Interventions for alleviating cancer-related dyspnea: a systematic review
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CRD summary
The authors supported the use of opioids for dyspnea relief in terminally ill cancer patients. Oxygen should be used to alleviate dyspnea in hypoxic cancer patients. Nursing led non-pharmacological interventions seemed valuable. Given the unclear quality of the included studies and the absence of tests of statistical significance, the authors' conclusions should be treated with caution.

Authors' objectives
To evaluate the effectiveness of pharmacological and non-pharmacological treatments for dyspnea in terminally ill cancer patients.

Searching
PubMed (January 1966 to November 2007), Cochrane Central Register of Controlled Trials (up to 2007 issue 1) and conference proceedings in oncology were searched. Search terms were reported. The bibliographies of included trials and reviews were handsearched for further studies.

Study selection
Randomised controlled trials (RCT) of any intervention for the relief of dyspnea in terminally ill cancer patients compared to no intervention, placebo or another intervention were eligible for inclusion. Studies of technical procedures and studies with no cancer patients or a minority of cancer patients were excluded.

A variety of interventions were assessed in the included studies: morphine, alone or combined with midazolam, in varying dosages and routes; oxygen compared to air or helium-enriched air; nebulized furosemide; acupuncture and acupressure; and nursing-led breathlessness rehabilitation programmes. The duration of included studies ranged from less than one hour for oxygen treatments to three months for breathlessness rehabilitation programmes. Patients with a wide range of cancers were included, the most common of which was lung cancer. Where stated, the age ranged from 42 to 73 years. A mixture of mean and median ages was reported. Outcomes reported in the included studies were Visual Analogue Scales (VAS) of subjective dyspnea relief, dyspnea intensity as measured using the modified Borg scale and adverse events.

Two reviewers independently selected the studies for review based on titles and abstracts. In the case of disagreement, the full text was retrieved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted independently by two reviewers. In the case of disagreement, a third reviewer extracted the data and results were obtained by consensus.

Methods of synthesis
The results were combined in a narrative synthesis.

Results of the review
Eighteen studies were included for review (n= 815): three parallel double blind RCT (n=100), one parallel single-blind trial (n=38), five parallel unblinded trials (n=504), seven double-blind crossover trials (n=139), one randomised continuous sequential double-blind study (n=33) and one study design that was not reported. Validity was not assessed, but the authors noted that allocation generation was not reported in nine studies and allocation concealment was not reported in 11 studies.
Morphine (seven studies, n=256)

Subcutaneous morphine resulted in significantly decreased dyspnea intensity compared to placebo (two studies, n=19; no p-values reported). In one study (n=101; no p-values reported) morphine combined with midazolam improved dyspnea significantly (92 per cent dyspnea relief) compared to morphine alone (69 per cent dyspnea relief) or midazolam alone (46 per cent dyspnea relief). Nebulized morphine and morphine dosage were not associated with any significant changes in dyspnea. Three trials reported adverse events of nausea, sedation and somnolence in 33 patients.

Oxygen (six studies, n=149)

Three studies found no significant difference between oxygen and air on dyspnea intensity (n=122). However, studies that included only hypoxic patients showed significant benefits of oxygen on dyspnea intensity (two studies n=15; no p-values reported). One study reported a significant reduction in dyspnea VAS scores with helium enriched air (n=12, no p-values reported).

All three studies of nursing led breathlessness rehabilitation reported significant benefits compared to no intervention control groups (no p-values reported). Furosemide and acupuncture and acupressure did not show any significant benefit on dyspnea.

Authors' conclusions
The review supports the use of opioids for dyspnea relief in terminally ill cancer patients. Oxygen should be used to alleviate dyspnea only in hypoxic cancer patients. Nursing led non-pharmacological interventions seemed valuable.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. Three relevant databases were searched. Limited attempts were made to identify unpublished studies and it was unclear whether any language restrictions were applied during the search, therefore, publication and language bias could not be ruled out. Appropriate steps were taken in the study selection and data extraction processes to minimise reviewer error and bias. The review provided details about 17 of the 18 studies in the data extraction tables, it was not clear why some data from the eighteenth study was omitted from these tables. No validity assessment appeared to have been carried out, so it was not possible to ascertain the quality of the included studies and the reliability of the data. Given the clinical heterogeneity between included studies, the decision to combine the results in a narrative synthesis was appropriate. The lack of presentation of levels of statistical significance meant that it was not possible to verify the findings reported in the review. The strength of any findings was also limited by the small number of participants in many studies. Given the unclear quality of the included studies and the absence of tests of statistical significance, the authors' conclusions should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that midazolam can be prescribed in conjunction with morphine. The role of nebulized morphine was less clear. Supplemental oxygen was not recommended for use in cancer patients who were not hypoxic. Acupuncture should not be used.

Research: The authors stated that further RCTs were needed to evaluate opioids over longer time frames. Nebulized morphine, corticosteroids and other benzodiazepines also warranted further investigation.

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