Clinical and cost-effectiveness of epoprostenol, iloprost, bosentan, sitaxentan and sildenafil for pulmonary arterial hypertension within their licensed indications: a systematic review and economic evaluation

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CRD summary
This review concluded that all five drugs added to supportive care were more effective than supportive care alone. There was insufficient evidence to compare the effectiveness of different drugs or to assess combinations of drugs. The review was generally well conducted and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the effectiveness of five drugs (alone or in combination) for the treatment of adults with pulmonary arterial hypertension within their licensed indications.

Searching
The authors searched The Cochrane Library, MEDLINE and EMBASE to February 2007. There were no language restrictions. Detailed search strategies were reported. Reference lists of relevant studies and research registers of ongoing trials were searched. Further information was sought from clinical experts and manufacturers (including reports of unpublished trials and data not reported in published papers).

Study selection
Randomised controlled trials (RCTs) of any of epoprostenol, iloprost, bosentan, sitaxentan (sitaxsentan) or sildenafil in adults diagnosed with pulmonary arterial hypertension were eligible for inclusion. These could be compared with any treatment other than different doses, formulations and methods of administration of the same intervention. Outcomes of interest were specified in advance (full list in report).

Included trials mostly lasted 12 to 18 weeks and compared one drug plus supportive care against supportive care plus placebo or alone. Many of the trials included patient populations and doses outside the licensed indications of the drugs.

One reviewer screened titles and abstracts for relevance. Approximately half of these were checked by a second reviewer. Full papers of potentially relevant studies were assessed by two reviewers independently. Disagreements were resolved by consensus or referral to a third reviewer.

Assessment of study quality
Study quality was assessed based on randomisation, allocation concealment, blinding, use of intention-to-treat analysis and follow-up.

Assessments were done by one reviewer and checked by another. Disagreements were resolved by consensus or referral to a third reviewer.

Data extraction
Relative risks were extracted or calculated for dichotomous outcomes and mean differences for continuous outcomes. Data were extracted independently by two reviewers using a specific pro forma. Disagreements were resolved by consensus or referral to a third reviewer. Additional data from manufacturer submissions, unpublished manuscripts and clinical study reports were extracted by one reviewer.

Methods of synthesis
Studies with the same intervention and comparator were pooled by meta-analysis using a random-effects model. Statistical heterogeneity was assessed using the \( \chi^2 \) test and \( I^2 \) statistic (\( I^2 \) of 25% indicated low heterogeneity, 50% indicated medium heterogeneity and 75% indicated high heterogeneity). The primary analysis involved all patients with pulmonary arterial hypertension in functional class (FC) II (and FC IV for epoprostenol) and using licensed drug doses. Sensitivity analyses were planned to take into account differences in functional and pulmonary hypertension classes,
intervention doses and other factors. Subgroup analyses were planned for idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with connective tissue disease.

**Results of the review**
Twenty RCTs were included (three unpublished). Most were of good quality.

Compared with supportive care, epoprostenol and bosentan added to supportive care significantly increased six-minute walk distance (weighted mean difference 58 metres, 95% confidence interval (CI) 6 to 110 for epoprostenol and 59 metres, 95% CI 20 to 99 for bosentan) within their licensed indications. No stratified data were available for the other drugs.

For functional class deterioration at 12 weeks (reported as an odds ratio), point estimates for epoprostenol, iloprost, bosentan and sitaxentan suggested a beneficial effect within their licensed indications, but 95% CIs included 1, so the results were not statistically significant. Results for sildenafil were not reported (commercial in confidence). Two RCTs involved direct comparisons between different drugs; no significant differences were observed.

Extensive further results were presented in the report.

**Cost information**
In general, sildenafil plus supportive care was reported to be more effective and less costly than supportive care alone. Incremental cost-effectiveness ratios for the other drugs per quality-adjusted life year (QALY) were: epoprostenol £277,000 for FC III and £343,000 for FC IV patients; iloprost £101,000; bosentan £27,000; and sitaxentan £25,000.

**Authors’ conclusions**
All five drugs added to supportive care were more effective than supportive care alone in RCTs that involved patients with pulmonary arterial hypertension of mixed functional class and with different types of pulmonary arterial hypertension. There was insufficient evidence to compare the effectiveness of different drugs or to assess combinations of drugs.

**CRD commentary**
The review question and inclusion criteria were clear. The search was thorough and included measures to locate unpublished trials. Publication bias was not formally assessed, but co-operation from drug manufacturers meant that the risk of bias was low. Measures were taken to reduce errors and bias in the review process. Quality of included studies was assessed using appropriate criteria and the results were used in the synthesis. Full details of included trials were reported. Some results for sildenafil could not be verified from the published report (commercial in confidence). Trials were included that involved patients or doses outside the licensed indications for the drugs, but the primary analyses used data for the licensed indications.

Standard methods were used for meta-analysis. Sources of heterogeneity were investigated by preplanned sensitivity and subgroup analyses.

The authors noted various limitations of the review, including a possible issue of generalisability in that patients seen in clinical practice may be more sick than those included in the trials. This was a generally well-conducted review and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors did not suggest any implications for practice.

**Research:** The authors stated that long-term double-blind RCTs are required to directly compare bosentan, sitaxentan and sildenafil. Outcomes evaluated should include survival, quality of life, maintenance on treatment and impact on use of resources by the NHS and personal social services.

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