Analyzing the short-term effect of placebo therapy in pulmonary arterial hypertension: potential implications for the design of future clinical trials

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CRD summary
This review aimed to assess the consequences of short-term treatment with placebo in patients with pulmonary arterial hypertension. It concluded that patients who received placebo were more likely to experience clinical deterioration than patients who received comparator treatments. Despite some reporting limitations, the authors’ conclusions appear broadly appropriate given the evidence presented.

Authors' objectives
To assess the consequences of short-term treatment with placebo in patients with pulmonary arterial hypertension.

Searching
MEDLINE and EMBASE databases were searched up to December 2006. Search terms were reported. Bibliographies of relevant trials, reviews and guidelines were searched for additional articles.

Study selection
Randomised, placebo-controlled trials, reporting data at baseline and after 12 to 18 weeks, of treatment for pulmonary arterial hypertension were eligible for inclusion in the review.

Most trials were of 12 week duration, with the remainder ranging from 16 to 52 weeks duration. Included trials compared placebo against a range of active treatments (prostacyclin analogues, endothelin receptor antagonists, a thromboxane synthetase inhibitor and a phosphodiesterase inhibitor).

Participants in the placebo study arms were predominately women (76%), aged on average 47.4 (standard deviation 4.8) years, in New York Heart Association/World Health Organization functional class III (68.9%). The most common aetiologies were idiopathic pulmonary arterial hypertension (56.8%) and connective tissue disease associated pulmonary arterial hypertension (24.2%).

The included trials reported a range of mortality, morbidity, functional and haemodynamic outcomes. Functional and haemodynamic outcomes included: six-minute walk distance, mean pulmonary artery pressure, pulmonary vascular resistance, cardiac index, mixed venous oxygen saturation, and Borg dyspnoea score.

The authors did not state how many reviewers performed the selection.

Assessment of study quality
Quality was independently assessed by two reviewers using the Jadad criteria.

Data extraction
Data were extracted on key trial characteristics and outcomes. Continuous outcomes were extracted as mean differences.

The authors did not state how many reviewers performed the extraction.

Methods of synthesis
Continuous outcomes were pooled as weighted mean differences, with 95% with confidence intervals, using a random-effects model. For dichotomous outcomes, pooled relative risks were calculated with 95% confidence intervals. Heterogeneity was visually assessed using Galbraith plots as well as by $\chi^2$ and $I^2$ statistics. Publication bias was assessed using Egger’s test.
Sensitivity analyses included systematic inclusion and exclusion of individual trials from pooled results, using the "trim and fill" method to measure the impact of any observed publication bias, using stratification and meta-regression to explore sources of heterogeneity, and component analysis of individual Jadad scale questions.

Results of the review
A total of 13 trials were included (868 placebo-treated, 1131 active comparator-treated patients). The median Jadad score was 6 points (range 4-8).

At 12 to 18 weeks, placebo-treated patients were more likely to experience a clinical worsening than patients on active treatment (relative risks 1.81, 95% confidence interval (CI): 1.30 to 2.53) but not death (p=0.22).

In placebo-treated patients, the 6-minute walk distance decreased by 8.4 m (95% CI: -14.6 to -2.2) and pulmonary vascular resistance increased by 58.9 dyne s/cm² (95% CI: 27.6 to 90.1). There were also significant decreases in cardiac index (p=0.01) and mixed venous oxygen saturation (p=0.003), and significant increases in mean pulmonary artery pressure (p=0.012) and Borg dyspnoea score (p<0.001). Only the cardiac index estimate incorporated significant statistical heterogeneity (p=0.008, I² 62.6%).

There was no evidence of publication bias and results were not significantly changed during sensitivity analyses.

Authors' conclusions
Patients with pulmonary arterial hypertension who received placebo were more likely to experience clinical deterioration.

CRD commentary
The review question was explicitly defined in terms of the intervention and study designs of interest, with an implicit suggestion that inclusion was limited to studies of pulmonary arterial hypertension patients. The search for relevant trials covered multiple sources, but it was not clear whether any attempt was made to identify unpublished or non-English language studies. Failure to identify such trials could introduce bias. However, the authors did state that they found no evidence to indicate the presence of publication bias. Validity assessment was undertaken by two independent reviewers using an established scale, but it was not clear whether similar efforts to minimise the potential for errors and bias in the selection and extraction of trials were undertaken. The authors presented some details of the included trials and analyses in the review, but additional information would have been helpful. Despite these limitations, given the evidence presented, the authors' conclusions appear broadly appropriate.

Implications of the review for practice and research
Research: The authors stated that future research should consider evaluating existing medications against one another, as well as comparing novel therapies with currently accepted ones.

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

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.