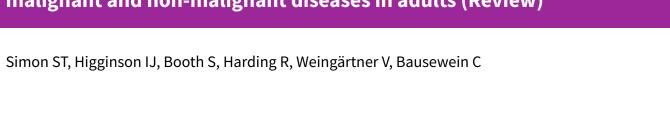


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Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults (Review)



Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD007354. DOI: 10.1002/14651858.CD007354.pub3.

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[Intervention Review]

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

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Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 10, 2016.

Citation: Simon ST, Higginson IJ, Booth S, Harding R, Weingärtner V, Bausewein C. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD007354. DOI: 10.1002/14651858.CD007354.pub3.

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 1, 2010, on 'Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults'. 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. At the time of the previously published Cochrane review, there was no evidence for a beneficial effect of benzodiazepines for the relief of breathlessness in people with advanced cancer and chronic obstructive pulmonary disease (COPD).

Objectives

The primary objective of this review was to determine the efficacy of benzodiazepines for the relief of breathlessness in people 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.

Search methods

This is an update of a review published in 2010. We searched 14 electronic databases up to September 2009 for the original review. We checked the reference lists of all relevant studies, key textbooks, reviews, and websites. For the update, we searched CENTRAL, MEDLINE, and EMBASE and registers of clinical trials for further ongoing or unpublished studies, up to August 2016. We contacted study investigators and experts in the field of palliative care asking for further studies, unpublished data, or study details when necessary.

Selection criteria

We included randomised controlled trials (RCTs) and controlled clinical trials (CCTs) assessing the effect of benzodiazepines compared with placebo or active control in relieving breathlessness in people 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 review authors independently 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

Overall, we identified eight studies for inclusion: seven in the previous review and an additional study for this update. We also identified two studies awaiting classification in this update. The studies were small (a maximum number of 101 participants) and comprised data from a total of 214 participants with advanced cancer or COPD, which we analysed. There was only one study of low risk of bias. Most of the studies had an unclear risk of bias due to lack of information on random sequence generation, concealment, and attrition. Analysis of all studies did not show a beneficial effect of benzodiazepines for the relief of breathlessness (the primary outcome) in people with advanced cancer and COPD (8 studies, 214 participants) compared to placebo, midazolam, morphine, or promethazine. Furthermore, we observed no statistically significant effect in the prevention of episodic breathlessness (breakthrough dyspnoea) in people with cancer (after 48 hours: risk ratio of 0.76 (95% CI 0.53 to 1.09; 2 studies, 108 participants)) compared to morphine. Sensitivity analyses demonstrated no statistically significant differences regarding type of benzodiazepine, dose, route and frequency of delivery, duration of treatment, or type of control. Benzodiazepines caused statistically significantly more adverse events, particularly drowsiness and somnolence, when compared to placebo (risk difference 0.74 (95% CI 0.37, 1.11); 3 studies, 38 participants). In contrast, two studies reported that morphine caused more adverse events than midazolam (RD -0.18 (95% CI -0.31, -0.04); 194 participants).

Authors' conclusions

Since the last version of this review, we have identified one new study for inclusion, but the conclusions remain unchanged. There is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD. Benzodiazepines caused more drowsiness as an adverse effect compared to placebo, but less compared to morphine. Benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness. There is a need for well-conducted and adequately powered studies.

PLAIN LANGUAGE SUMMARY

Benzodiazepines for the relief of breathlessness in advanced diseases in adults

Background

Breathlessness is a common and distressing symptom in advanced cancer and other diseases at the end of life. Treating breathlessness sufficiently remains very difficult. Benzodiazepines are a group of sedating medicines (drugs), including lorazepam, clorazepate, diazepam, alprazolam, and temazepam, that are used mainly for sleep disturbance and anxiety, but are widely used for the relief of breathlessness.

Key results

In this updated systematic review we aimed to determine whether benzodiazepines relieved breathlessness in adults with advanced disease. In August 2016, we found eight studies.

Benzodiazepines caused more side effects such as drowsiness or somnolence when compared to placebo but caused less side effects when compared to morphine. Our review therefore 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 people with advanced diseases.

We concluded in summary that there is no evidence that benzodiazepines relieve breathlessness in adults with advanced disease.