Pharmacological management of intermittent claudication: a meta-analysis of randomised trials

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Authors' objectives
To systematically review all pharmacological treatments to help guide clinicians in their treatment of patients with intermittent claudication.

Searching
MEDLINE (January 1966 to April 1998) and EMBASE (1974 and April 1998) were searched (search terms provided in a table). In addition manual searches were carried out using the reference lists from retrieved articles. The Cochrane Controlled Trials Register, Cochrane Library, was also searched. Several content experts and pharmaceutical companies were contacted for information about the existence of any unpublished or current trials.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled, double blind trials. Data from the first phase of cross-over trials were considered for inclusion. Single-blind, non-blind and non-comparative studies were excluded. Surgical trials and exercise trials were also excluded.

Specific interventions included in the review
Inclusion criteria were all pharmacological therapies. Included in the studies were therapy with vasodilators (naftidrofuryl, pentoxifylline), antiplatelet agents (ketanserin, diprydamol, sulocitidil, picotamide and indobufen) and others (levocarnitine, ticlopidine, ginkgo biloba). The mean duration of the studies was 24 weeks, and dosages varied according to the intervention.

Participants included in the review
Patients with moderate intermittent claudication due to peripheral vascular disease at stage II or III according to Fontaine's classification (pain-free walking distance of 50 to 200m, or less than 50m, respectively). The duration of intermittent claudication ranged from 3 months to less than 5 years. Most trial participants were men in their sixth decade of life diagnosed with moderate intermittent claudication.

Outcomes assessed in the review
The primary outcomes measures were pain-free walking distance (PFWD; the distance walked on a treadmill before the onset of pain) and absolute claudication distance (MWD; the maximum walking distance walked on a treadmill).

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed each potentially relevant study for inclusion. Inter-observer agreement was established and consensus was reached before a trial was included in the review.

Assessment of study quality
A three-item scale was used which accounted for the quality of randomisation, double-blinding, and inclusion of data for drop-outs and withdrawals (see Other Publications of Related Interest no.1). The assessment scale scores ranged from 0 to 5, with higher scores indicating a superior quality of reporting. The adequacy of allocation concealment was also assessed. Each trial was assessed independently by two reviewers. The trials were scored under masked conditions (the authors, their affiliation, all journal identifiers, references and funding sources were deleted), and final scores were obtained through group consensus.
Data extraction
The authors do not state how data were extracted for the review, or how many of the authors performed the extraction. Data were extracted on trial design, patient baseline characteristics, medications, primary and secondary outcomes, and adverse events.

Methods of synthesis
How were the studies combined?
Pooled estimates of treatment efficacy were derived for both PFWD and MWD at each assessment using the DerSimonian-Laird random-effects model. A trial effect size was defined in the difference in mean changes in baseline in these two groups between treatment groups. Publication bias was assessed by funnel plots for both primary outcomes at two assessment times: 12 and 24 weeks.

How were differences between studies investigated?
A test for heterogeneity was performed. Sensitivity analyses were performed for the primary outcomes at two assessment time points: 12 and 24 weeks. Separate subgroup analyses were performed for naftidrofuryl, and pentoxifylline, the two medications with the largest number of studies.

Results of the review
Fifty-two trials with a total of 5088 patients were included.

Pain-free walking distance (PFWD).
Individuals in all the treatment groups walked significantly further that those in the non-treatment groups. The greatest pooled treatment effects were noted for 24-week trials of vasodilators, and antiplatelets compared with levocarnitine and gingko biloba. The treatment effects for 24-week trials of vasodilators (n=5 trials) were 138.4 metres (m) (95% CI: 12.7, 264.0). For naftidrofuryl (n=2 trials) it was 101.5m (95% CI: 43.5, 159.5) and for pentoxifylline (n=3 trials) the treatment effect was 208m (95% CI: 14.0, 50.5). The treatment effect for antiplatelet agents (n=6 trials) was 61.8m (95% CI: -66.6, 482.5), compared with 30.9 m (95% CI: 20.6, 41.2) for levocarnitine (n=2 trials) and 32.3m (95% CI: 14.0, 50.5) for gingko biloba (n=4 trials). There was a time response relationship with longer trials (>16 weeks) showing a greater effect on PFWD for all treatments.

Sensitivity analysis of quality weight and English only trials made little difference for assessments of primary outcomes in 12-week studies, but reduced PFWD from 47.3 to 39.7 and 37.9m respectively in 24-weeks studies. Sensitivity analysis of study sponsorship showed the greatest decrease of treatment effect, but this was probably due to the inclusion of few trials in this category.

Maximum walking distance (MWD).
The pooled effect of vasodilators in general (n=3 trials) and pentoxifylline (n=2 trials) at 24 weeks showed the greatest change (321.6m, 95% CI: 169.4, 473.7) and (356.9m, 95% CI: 208, 505.8) respectively, compared with 44 to 59m for other treatments. However, the combined results of the vasodilator studies should be interpreted with caution as 2 trials reported large improvements with only 20 and 16 patients respectively.

Secondary outcomes.
Very little consistent information was available for other clinical end-points, such as overall mortality and adverse effects.

Assessment of publication bias.
Assessment of publication bias by a funnel plot suggested the possibility of bias. There was a positive correlation between effect size and precision. Specifically the coefficients of bias were 2.48 (standard error (SE) 0.67, p<0.001) for PFWD and 1.18 (SE 0.45, p=0.005) for MWD.
Authors' conclusions
These data suggest that some of the medical therapy, pentoxifylline in particular, can only modestly increase functional status in patients with moderate intermittent claudication. There is a need for uniformity in research design and reporting of trials. A future trial comparing medical therapy with physical therapy is indicated.

CRD commentary
This is a very well-written and conducted systematic review. Inclusion and exclusion are thorough and the search strategy is good. The possibility of publication bias is addressed in the review. The methods of the review are clearly described, although the authors do not state how data were extracted, or how many reviewers performed the data extraction. An assessment of the validity of the studies is made, and the quality of the trials is taken into account in sensitivity analyses. The authors' conclusions follow on from the results of the review.

Implications of the review for practice and research
Practice: The authors state that some of the medical therapy, pentoxifylline in particular, can only modestly increase functional status in patients with moderate intermittent claudication.

Research: The authors state that a future trial comparing medical therapy with physical therapy is indicated.

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Other publications of related interest

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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.