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

Simon S, Bausewein C, Booth S, Harding R, Higginson IJ

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[Intervention protocol]

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

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

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

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

BACKGROUND

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 far advanced diseases it is highly prevalent in chronic obstructive pulmonary disease (COPD, 90 to 95%), chronic heart failure (CHF, 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, CHF, 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 $P0_2$ (partial pressure of oxygen) or increase of PCO_2 (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 evidence for the use in cancer (Uronis 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 applications 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).

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, alprazolm and lorazepam. However, there are more than 40 different benzodiazepines (Hardman 2005). Benzodiazepines belong to the group of hypnotics and sedatives. The 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 benzodiazepine with specific subunits of GABA (gamma-aminobutyric acid) receptors is responsible for their properties. 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, 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 nonbenzodiazepines (e.g. zolpidem) acts on the same receptors with similar effects, but has a different chemical structure. They are not included in this review as they do not belong to the benzodiazepine group.

Despite the frequent use of benzodiazepines for the relief of breathlessness in palliative care, the evidence for the efficacy and effectiveness of benzodiazepines is still unclear. There is no systematic review on this specific topic published so far.

OBJECTIVES

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

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

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised Controlled Trials (RCTs). 'Randomised' is defined as studies which were described by authors as 'randomised' anywhere in the manuscript.
- Controlled Clinical Trials.

We expect that the number of studies will be very limited and therefore we plan to include controlled trials but will give special consideration to the higher risk of bias in our analysis.

Types of participants

Adult participants described as suffering from either breathlessness, dyspnoea, shortness of breath, difficulty breathing or laboured breathing due to malignant and advanced non-malignant diseases. Malignant diseases will include both primary and secondary cancer.
The advanced stage in non-malignant diseases will include the following:

- COPD: severe stage III or IV of the GOLD classification (Global Initiative for Obstructive Lung Disease), which include the airflow limitation measured by spirometry FEV_1 < 50%, FEV_1/FVC < 0.7 (FEV_1: 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: severe stage III or IV of the NYHA classification (New York Heart Association) which include symptoms such as dyspnoea 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.

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

We will include studies evaluating participants on oxygen as long as oxygen is used in both intervention and control arms.

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. All drugs which belong to the pharmacological group of benzodiazepines will be included (Hardman 2005).

Types of outcome measures

Primary outcome
Primary outcomes will include 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 will include studies that measure breathlessness as a primary or secondary outcome. We will include studies evaluating breathlessness at rest or on exercise.
Secondary outcomes
Secondary outcomes will include:

- measurement of anxiety,
- measurement of depression,
- adverse effects of benzodiazepines,
- functional exercise capacity (e.g. walking tests),
- measurement of Quality of Life,
- attrition.

Search methods for identification of studies

Electronic databases (access via Ovid)
Studies will be identified from a search of the following databases:

- Cochrane Pain, Palliative and Supportive Care Trials Register
- The Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (current issue)
- The Cochrane Database of Systematic Reviews (CDSR) in The Cochrane Library (current issue)
- Database of Abstracts of Reviews of Effectiveness (DARE) (current issue)
- MEDLINE (1950 to present)
- EMBASE (1980 to present)
- CINAHL (1980 to present)
- PsychINFO (1806 to present)
- International Pharmaceutical Abstracts (1970 to present)
- Iowa Drug Information System (IDIS) (1966 to present)

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 selected a wider search strategy. The decision on inclusion or exclusion of studies regarding disease and disease stage will be 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 databases developed for this review.

Hand searching

The reference list of all relevant studies, key textbooks, and key websites will be checked for further relevant studies.

Personal contact

Investigators who are known to be carrying out research in this area will be contacted for unpublished data or knowledge of the grey literature. Members of the Association of Palliative Medicine (APM, UK) will be asked via letter for unpublished data.

Language

There will be no language restriction in the selection of studies.

Data collection and analysis

Selection of studies

Three review authors (SS, CB, SB) will independently assess the titles and abstracts identified for relevance. Disagreement will be resolved by consensus and with a fourth review author (IH). Full text of all potentially relevant studies will be assessed by three independent review authors (SS, CB, SB). Disagreement at this stage will be resolved again by consensus and with a fourth review author (IH). At this stage we will exclude all studies investigating an early stage of non-malignant diseases.

Assessment of methodological quality of included studies

All selected studies will be assessed for methodological quality by three independent review authors (SS, CB, SB). Two measures of methodological quality will be used. Quality will be assessed using the RevMan risk of bias table following guidance from the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008). We will also grade the studies according to the "Method Score" from Edwards 2000. This checklist for methodological quality contains 11 items which assess the primary research quality of the studies and its published description. The following items will be 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. The results of the quality assessment will be integrated in to the data analysis, as well as in the meta-analysis (cumulative meta-analysis in order of their validity).

Data extraction

Data from each appropriate study will be extracted independently by two review authors (SS, CB). A data extraction form specifically designed for the review will be developed and will include:

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,
- details of analysis.

Patient characteristics, including:

- demographics,
- diagnosis,
- performance status,
- number and description of participants in the intervention and control groups,
- setting.

Intervention, including:

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

Primary outcomes, including:

- measurement of breathlessness,
- 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,
- arterial blood gas measurements.

Additional information, including:

- patient comments of intervention.

Authors of studies will be contacted if possible to provide unpublished data if required for analysis.

Data analysis

Studies will be combined using RevMan (Version 5).

The primary outcome measure (breathlessness) will be either in the form of continuous or ordinal data. For each study we will

treat ordinal data as binary data when scales are short and as continuous data when scales are long. For binary data we will calculate the odds ratio (OR) if appropriate. Number needed to treat to benefit and to harm (NNT/NNH) will be calculated where appropriate. For continuous data weighted mean difference (WMD) and standardized mean difference (SMD) with a 95% confidence interval (CI) will be calculated to show the size of the effect of interventions. A P value of < 0.05 will be considered as statistically significant.

As we decided to include controlled trials we will give special consideration to the higher risk of bias of this study design.

We will conduct meta-analysis if there are appropriate studies. As we anticipate heterogeneity (differences e.g. in diagnosis groups or types of benzodiazepines) we plan to use a random-effects model. Where more than one dose of the drug was used, an average of all doses will be used in meta-analysis.

Heterogeneity due to participants, interventions, outcomes and study design will be statistically evaluated and explored by subgroup analysis.

Sensitivity analysis will be performed according to methodological quality and the robustness of results.

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Booth 2008

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Davis 2005

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Nordgren 2003

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Solano 2006

Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *Journal of Pain and Symptom Management* 2006;**31**:58–69.

Uronis 2008

Uronis HE, Abernethy AP. Oxygen for relief of dyspnea: what is the evidence?. *Current Opinion in Supportive and Palliative Care* 2008;**2** (2):89–94.

* *Indicates the major publication for the study*

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 clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 prazepam 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 Benzodiazepine 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 clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 prazepam 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 clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam
11. 8 or 9 or 10
12. 7 AND 11

Appendix 4. PsychINFO 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 clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 prazepam or quazepam or temazepam or tetrazepam or tofisopam or triazolam

11. 8 or 9 or 10
12. 7 AND 11

Appendix 5. Cochrane Library 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 clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 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 bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 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 bentazepam or bromazepam or brotizolam or chlordiazepoxide or cinolazepam or clobazam or clonazepam or clorazepate or clotiazepam or cloxazolam or delorazepam or demoxepam or desmethyldiazepam or diazepam or estazolam or etizolam or etozolam 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 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 nitrazepam or zolazepam or flurazepam or flutoprazepam 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

Protocol first published: Issue 4, 2008

CONTRIBUTIONS OF AUTHORS

For the protocol

All review authors: contributed to the development of the idea and of the protocol.

SS: developed and wrote the protocol, developed the search strategies and the data extraction form.

CB: discussed the protocol with SS and contributed to the development of the search strategy and the data extraction form.

SB, RH, IJH: discussed and approved the protocol, the search strategy and the data extraction form.

For the review

SS: search for studies, obtain copies of the studies, extract data from studies, enter data into RevMan, carry out analysis, draft the review and finalise it after discussion with the other review authors.

CB: search for studies, extract data from studies, carry out analysis, discuss the outcomes with the other review authors and revise the manuscript.

SB: obtain copies of the studies, discuss the outcomes with the other review authors and revise the manuscript.

RH, IJH: discuss the outcomes with the other review authors and revise the manuscript.

All review authors will: select which studies to include, interpret analysis, draft the final review and be involved with the update of the review.

DECLARATIONS OF INTEREST

None known

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Internal sources

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External sources

- The Werner Jackstaedt Foundation, Germany.