**Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of randomised controlled trials**

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**CRD summary**
The review concluded that there was an absence of a clinically relevant improvement in exercise capacity in patients with connective tissue disease after 12 to 18 weeks of treatment. There were some methodological problems with the review, but the authors’ conclusions were suitably cautious and appear reasonable.

**Authors’ objectives**
To examine the effects of recently available oral therapies (such as endothelin receptor antagonists and phosphodiesterase-5 inhibitors) on exercise capacity in patients with pulmonary arterial hypertension related to connective tissue disease, mostly systemic sclerosis.

**Searching**
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and abstract archives of European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) were searched from 1966 to April 2007. There were no language and publication restrictions. Search terms were reported. Reference lists of retrieved articles were searched.

**Study selection**
Randomised controlled trials (RCTs) of pulmonary arterial hypertension therapies versus placebo in adults with pulmonary arterial hypertension (idiopathic, secondary to connective tissue disease and congenital heart disease) were eligible for inclusion. Trial participants had to require medical treatment for pulmonary arterial hypertension and had to require anticoagulation. Pulmonary arterial hypertension was defined as a mean arterial blood pressure greater than 25mmHg at rest or 30mmHg with exercise. The outcome of interest was a six-minute walk test.

The included RCTs evaluated Bosentan (62mg twice per day for four weeks and then 125mg twice daily or 250mg once daily), Sitaxsentan (50mg to 300mg daily) and Sildenafil (20mg to 80mg three times daily). Study duration ranged from 12 to 18 weeks. Mean age of patients ranged from 48 to 50. The proportion of females ranged from 69% to 79%. The proportion of patients with systemic sclerosis ranged from 14% to 79% (where reported).

The authors did not state how many reviewers were involved in study selection.

**Assessment of study quality**
Trial quality was assessed using the Jadad five-point scale of randomisation, blinding, withdrawals and dropouts to score trials from 0 (low quality) to 5 (high quality).

The authors did not state how many reviewers assessed trial quality.

**Data extraction**
Two reviewers independently extracted data on the six-minute walk test using a pre-specified data extraction sheet. Data were used to calculate mean effect sizes and 95% confidence intervals (CIs). Effect sizes were graded according to clinical significance (<0.2 trivial, >0.2-0.5 small, >0.5-0.8 moderate, >0.8-1.2 important and >1.2 very clinically important). Where standard deviations (SD) were available for only one study group, the available standard deviation was used as the baseline for both groups. Where no standard deviation was provided the effect size could not be extrapolated.

**Methods of synthesis**
Pooled effect sizes, with 95% CIs, were calculated using a fixed-effects meta-analysis in the absence of heterogeneity.
or a random-effects meta-analysis if statistical heterogeneity was detected. Statistical heterogeneity was assessed using the \( \chi^2 \) statistic. Subgroup analysis grouped trials according to trial quality, functional class, treatment dose and nature of the drug. One study was used only within sensitivity analyses.

**Results of the review**

Ten RCTs (n=885 patients) were included in the review. Trial quality was high (all trials scored at least 4 and half of the trials scored 5 out of 5).

For the whole pulmonary arterial hypertension population there was a small clinical difference in the walk test effect size with endothelin receptor antagonists (effect size 0.44, 95% CI 0.29 to 0.58) that was statistically significant and a moderate clinical difference in effect sizes with phosphodiesterase-5 inhibitors (0.58, 95% CI 0.38 to 0.79) that was statistically significant.

For the connective tissue disease population, there was a small clinical difference in effect sizes with endothelin receptor antagonists (0.27, 95% CI -0.01 to 0.54) that was not statistically significant and a moderate clinical difference in effect sizes with phosphodiesterase-5 inhibitors (0.53, 95% CI -0.02 to 0.89) that was not statistically significant.

Subgroup analyses for the whole population showed small to moderate clinical effect sizes that were generally statistically significant (apart from 50mg and 300mg of sitaxsentan). Subgroup analyses for the connective tissue disease population showed insignificant to moderate clinical effect sizes that were not statistically significant apart from one analysis (high quality cut off 4).

**Authors’ conclusions**

There was an absence of a clinically relevant improvement in exercise capacity in patients with connective tissue disease (mostly systemic sclerosis) after 12 to 18 weeks of treatment.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Several relevant databases were searched. Publication bias was not assessed and could not be ruled out. Two reviewers undertook data extraction, minimised risks of error and bias in the analysis; it was unclear whether the same methodology was extended to study selection and quality assessment. The included trials were generally high quality. Sample sizes of some trials were small. Trials were combined using meta-analysis and subgroup analyses were undertaken, which appeared appropriate. Statistical heterogeneity was not discussed.

There were some methodological problems with this review, but the authors' conclusions were suitably cautious and appear reasonable.

One author declared consulting fees and honoraria from Actelion Pharmaceuticals.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that longer terms studies in patients with connective tissue disease were needed to confirm the findings of this review. Studies should use well-defined methods. Tools other than the six-minute walk test needed to be developed.

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