0 %</td>
<td><strong>0.74</strong></td>
<td><strong>[0.37, 1.11]</strong></td>
</tr>
</tbody>
</table>

Total events: 16 (Experimental), 3 (Control)
Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 5.74$, df = 2 ($P = 0.06$); $I^2 = 65$
Test for overall effect: $Z = 3.94$ ($P = 0.000082$)

Analysis 5.5. Comparison 5 Secondary outcomes, Outcome 5 Adverse effects - drowsiness and somnolence only (morphine controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 5 Adverse effects - drowsiness and somnolence only (morphine controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental n/N</th>
<th>Control n/N</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navigante (unpublished)</td>
<td>22/43</td>
<td>21/43</td>
<td>62.3 %</td>
<td>0.02</td>
<td>[-0.19, 0.23]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>7/18</td>
<td>11/18</td>
<td>37.7 %</td>
<td>-0.22</td>
<td>[-0.54, 0.10]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>61</strong></td>
<td><strong>61</strong></td>
<td>100.0 %</td>
<td><strong>-0.07</strong></td>
<td><strong>[-0.30, 0.16]</strong></td>
</tr>
</tbody>
</table>

Total events: 29 (Experimental), 32 (Control)
Heterogeneity: $\tau^2 = 0.01$; $\chi^2 = 1.59$, df = 1 ($P = 0.21$); $I^2 = 37$
Test for overall effect: $Z = 0.58$ ($P = 0.56$)
### Analysis 5.6. Comparison 5 Secondary outcomes, Outcome 6 Attrition (placebo-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 6 Attrition (placebo-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N n/N</td>
<td></td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Harrison (unpublished)</td>
<td>3/26</td>
<td>6/26</td>
<td>35.0 %</td>
<td>-0.12</td>
<td>[-0.32, 0.09]</td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>0/12</td>
<td>4/12</td>
<td>27.2 %</td>
<td>-0.33</td>
<td>[-0.61, -0.05]</td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>2/18</td>
<td>1/18</td>
<td>37.7 %</td>
<td>0.06</td>
<td>[-0.12, 0.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>56</td>
<td>56</td>
<td>100.0 %</td>
<td>-0.11</td>
<td>[-0.32, 0.10]</td>
</tr>
</tbody>
</table>

Total events: 5 (Experimental), 11 (Control)

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 5.68$, df = 2 ($P = 0.06$); $I^2 = 65$

Test for overall effect: $Z = 1.02$ ($P = 0.31$)

### Analysis 5.7. Comparison 5 Secondary outcomes, Outcome 7 Attrition (morphine-controlled).

Review: Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

Comparison: 5 Secondary outcomes

Outcome: 7 Attrition (morphine-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N n/N</td>
<td></td>
<td>M-H,Random,95% CI</td>
<td></td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Navigante (unpublished)</td>
<td>1/32</td>
<td>1/31</td>
<td>86.5 %</td>
<td>0.00</td>
<td>[-0.09, 0.09]</td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>10/33</td>
<td>11/35</td>
<td>13.5 %</td>
<td>-0.01</td>
<td>[-0.23, 0.21]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>65</td>
<td>66</td>
<td>100.0 %</td>
<td>0.00</td>
<td>[-0.08, 0.08]</td>
</tr>
</tbody>
</table>

Total events: 11 (Experimental), 12 (Control)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.02$, df = 1 ($P = 0.90$); $I^2 = 0$

Test for overall effect: $Z = 0.06$ ($P = 0.95$)
### Analysis 5.8. Comparison 5 Secondary outcomes, Outcome 8 Deaths (placebo-controlled).

**Review:** Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

**Comparison:** 5 Secondary outcomes

**Outcome:** 8 Deaths (placebo-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Harrison (unpublished)</td>
<td>0/13</td>
<td>2/13</td>
<td>-0.15 [ -0.38, 0.07 ]</td>
<td>6.5 %</td>
<td></td>
</tr>
<tr>
<td>Man 1986</td>
<td>0/29</td>
<td>0/29</td>
<td>0.0 [ -0.06, 0.06 ]</td>
<td>76.4 %</td>
<td></td>
</tr>
<tr>
<td>Shivaram 1989</td>
<td>0/12</td>
<td>0/12</td>
<td>0.0 [ -0.15, 0.15 ]</td>
<td>14.7 %</td>
<td></td>
</tr>
<tr>
<td>Woodcock 1981</td>
<td>1/6</td>
<td>0/6</td>
<td>0.17 [ -0.19, 0.53 ]</td>
<td>2.5 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>60</td>
<td>60</td>
<td>100.0 %</td>
<td>-0.01</td>
<td>[ -0.06, 0.05 ]</td>
</tr>
</tbody>
</table>

Total events: 1 (Experimental), 2 (Control)

Heterogeneity: $T^2 = 0.0$; $\chi^2 = 2.76$, df = 3 ($P = 0.43$); $I^2 = 0.0$

Test for overall effect: $Z = 0.20$ ($P = 0.84$)

### Analysis 5.9. Comparison 5 Secondary outcomes, Outcome 9 Deaths (morphine-controlled).

**Review:** Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults

**Comparison:** 5 Secondary outcomes

**Outcome:** 9 Deaths (morphine-controlled)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk Difference</th>
<th>Weight</th>
<th>Risk Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Random, 95% CI</td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Navigante (unpublished)</td>
<td>0/32</td>
<td>0/31</td>
<td>0.0 [ -0.06, 0.06 ]</td>
<td>93.1 %</td>
<td></td>
</tr>
<tr>
<td>Navigante 2006</td>
<td>10/33</td>
<td>11/35</td>
<td>0.01 [ -0.23, 0.21 ]</td>
<td>6.9 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>65</td>
<td>66</td>
<td>100.0 %</td>
<td>0.00</td>
<td>[ -0.06, 0.06 ]</td>
</tr>
</tbody>
</table>

Total events: 10 (Experimental), 11 (Control)

Heterogeneity: $T^2 = 0.0$; $\chi^2 = 0.04$, df = 1 ($P = 0.84$); $I^2 = 0.0$

Test for overall effect: $Z = 0.03$ ($P = 0.98$)
APPENDICES

Appendix 1. MEDLINE search strategy via OVID
1. exp dyspnea
2. dyspn$.mp.
3. breathing adj3 labour$
4. breathless$.mp.
5. shortness of breath.mp.
6. breathing difficult$.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp benzodiazepines
9. benzodiazepine$.mp.
10. adinazolam or alprazolam or bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clorazepam or cloxazolam or delorazepam or demoxepam or desmethyl Diazepam or diazepam or estazolam or etizolam or fludiazepam or flunitrazepam or flurazepam or flutoprazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclazepam or mexazolam or midazolam or nimetazepam or nitrazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazeepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
11. 8 or 9 or 10
12. 7 AND 11

Appendix 2. EMBASE search strategy via OVID
1. exp DYSPNEA
2. dyspn$.mp.
3. breathing adj3 labour$
4. breathless$.mp.
5. shortness of breath.mp.
6. breathing difficult$.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Benzdiazepine Derivative
9. benzodiazepine$.mp.
10. adinazolam or alprazolam or bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clorazepam or cloxazolam or delorazepam or demoxepam or desmethyl Diazepam or diazepam or estazolam or etizolam or fludiazepam or flunitrazepam or flurazepam or flutoprazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclazepam or mexazolam or midazolam or nimetazepam or nitrazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazeepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
11. 8 or 9 or 10
12. 7 AND 11

Appendix 3. CINAHL search strategy via OVID
1. MH "dyspnea+"
2. dyspn*
3. breathing N3 labour*
4. breathless*
5. shortness of breath
6. breathing difficult*
7. 1 or 2 or 3 or 4 or 5 or 6
8. MH "Anxiety Agents, Benzodiazepine+"
9. benzodiazepine
10. adinazolam or alprazolam or bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clorazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etoxolam or fludiazepam or flunitrazepam or flurazepam or flutoprazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclozapine or mexazolam or micazolam or midazolam or nimetazepam or nitrazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
11. 8 or 9 or 10
12. 7 AND 11

Appendix 4. PsycINFO search strategy via OVID
1. exp DYSPNEA
2. dyspn$.mp.
3. breathing adj3 labour$
4. breathless$.mp.
5. shortness of breath.mp.
6. breathing difficult$.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp BENZODIAZEPINES
9. benzdiazepine$.mp.
10. adinazolam or alprazolam or bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clorazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etoxolam or fludiazepam or flunitrazepam or flurazepam or flutoprazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclozapine or mexazolam or micazolam or midazolam or nimetazepam or nitrazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
11. 8 or 9 or 10
12. 7 AND 11

Appendix 5. CENTRAL search strategy
#1 MeSH descriptor Dyspnea explode all trees
#2 dyspn*
#3 breathing adj3 labour*
#4 breathless*
#5 shortness of breath
#6 breathing difficult*
#7 1 or 2 or 3 or 4 or 5 or 6
#8 exp benzodiazepines
#9 benzodiazepine*
#10 adinazolam or alprazolam or bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clorazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etoxolam or fludiazepam or flunitrazepam or flurazepam or flutoprazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclozapine or mexazolam or micazolam or midazolam or nimetazepam or nitrazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
#11 8 or 9 or 10
#12 7 AND 11
Appendix 6. PaPaS Register search strategy
((dyspn* or (breathing AND (laboured or labored)) or breathless* or “shortness of breath” or “breathing difficult*”) AND (benzodiazepines or adinazolam or alprazolam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or cllobazam or clonazepam or clorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozonepam or fludiazepam or flunitrazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclazepam or mexazolam or midazolam or nimetazepam or nitratazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam))

Appendix 7. Search strategy for Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED via OVID
1. dyspn$.mp.
2. breathing adj3 labour$
3. breathless$.mp.
4. shortness of breath.mp.
5. breathing difficult$.mp.
6. 1 or 2 or 3 or 4 or 5
7. benzodiazepine$.mp.
8. adinazolam or alprazolam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or cllobazam or clonazepam or clorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozonepam or fludiazepam or flunitrazepam or halazepam or haloxazolam or ketazolam or loprazolam or lorazepam or lormetazepam or medazepam or metaclazepam or mexazolam or midazolam or nimetazepam or nitratazepam or nordazepam or oxazepam or oxazolam or pinazepam or prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
9. 7 or 8
10. 6 AND 9

Appendix 8. Search strategy for Iowa Drug Information System (IDIS) and International Pharmaceutical Abstracts
((benzodiazepines or tetrazepam or diazepam or oxatepam or lorazepam or lormetazepam or clotiazepam or pinazepam or uldazepam or quazepam or temazepam or metaclazepam nordazepam or fludiazepam or flunitrazepam or halazepam or clonazepam or nitratazepam or zolazepam or flurazepam or fluoroprazepam or prazepam or clazepam or meclonazepam or fosazepam or midazolam or medazepam or clotiazepam or doxefazepam or premazepam or camazepam or ritazepam or delorazepam or bentazepam or bromazepam) AND ((abnormality, resp & dyspnea) or (apnea, unspecified)))

HISTORY
Review first published: Issue 1, 2010
CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of the idea for this review, revised the manuscript and approved the final version.

SS: developed and wrote the protocol, developed the search strategies and the data extraction form, searched for studies, obtained copies of the studies, extracted data from studies, entered data into RevMan, carried out analysis and meta-analysis, drafted the review and finalised it after discussion with the other review authors. Responsible for further updates.

IJH: discussed and approved the protocol, the search strategy and the data extraction form, discussed the outcomes and analysis with the other review authors and provided epidemiological and wider systematic review expertise.

SB: discussed and approved the protocol, the search strategy and the data extraction form, checked extracted information from studies, discussed the outcomes and analysis with the other review authors.

RH: discussed and approved the protocol, the search strategy and the data extraction form, discussed the outcomes and analysis with the other review authors, and provided social science expertise.

CB: supervised the protocol, contributed to the development of the search strategy and the data extraction form, searched the titles, extracted data from studies, supervised the analysis, discussed the outcomes and analysis with the other review authors, and provided wider systematic review expertise.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

- The Werner Jackstaedt Foundation, Germany.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title was slightly changed by inserting ‘advanced’ in front of ‘malignant’. This caused no changes to the included and excluded studies.