Dyspnea in idiopathic pulmonary fibrosis: a systematic review

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CRD summary
This review concluded that sildenafil and pulmonary rehabilitation are potential therapies for dyspnoea in selected patients with idiopathic pulmonary fibrosis. Additional research was suggested to examine the effects of supplemental oxygen and opioids. These conclusions reflect some of the evidence presented; limitations of the small evidence base mean that the recommendations for further research are justified.

Authors' objectives
To evaluate the evidence for the treatment and correlates of dyspnoea in idiopathic pulmonary fibrosis.

Searching
MEDLINE, EMBASE and EBM Reviews were searched from inception to November 2010 for publications in English. Search terms were reported. Reference lists of retrieved articles and relevant reviews were hand searched.

Study selection
Studies of any design were included if they reported on treatments or correlates of dyspnoea in 10 or more adults with idiopathic pulmonary fibrosis. Diagnosis of idiopathic pulmonary fibrosis had to have been made using appropriate criteria (as stated in the review). Studies that also contained patients with other forms of interstitial lung disease were included so long as they separated these data from those of patients with idiopathic pulmonary fibrosis.

Just under half of the included studies evaluated potential treatments of dyspnoea; the other studies evaluated the correlates of dyspnoea. Measures of dyspnoea severity varied across the studies. Where reported, the mean age of patients ranged from 52 to 78 years, between 19% and 100% had had a surgical biopsy and between 40% and 91% had ever smoked. Mean predicted values ranged from 38% to 81% for forced vital capacity and from 26% to 68% for diffusing capacity of carbon monoxide.

Two reviewers independently selected studies for inclusion in the review; any discrepancies were resolved through consensus.

Assessment of study quality
The quality of included clinical trials was assessed using the Cochrane Collaboration risk of bias tool. Overall strength and quality of evidence for each outcome was assessed using GRADE criteria.

Two reviewers performed the GRADE assessments; the number of reviewers for the risk of bias assessment was not reported explicitly.

Data extraction
Two reviewers extracted data on the outcomes; any discrepancies were resolved by consensus.

Methods of synthesis
Data were presented in a narrative synthesis, with different sections relating to treatment of dyspnoea and correlates of dyspnoea.

Results of the review
Twenty-nine studies were included in the review (2,472 patients, ranging from 10 to 826 per study). Among the seven randomised controlled trials (RCTs) assessed for quality, the number of quality criteria met ranged from 3 to 6 (out of a total of 6); no other risk of bias assessment results were reported. According to GRADE criteria, the evidence was of moderate quality for sildenafil and of very low to low quality for the other treatments evaluated.

Disease-modifying treatments: Only one RCT demonstrated a significant improvement in dyspnoea with administration of prednisone combined with colchicine; the other studies all showed no effects of treatment on dyspnoea (five RCTs...
and two open studies with no control). These treatments included prednisone combined with colchicine, pirfenidone, acetylcysteine, bosentan, interferon gamma and etanercept.

**Non-disease modifying treatments:** Three studies (two RCTs and one open study with no control) found no significant improvements in dyspnoea with use of sildenafil. Two studies (one randomised trial with an unclear control and one open study with no control) examined the effect of pulmonary rehabilitation on dyspnoea. The open study reported a significant improvement in dyspnoea and the randomised trial found no significant effect. One crossover study found that non-invasive ventilatory assistance significantly improved exertional dyspnoea during a bicycle exercise test.

Statistically significant correlations were found between dyspnoea severity and several variables (such as depression, measures of function and physiology). Further results were reported in the review paper.

**Authors’ conclusions**
Sildenafil and pulmonary rehabilitation are potential therapies for dyspnoea in selected patients with idiopathic pulmonary fibrosis. Additional research is needed to examine the effects of supplemental oxygen or opioids and the management of functional status and comorbidities.

**CRD commentary**
The review question was suitably broad and supported by reproducible inclusion criteria. Relevant electronic databases were searched. The restriction to publications in English meant that relevant studies may have been missed. Study selection, data extraction and GRADE assessment processes were all performed in duplicate, which reduced the risk of reviewer error and/or bias. Suitable quality assessment criteria were employed although the results were not reported. Study details were presented and the narrative form of synthesis was appropriate given the diversity in the studies. Excluded studies were discussed in the synthesis, which was potentially confusing.

It should be noted that the number of studies examining each treatment was small (ranging from one to three). The authors acknowledged that most of the included studies did not measure dyspnoea as a primary endpoint and that some studies were underpowered to detect change in dyspnoea. Most of the dyspnoea measures employed were not specifically developed for populations with idiopathic pulmonary fibrosis.

The authors’ tentative conclusions reflect some of the evidence presented; limitations of the small evidence base mean that their recommendations for further research are justified.

**Implications of the review for practice and research**
**Practice:** The authors stated that symptom-based therapy for dyspnoea remained an important potential alternative to disease-modifying therapies and lung transplantation.

**Research:** The authors stated that future research should use a multivariate approach to examine the correlates of dyspnoea and investigate the impact of treating comorbidities (such as emphysema, cardiovascular disease) in idiopathic pulmonary fibrosis. Research was needed to examine the evidence for supplemental oxygen, opioid therapy and other therapies directed at other mechanisms of dyspnoea.

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