CRD summary
The author stated that all oral treatments (sildenafil, bosentan, sitaxsenten and ambrisentan) improved exercise ability in patients with pulmonary arterial hypertension, but the results for other outcomes were not consistent. The data appear to support these conclusions, but poor reporting of review methods, a failure to assess quality and inadequate synthesis mean it is difficult to confirm their reliability.

Authors' objectives
To evaluate oral treatments for patients with pulmonary arterial hypertension (PAH).

Searching
MEDLINE was searched from inception to January 2007; the search terms were reported. In addition, online abstracts from recent conferences were screened. Only English language reports were eligible.

Study selection
Study designs of evaluations included in the review
Double-blind-randomised controlled trials (RCT) and open-label extensions of double-blind RCTs were eligible for inclusion. The duration of the double-blind studies ranged from 6 to 18 weeks.

Specific interventions included in the review
Studies of oral treatments with a minimum duration of 3 weeks were eligible for inclusion. Studies that only involved single administration of the drug were excluded. The review evaluated sildenafil (20 to 100 mg thrice daily), bosentan (250 mg/day to 250 mg twice daily), sitaxsenten (50 to 300 mg) and ambrisentan (1 to 10 mg/day) compared with placebo, sildenafil versus bosentan, bosentan plus epoprostenol versus epoprostenol alone, and bosentan plus inhaled iloprost versus bosentan alone.

Participants included in the review
Studies of patients with PAH were eligible for inclusion in the review. The primary studies included patients with idiopathic PAH, PAH due to scleroderma or other connective tissue disease, and Eisenmenger syndrome.

Outcomes assessed in the review
Studies that only assessed pharmaceutical measures were excluded but, otherwise, inclusion criteria were not specified in terms of the outcomes. In most of the included studies, the primary outcomes included the 6-minute walking distance (6MWD); other primary outcomes included cardiopulmonary exercise testing, peak oxygen uptake (peak VO2), pulmonary vascular resistance, change in exercise time on treadmill, and change in right ventricular mass.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

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

Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the statistical significance of outcome measures was reported as statistically significant or not.

Methods of synthesis
How were the studies combined?
The studies were grouped by the specific drug and individual studies described. No overall synthesis was undertaken.

How were differences between studies investigated?
Some differences were reported in the text.

Results of the review
Fifteen double-blind RCTs were included (n=1,664). Twelve of these studies were reported in peer-reviewed journals. The review also included seven abstract only papers (n=1144) and some open-label extension reports, but these are not included in this abstract since few details were reported.

The results reported below focus on primary outcomes in the 12 included fully-published RCTs and adverse events. Other results and results from open-label extensions and abstracts were also reported in the review.

Bosentan versus placebo (5 RCTs, n=453).

Three RCTs reported statistically significant increases in 6MWD in patients allocated to bosentan compared with placebo: differences of 76 metres (p=0.021), 44 metres (p<0.001) and 53 metres (p=0.008). An additional RCT compared the combination of bosentan plus iloprost with placebo and found a non-statistically significant increase in 6MWD (26 metres; p=0.051), and a statistically significant improvement in New York Heart Association status (34% improved by one class versus 6%, p=0.002) and a significant delay in the time to clinical worsening (p=0.0219). Two studies reported no significant difference in adverse events between treatment groups; the largest study reported an increase in abnormal hepatic function in the bosentan group but similar numbers of other adverse events between treatment groups. The combination treatment was well tolerated: overall, 2 patients withdrew due to adverse events.

One RCT (n=33) reported no significant difference in total pulmonary resistance between bosentan plus epoprostenol and epoprostenol alone, but more patients withdrew in the bosentan-epoprostenol group (4 withdrawals versus 1).

Sildenafil versus placebo (3 RCTs, n=320).

One crossover RCT (n=22) reported that sildenafil was associated with a statistically significant increase in exercise time on the treadmill compared with placebo (44% increase; p<0.0001). Minor adverse effects were associated with placebo, but no patients discontinued treatment due to adverse events. One RCT (n=278) reported a statistically significant increase in 6MWD in patients allocated to sildenafil compared with placebo (p<0.001). Serious adverse events considered to be related to sildenafil were reported in 2 patients. Epistaxis was more common among patients taking sildenafil plus warfarin. One crossover RCT (n=20) that compared sildenafil with placebo reported a statistically significant increase in 6MWD from baseline (p<0.0001). No serious adverse events were reported.

Sitaxsenten (2 fully published RCTs).

One RCT (n=178) reported a statistically significant increase in peak VO2 in patients allocated to 300 mg sitaxsenten compared with placebo (p<0.01), but no difference between 100 mg sitaxsenten and placebo. No 'clinically meaningful' differences in adverse events were reported between treatment groups. One RCT (n=185) reported a statistically significant increase in 6MWD in patients allocated to 100 mg sitaxsenten compared with placebo (difference 31.4 metres; p=0.03), but no significant difference between 50 mg sitaxsenten and placebo. No differences in the number of patients with adverse events were reported between treatment groups.

Ambrisentan (1 RCT).

This study (n=64) reported a statistically significant increase in 6MWD in patients allocated to ambrisentan (1 to 10 mg/day) compared with placebo (36 metres; p<0.001). The RCT reported no 'clinically meaningful' differences in adverse events between treatment groups.

Authors' conclusions
All oral treatments (sildenafil, bosentan, sitaxsenten and ambrisentan) improved exercise ability in patients with PAH, but the results for other outcomes were not consistent.

CRD commentary
The review question was defined in terms of the participants and intervention; inclusion criteria for the study design and outcomes were broad. The lack of specified primary review outcome measures could have led to selective reporting of the results, however, the author did highlight which measures were the primary study outcomes. Only one database plus unspecified online conference abstracts were searched for reports in English, and this might have resulted in the omission of other relevant studies. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Although all of the included RCTs were double-blind, no other aspect of validity was assessed. The results from these studies and any synthesis may not, therefore, be reliable.

The results from the individual studies were simply described, and not synthesised, which makes it difficult to interpret the results of this review. In addition, it was not clear why some studies that were only reported as abstracts were included whilst others were not. This abstract was therefore limited to fully published studies for consistency. The author’s conclusions appear to be supported by the data presented, but the lack of reporting of review methods, selective reporting of studies, inadequate quality assessment of the included studies and inadequate synthesis mean it is difficult to confirm their reliability.

It should be noted that the author is a consultant for Actelion Pharmaceuticals.

Implications of the review for practice and research
Practice: The author did not state any implications for practice.

Research: The author stated that studies comparing different drugs and evaluating combinations of treatments are needed.

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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.