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Pharmacological Management of Intermittent Claudication

A Meta-Analysis of Randomised Trials

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Abstract

Intermittent claudication, a symptom of atherosclerosis in the large vessels of the lower limbs, greatly affects patient mobility and quality of life. Medical therapy for a moderate form of this condition includes vasodilators, antiplatelet agents and alternative treatments such as ginkgo biloba.

A meta-analysis of results from 52 trials (including 5088 patients) was conducted for all current medical therapies for intermittent claudication. After 24 weeks, some of the medical therapies were found to be more effective than placebo for the primary end-points of either pain-free walking distance or maximum walking distance.

Vasodilators presented the best results in walking distance. Pentoxifylline offered better results than naftidrofuryl, although the treatment benefit, measured in additional metres walked with treatment than without, was modest. Antiplatelets, ginkgo biloba and levocarnitine were slightly more effective than placebo, although the treatment benefit was of limited clinical importance. On average, patients walked 60m further with therapy than without, and only about half of that added distance was pain-free. Very little consistent information was available for other clinical end-points, such as overall mortality and adverse effects.

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.

The most common symptom of peripheral arterial occlusive disease is intermittent claudication. This has been defined as pain, ache, cramp, numbness or sense of fatigue in the leg muscles with activity, which appears when blood flow to the lower limb is inadequate to meet the needs of the exercising muscle. This results in reduced mobility of the patient.[1]

The prevalence of intermittent claudication in the general population is estimated to be between 1 and 3% in men and women aged >60 years, with a higher prevalence in males.[2] The annual incidence of intermittent claudication is approximately 20 per 1000 people aged >65 years.[3] Intermittent claudication is thought to greatly affect a patient's quality of life because of their reduced walking range. The management of these patients should include both treatment of the symptomatic disease and prevention of all thrombotic events via physical exercise, smoking cessation, diet and pharmacological therapy.

Unfortunately, there is no 'magic bullet' in the pharmacological management of intermittent claudication. However, randomised controlled trials examining the use of various pharmacological therapies such as vasodilators, antiplatelets and other medications have suggested possible benefit for patients with intermittent claudication. To date, no review has compared the results of trials for all of the different types of treatment.

Vasodilators, such as naftidrofuryl, inhibit serotonin 5-HT_2 receptors in the blood vessel wall and influence cell metabolism.[4] Pentoxifylline is a haemorheological agent that increases erythrocyte flexibility, reduces blood viscosity and increases microcirculatory flow.[5]

Antiplatelet agents, such as ticlopidine, inhibit platelet aggregation induced by adenosine diphosphate and improve platelet function in patients with peripheral arterial disease.[6] Other antiplatelets that have been used for intermittent claudication are ketanserin (which inhibits the platelet aggregation induced by serotonin[7]) dipyridamol, suloctidil, picotamide and indobufen.

Other products have been tested for intermittent claudication, such as carnitine analogues, which increase carnitine concentrations in the ischaemic muscles of patients with severe peripheral arterial disease.[8]

Extracts from the leaves of *Ginkgo biloba*, mentioned in the traditional Chinese pharmacopoeia, are used in patients with intermittent claudication. Several mechanisms of action have been described, such as vasoregulatory effects on arteries, capillaries and veins, metabolic changes, and prevention of damage to membranes caused by free radicals.[9]

There have been many randomised controlled trials on the pharmacological management of intermittent claudication and at least 6 meta-analyses have been conducted on pentoxifylline, the most widely used and studied single therapeutic agent.[10-14] However, the literature currently lacks a comprehensive systematic review of all pharmacological treatments to help guide clinicians in their treatment of such patients.

1. Methods

1.1 Literature Search

A comprehensive literature search was conducted using the Medline and EMBASE electronic databases. All randomised, controlled trials published on Medline between January 1966 and April 1998 and on EMBASE between 1974 and April 1998 were examined. One such search strategy is outlined in table I, including the key words and text words searched in the titles and abstracts of all citations. The search reflects, in part, the approach recommended by the Cochrane Collaboration. We attempted to identify all randomised trials in all languages. In addition to the electronic database search, manual searches were carried out using reference lists from retrieved articles. The Cochrane Controlled Trials Register, Cochrane Library, was also searched. We also consulted several content experts and pharmaceutical companies for information about the existence of any unpublished or current trials.

Table I. Example of a search strategy used in the comprehensive literature search

Set	Items	Description
1	827	Intermittent claudication!(L)DT
2	0	Intermittent claudication(N)drug therapy
3	230	Intermittent claudication(N)DT
4	867	S1 or S3
5	858	S4/human
6	296 551	DT = randomised controlled trial or DT = controlled clinical or DT = clinical trial or DT = major clinical study or DT = clinical article or DT = controlled study
7	413 639	Randomised controlled trials/DE or random allocation/DE or double-blind method/DE or single-blind method/DE or clinical trials! or placebos/DE or placebo?/TI, AB or random?/TI, AB or randomised?/TI, AB
8	341 925	Comparative study/DE or follow-up studies/DE or prospective studies/DE or multicentre study/DE or drug comparison/DR, DE or crossover procedure/DE or phase 3 clinical trial/DE or intermethod comparison/DE or single blind procedure/DE
9	341 931	DT = follow-up studies or prospective studies or multicentre study/DE or prospective studies/DE or drug comparison/DE or crossover procedure/DE or phase 3 clinical trial or intermethod comparison/DE or single blind procedure/DE
10	66 337	Prospective study/DE or follow-up/DE or placebo/DE or longidutinal study/DE
11	808 289	S6 or S7 or S8 or S9 or S10
12	423	S5 and S11

1.2 Selection

For inclusion in this meta-analysis, studies had to be randomised, placebo-controlled, double-blind clinical trials. Data from the first phase of crossover trials were considered for inclusion. The patient population included those 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).[15] The duration of intermittent claudication ranged from 3 months to less than 5 years. The interventions included in this study were therapy with vasodilators (naftidrofuryl, pentoxifylline), antiplatelet agents (ketanserin, dipyridamol, suloctidil, picotamide and indobufen) and others (levocarnitine, ticlopidine, ginkgo biloba). The primary outcome 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 distance walked on a treadmill).

Single-blind, non-blind and non-comparative studies were excluded from this analysis because of evidence of a large placebo response in claudication trials.[16] Surgical trials and exercise trials were also eliminated from the analysis. Two review-

ers 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.

1.3 Quality Assessment

The quality of reporting each trial was assessed using a validated 3-item scale which accounted for the quality of randomisation, double-blinding, and inclusion of data for dropouts and withdrawals.[17] 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.[18]

Each trial was assessed independently by 2 reviewers. The trials were scored under masked conditions (the authors, their affiliations, all journal identifiers, references and funding sources were deleted), and final scores were obtained through group consensus.[19]

1.4 Data Abstraction

We collected data on trial design, patient baseline characteristics, medications, primary and secondary outcomes and adverse events. Details on trial design included treadmill speed and inclination, duration of run-in period, and trial duration. Details on patient characteristics included age, gender, Fontaine classification, and baseline performance on treadmills. Details on medications included type, dose and route of administration. Primary outcomes included PFWD and MWD. All comparisons were made between treatment and control groups preserving randomisation. Outcomes were collected at 4, 8, 12, 16, 20 and 24 weeks. Secondary outcomes included mortality, myocardial infarction, stroke, arrhythmia or angina pectoris, surgery requirement and indication of improvement in quality of life. Frequently reported adverse events data associated with specific medications were also collected.

1.5 Statistical Analysis

Pooled estimates of treatment efficacy were derived for both PFWD and MWD at each assessment time using the DerSimonian-Laird random effect model.[20] This was done for the following major classes of medications: vasodilators (subdivided into naftidrofuryl and pentoxifylline), antiplatelets, levocarnitine, ginkgo biloba and all medications together. Evidence of statistical heterogeneity is indicated for the pooled estimates (see section 2.2).

1.6 Publication Bias

From the outset, there were a number of small trials (<50 patients) assessing the effectiveness of treatment for intermittent claudication. These trials were likely to be susceptible to publication bias.[21] We assessed publication bias by funnel plots for both primary outcomes at 2 assessment times: 12 and 24 weeks. The correlation between treatment effect size and its precision (e.g. sample size) was investigated using the graphical method suggested by Egger et al.,[22] adjusting for different assessment time. In brief, we performed a linear regression of the effect size derived z-score against precision and time.[22] We also adjusted pooled estimates for possible publication bias using the trim-and-fill method as suggested by Sutton et al.[23]

1.7 Primary Outcomes

The primary outcome measures were the change from baseline for both MWD and PFWD. A trial effect size was defined as the difference in mean changes from baseline in these two measures between treatment groups. We estimated effect sizes from cross-sectional summaries (i.e. baseline, 4, 8, 12, 16, 20 and 24 weeks) for trials that did not report effect sizes directly. The standardised effect size (i.e. an effect size divided by the common standard deviation of the change from baseline) was used to combine trials reporting primary outcomes on different scales (e.g. time in seconds, percentage improvement from baseline). The variance of an effect size was derived from the common variance of a single distance measure assuming a pre-post correlation of 0.5. Variances of single distance measures were also derived from the reported p values according to Follman et al.,[24] when necessary.

1.8 Secondary Outcomes and Adverse Events

For secondary outcomes and adverse events under direct influence of the study medications, we counted the total number of events over the total patient-duration. The duration was expressed in patient-years.

Because of lack of data on both secondary outcomes and adverse events, we only summarised the rate of these events descriptively, without any statistical treatment comparisons. Only the two most frequently reported adverse events, namely gastrointestinal problems and dizziness, were summarised by type of therapy.

1.9 Sensitivity and Subgroup Analyses

Sensitivity analyses were performed for the primary outcomes at two assessment time points: 12 and 24 weeks. Empirical dimensions that possibly induced bias into the treatment effect estimates were also considered. These included allocation concealment, trial quality, language and source of funding. Quality assessment was incorporated in the primary end-point estimates using a quality weight approach.[25] Separate subgroup analyses were performed for naftidrofuryl and pentoxifylline, the two medications with the largest number of studies.

2. Results

2.1 Study Characteristics

The search strategy (see table I) resulted in the identification of 423 studies, of which 182 were considered potentially relevant. By group consensus it was determined that 52 randomised trials met the inclusion criteria.[8,26-76] The most common reasons for exclusion were duplicate publications, lack of a placebo group, less than 2 weeks' treatment, and no description of sample size, outcomes or baseline data. In total, 5088 patients were included in the meta-analysis.

The overall characteristics of the trials are summarised in table II. The majority of the studies were receiving pentoxifylline (33%) and naftidrofuryl (15%). Most trials involved a relatively small number of patients (median sample size of 43). Almost one-third of the trials (30%) reported being supported by the pharmaceutical industry. The median quality score was 3 out of 5. Most trials were reported in English (76%); the remainder were in German (17%), Italian (5%) or Danish (1.7%). The length of trials and the primary end-points differed markedly among trials. The median study duration was 24 weeks (inter-quartile range 12 to 24). Excluding 1 study lasting 260 weeks, the mean duration was 22 weeks.

Most trial participants were men in their sixth decade of life diagnosed with moderate intermittent claudication (table III). Typically, they participated in studies lasting 24 weeks and took one of several interventions (vasodilators being the most common) in varying doses. The quality of reports of the studies was moderate, and similar to those reported elsewhere (60% of the maximum possible) with plenty of room for improvement.

Table II. Overall characteristics of trials included in the meta-analysis

Characteristic	No. of studies/total patients
All studies	52/5088
Type of medication	
Vasodilators	25/1942
naftidrofuryl	8/901
pentoxifylline	17/1041
Antiplatelets	19/2417
ketanserin	5/826
dipyridamol	1/32
suloctidil	6/192
indobufen	2/353
ticlopidine	4/979
picotamide	1/35
Other	
levocarnitine	3/516
ginkgo biloba	5/213
Source of funding	
Pharmaceutical	16/2557
Other	1/31
Not noted	35/2500
Quality score [median (range)]	3/5 (2-5)
Sample size [median (inter-quartile)]	43 (30-121)

Table III. Descriptive characteristics of study population by treatment

	Vasodilators (n = 25)	Antiplatelets (n = 19)	Levocarnitine (n = 3)	Ginkgo biloba (n = 5)	All medications (n = 52)
Mean patient age [y; median (1st, 3rd quartiles)]	62 (60, 65)	63 (61, 64)	60 (59, 60)	64 (63, 66)	62 (60, 64)
Male [%; median (1st, 3rd quartiles)]	80 (76, 88)	79 (72, 86)	91 (76, 96)	64 (61, 67)	79 (70, 89)
Fontaine score					
II	12	11	2	3	28
IIB	2			2	4
II-III	6	1			7
II-IV	3				3
not reported	2	7	1		10
Commonly reported dose (mg/day) by number of studies	Naftidrofuryl 5 @ 600	Ketanserin 1 @ 60	2 @ 4000	2 @ 120	
	Pentoxifylline 4 @ 600, 10 @ 1200	Dipyridamol 1 @ 400			
		Suloctidil 5 @ 300			
		Indobufen 1 @ 200, 1 @ 400			
		Ticlopidine 4 @ 500			
		Picotamide 1 @ 900			
Study duration [wk; median (1st, 3rd quartiles)] / (min, max)	12 (8, 24) / (4, 52)	24 (24, 52) / (8, 260)	4, 24, 24[a]	12, 24, 24, 24, 24[a]	24 (8, 24) / (4, 260)
Quality of reports[b] [median (1st, 3rd quartiles)] / (min, max)	3 (2, 3) / (2, 4)	3 (3, 4) / (2, 5)	2, 3, 3[c]	3, 3, 3, 3, 5[c]	3 (3, 3) / (2, 5)

a Individual study durations (wk).

b Jadad quality scores.

c Individual study quality scores.

2.2 Primary Outcomes

Pooled estimates of treatment efficacy were measured in terms of both metres and effect size. For PFWD, individuals in all the treatment groups under study walked significantly further than those in the nontreatment groups (table IV, fig. 1). The greatest treatment effects were noted for 24-week trials of vasodilators [138.4m; 95% confidence interval (CI) 12.7, 264.0] (naftidrofuryl 101.5m; 95% CI 43.5, 159.5 and pentoxifylline 208.0m; 95% CI –66.6, 482.5) and antiplatelet agents (61.8m; 95% CI 31.9, 91.7) compared with levocarnitine (30.9m; 95% CI 20.6, 41.2) and ginkgo biloba (32.3m; 95% CI 14.0, 50.5). There was a time-response relationship, with the longer trials (>16 weeks) showing a greater effect on PFWD for all treatments.

For MWD (table V, fig. 2), the pooled effect of vasodilators at 24 weeks showed the greatest change (321.6m; 95% CI 169.4, 473.7 – pentoxifylline 356.9m; 95% CI 208.0, 505.8) compared with 44 to 59m for the other treatments. However, the combined result of the vasodilator studies should be interpreted with caution, as 2 trials[67] reported large improvements with only 20 and 16 patients, respectively.

The heterogeneity of the trials was explored using sensitivity analysis (table VI). Virtually all trials had inadequate reporting of allocation concealment. 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-week 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.

Table IV to placed here.

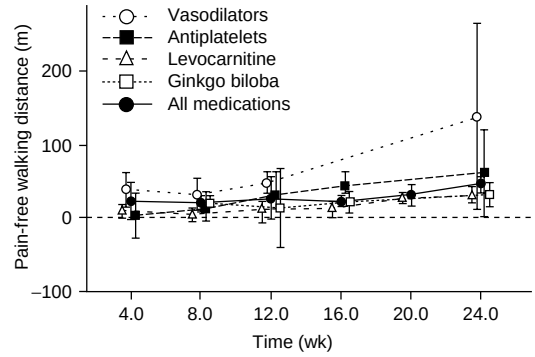

Fig. 1. Pain-free walking distance. Pooled estimates of treatment effect from a meta-analysis of randomised trials.

Assessment of publication bias by a funnel plot suggested the possibility of bias (fig. 3). 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. Thus, the effect of publication bias appears to be more important for PFWD than MWD. This is probably due to a preponderance of small and positive studies.

2.3 Secondary Outcomes

Data on secondary outcomes were limited, with the majority being available for ticlopidine (table VII). Data on mortality, myocardial infarction, arrhythmia/angina and stroke were reported for a maximum of 3 medications. The need for surgery was reported for only 5 medications and was generally quite low. Even when secondary outcome data were available for a medication, they were sparse. Of the 20 trials on pentoxifylline, for example, only one-third (7 trials) reported data on mortality outcome. No data were reported on adverse outcomes for levocarnitine, indobufen, picotamide, dipyridamol or ginkgo biloba.

Data on quality of life were also lacking in the majority of studies. Of the 5 studies that had data, patients treated with pentoxifylline and ketanserin showed no more improvement in quality of life than controls, whereas patients in one naftidrofuryl and

Table IV. Pain-free walking distance (m) – estimates of treatment effect; data presented are pooled estimates with 95% confidence intervals (no. of studies in square brackets)

	Assessment time (wk)					
Treatment	4	8	12	16	20	24
Metres						
Vasodilators	38.2 (14.5, 61.8)[a] [6]	31.0 (4.5, 57.0)[a] [5]	46.6 (29.7,63.6) [7]			138.4 (12.7, 264.0)[a] [5]
naftidrofuryl	46.7 (5.6, 87.7)[a] [2]	17.2 (3.2, 31.2) [2]	58.4 (30.3, 86.5) [3]			101.5 (43.5, 159.5) [2]
pentoxifylline	30.3 (16.7, 43.8) [4]	44.0 (–2.4, 90.4) [3]	22.3 (–22.2, 66.9) [4]			208.0 (–66.6, 482.5) [3]
Antiplatelets	2.1 (–29.1, 33.3) [2]	14.8 (–4.5, 34.2) [4]	31.9 (0.4, 63.4)[a] [4]	44.0 (24.9, 63.2) [2]		61.8 (31.9, 91.7)[a] [6]
ticlopidine			37.7 (18.1, 57.4) [2]			54.9 (31.2, 78.6) [2]
Levocarnitine	8.6 (–0.2, 17.5) [2]	3.4 (–5.9, 12.7) [2]	12.0 (–6.4, 30.3) [2]	13.2 (1.0, 25.3) [2]	26.6 (16.9, 36.4) [2]	30.9 (20.6, 41.2) [2]
Ginkgo biloba		19.2 (8.0, 30.3) [3]	13.4 (–40.6, 67.4) [2]	21.6 (5.6, 37.7) [2]		32.3 (14.0, 50.5) [4]
All medications	22.3 (–2.6, 47.1)[a] [11]	20.5 (6.2, 34.7)[a] [14]	27.1 (12.7, 41.5)[a] [16]	22.3 (12.2, 32.3)[a] [6]	31.2 (14.8, 47.5) [4]	47.3 (33.7, 60.9) [17]
Effect size						
Vasodilators	1.1 (0.2, 2.0)[a] [10]	0.9 (0.06, 1.8)[a] [6]	0.3 (0.05, 0.6)[a] [9]		0.3 (0.04, 0.5) [2]	0.3 (0.07, 0.5)[a] [9]
naftidrofuryl	2.4 (–1.4, 6.1)[a] [3]	0.4 (0.07, 0.8) [2]	0.4 (0.1, 0.7) [3]			0.2 (0.00, 0.5) [4]
pentoxifylline	0.4 (0.2, 0.6) [7]	1.5 (–0.2, 3.1)[a] [4]	0.3 (–0.1, 0.7)[a] [6]		0.3 (0.04, 0.5) [2]	0.4 (–0.02, 0.8)[a] [5]
Antiplatelets	0.01 (–0.5, 0.5) [3]	0.2 (0.06, 0.4) [5]	0.4 (0.2, 0.7) [6]	0.5 (0.3, 0.7) [2]		0.5 (0.1, 0.8)[a] [9]
ticlopidine			0.5 (0.1, 0.8) [2]			0.3 (–0.1, 0.8)[a] [3]
Levocarnitine	0.1 (–0.1, 0.4) [2]	0.07 (–0.1, 0.3) [2]	0.2 (–0.2, 0.6)[a] [2]	0.2 (–0.2, 0.5)[a] [2]	0.4 (–0.1, 0.9)[a] [2]	0.46 (0.05, 0.87)[a] [2]
Ginkgo biloba		1.0 (0.2, 1.8) [3]	0.1 (–0.4, 0.7) [2]	1.3 (0.3, 2.4)[a] [2]		1.02 (0.25, 1.78)[a] [4]
All medications	0.7 (0.2, 1.2)[a] [16]	0.5 (0.2, 0.8)[a] [16]	0.3 (0.2, 0.5)[a] [19]	0.5 (0.2, 0.8)[a] [7]	0.4 (0.2, 0.6) [6]	0.5 (0.3, 0.6)[a] [26]

a Random effect estimates and test of heterogeneity at a significance level of 5%.

Table V to placed here.

one suloctidil study showed more improvement than controls (table VII). These data can be regarded only as preliminary because of the small number of patients involved.

2.4 Adverse Events

Few data were presented on adverse events, and there were large reporting discrepancies across trials (table VIII). The main adverse effect reported was gastrointestinal, which appeared to be most associated with ticlopidine and pentoxifylline. Dizziness was also reported with ketanserin. There were virtually no data on adverse effects from trials evaluating levocarnitine, indobufen, picotamide, dipyridamol, suloctidil or ginkgo biloba.

3. Discussion

Medical therapy for patients with intermittent claudication generally has two goals: improvement of the symptoms secondary to poor limb blood flow, and prevention of cardiac and cerebrovascular events.[78]

This meta-analysis of 52 randomised trials (vasodilators, antiplatelet agents and other agents, such as levocarnitine and ginkgo biloba) and over 5000 patients indicates that there are effective management options for the treatment of intermittent claudication. However, there is inconsistency, sometimes substantial, between the studies, which results in difficulty making strong recommendations. Figures 1 and 2 show a big difference in walking distance between vasodilators and the other interventions. The statistical analysis also suggests a considerable lack of precision in the benefits offered when using vasodilators. Finally, the overall quality of reports of the included studies may cast doubt on their conclusions. Similar claims have been made elsewhere.[17]

To improve this situation there has been a call for more standardised procedures when conducting trials in intermittent claudication.[17] The plan requires a more objective initial diagnosis (and quantitative evaluation of results of treatment, such as treadmill walking distance). Since studies of the natural history of intermittent claudication have demonstrated that a significant number of patients

Table V. Maximum walking distance (m) – estimates of treatment effect; data presented are pooled estimates with 95% confidence intervals (no. of studies in square brackets)

	Assessment time (wk)					
Treatment	4	8	12	16	20	24
Metres						
Vasodilator	38.6 (3.9, 73.3) [2]	37.0 (–11.8, 85.9)[a] [7]	40.0 (–11.5, 91.5) [3]			321.6 (169.4, 473.7) [3]
naftidrofuryl		15.3 (–14.5, 45.0) [2]	31.8 (–26.5, 90.2) [2]			
pentoxifylline		61.5 (–30.1, 153.1)[a] [5]				356.9 (208.0, 505.8) [2]
Antiplatelets	59.8 (–18.6, 138.1)[a] [4]	81.6 (14.3, 148.9)[a] [5]	62.7 (2.6, 122.8)[a] [5]	43.6 (17.9, 69.3) [2]		54.3 (25.2, 83.4) [5]
ticlopidine			17.5 (–7.8, 42.8) [2]			43.9 (10.3, 77.6) [2]
Levocarnitine	34.5 (–15.8, 84.8)[a] [3]	16.6 (3.7, 29.5) [2]	32.4 (2.0, 62.7) [2]	41.7 (28.2, 55.2) [2]	45.9 (25.1, 66.7) [2]	57.1 (42.8, 71.4) [2]
Ginkgo biloba		20.1 (–2.8, 42.9) [3]	100.7 (15.9, 185.5) [2]	20.7 (–3.5, 45.0) [2]		58.7 (3.6, 113.8) [3]
All medications	34.5 (11.1, 57.9)[a] [10]	30.9 (10.8, 50.9)[a] [17]	43.2 (17.2, 69.1)[a] [12]	37.9 (27.2, 48.6) [6]	54.4 (22.0, 86.8) [4]	60.3 (36.5, 84.1)[a] [13]
Effect size						
Vasodilator	0.3 (0.1, 0.5) [4]	0.3 (–0.04, 0.6)[a] [8]	0.2 (–0.04, 0.4) [4]		0.3 (0.1, 0.5) [2]	0.3 (0.1, 0.6) [6]
naftidrofuryl	0.3 (–0.006, 0.7) [2]	0.2 (–0.2, 0.5) [2]	0.1 (–0.2, 0.4) [2]			0.2 (–0.08, 0.4) [2]
pentoxifylline	0.3 (0.08, 0.6) [2]	0.4 (–0.1, 0.9) [6]	0.2 (–0.07, 0.6) [2]		0.3 (0.1, 0.5) [2]	0.5 (0.06, 1.02) [4]
Antiplatelets	0.3 (–0.1, 0.7) [5]	0.4 (–0.01, 0.8)[a] [6]	0.3 (–0.06, 0.7)[a] [6]	0.3 (0.1, 0.5) [2]		0.2 (–0.07, 0.6)[a] [6]
ticlopidine			0.2 (–0.05, 0.4) [2]			0.1 (–0.3, 0.5)[a] [3]
Levocarnitine	0.3 (–0.2, 0.7)[a] [3]	0.2 (0.04, 0.4) [2]	0.4 (–0.2, 1.0)[a] [2]	0.4 (–0.1, 1.0)[a] [2]	0.5 (–0.1, 1.1)[a] [2]	0.6 (0.02, 1.2)[a] [2]
Ginkgo biloba		0.3 (–0.05, 0.6) [3]	0.5 (–0.4, 1.3) [2]	0.3 (–0.07, 0.7) [2]		0.7 (0.2, 1.1) [3]
All medications	0.3 (0.1, 0.4) [13]	0.3 (0.1, 0.5)[a] [19]	0.3 (0.1, 0.5)[a] [14]	0.3 (0.2, 0.5)[a] [7]	0.5 (0.2, 0.7)[a] [6]	0.4 (0.2, 0.6)[a] [17]

a Random effect estimates and test of heterogeneity at a significance level of 5%.

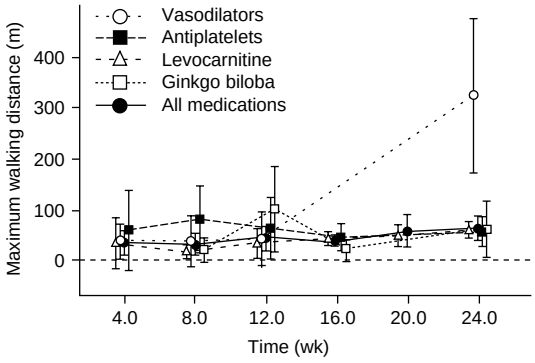

Fig. 2. Maximum walking distance. Pooled estimated of treatment effect from a meta-analysis of randomised trials.

improve over time without any specific treatment, there is also a requirement for placebo controls in claudication treatment trials.

Vasodilators provide the most consistently effective treatment benefit, especially for MWD. The analysis of pentoxifylline is based on 6 new trials since the publication of an earlier review.[10] Our results confirm that pentoxifylline therapy may be efficacious in improving the walking capacity of patients with moderate intermittent claudication, although its treatment effect, measured in additional metres walked with treatment, is modest. The effects of pentoxifylline and exercise have also been examined.[12] Unfortunately, the amount and quality of data available were inadequate to support or refute the efficacy of pentoxifylline therapy for intermittent claudication. Despite the positive conclusions reported by some investigators, differences in baseline severity of the claudication, variation in the analysis and reporting of outcomes, and incomplete data presentation allow for only a limited number of studies to be evaluated by meta-analytical techniques.

Compared with other reviews examining the benefits of naftidrofuryl,[4] including a recent one,[79] our meta-analysis has included about 50% more information. Our results indicate a lack of consistency of effect. The treatment benefit, in terms of additional PFWD, only borders on statistical significance at 24 weeks. It is not significant at 24 weeks on MWD. Readers should view the benefits of naftidrofuryl cautiously, as it was been reported that aspects of study design, such as duration, washout period, treadmill testing method and recording of risk factors may influence outcome assessments and treatment results.

We observed reasonable short term benefits for ticlopidine. However, longer term benefits are not apparent when compared with those of placebo.

Table VI. Sensitivity and subgroup analyses

Analysis	Assessment at 12 weeks		Assessment at 24 weeks	
	MWD (m; CI) [no. of trials]	PFWD (m; CI) [no. of trials]	MWD (m; CI) [no. of trials]	PFWD (m; CI) [no. of trials]
Main analysis	43.2 (17.2, 69.1) [12]	27.1 (12.7, 41.5) [16]	60.3 (36.5, 84.1) [13]	47.3 (33.7, 60.9) [17]
Sensitivity analysis				
adjusting for possible publication bias[a]	31.8 (2.6, 60.9) [12]	17.8 (5.5, 30.0) [16]	44.0 (17.1, 70.9) [13]	37.4 (22.0, 52.9) [17]
quality weight[b]	43.2 (16.5, 69.8) [12]	27.1 (12.0, 42.2) [16]	60.3 (35.6, 85.1) [13]	39.7 (33.0, 61.5) [17]
trials reported only in English	39.7 (11.3, 68.1) [9]	32.8 (17.7, 47.9) [12]	59.4 (27.4, 91.3) [9]	37.9 (27.8, 57.9) [14]
trials funded by the pharmaceutical industry	8.9 (-13.9, 31.6) [3]	20.4 (-3.8, 44.5) [6]	55.3 (19.1, 91.4) [3]	29.7 (19.1, 40.3) [8]
allocation concealment[c]	NA [0]	NA [0]	NA [1]	NA [1]

a Adjusting for publication bias using the 'trim-and-fill' method proposed by Duval and Tweedie.[77]

b Jadad quality score was incorporated in the pooled analyses using the method proposed by Moher et al.[25]

c Allocation concealment was unclear in almost all trials.

CI = 95% confidence interval of pooled estimate; **m** = metres walked; **MWD** = maximum walking distance; **NA** = not available or not done (pooled estimates were provided only when there were 2 or more trials); **PFWD** = pain-free walking distance.

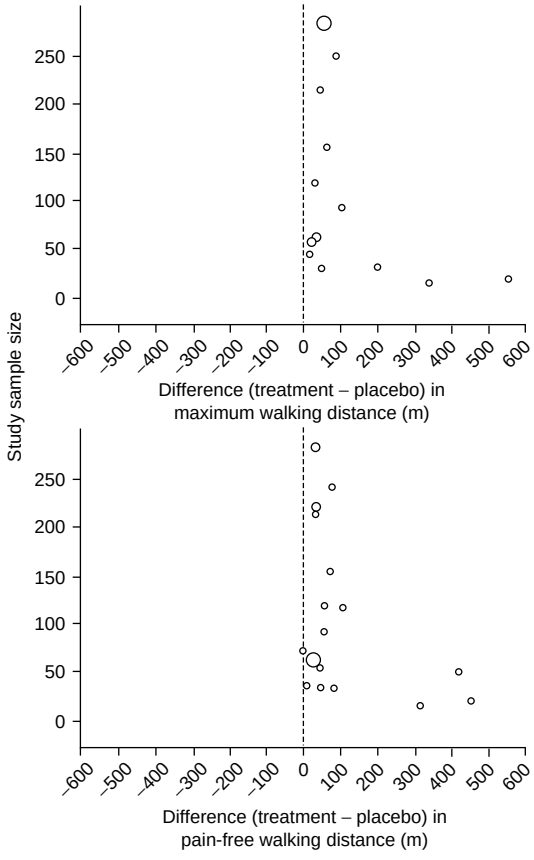

Fig. 3. Funnel plots of treatment effect (i.e. maximum and pain-free walking distance measured in metres) versus sample size. Note: Plot symbols were according to study precision.

Other antiplatelet agents showed better results than ticlopidine but again the clinical benefit was modest and the improvement in walking distance generally very small.

Only 3 relatively small, randomised trials evaluating the benefits of levocarnitine, considered a promising therapy for intermittent claudication, were included in this review. Here the benefits of intervention appeared to be the most inconsistent. Overall, the improvement in walking distance was very small.

We included 5 small trials evaluating the benefits of ginkgo biloba compared with placebo. Together these studies included a total of only 213 patients and, probably, this sparsity of data helps explain some of the inconsistency we observed in the results. Short term benefits of treatment were not statistically significant, although long term benefits were. Because of the inconsistency of results we cannot comment on the clinical benefits of ginkgo biloba.

3.1 Strength of Findings

To our knowledge, this is the most comprehensive summary of the medical treatment of intermittent claudication to date. Strengths of our study include the inclusion of alternative therapies in the treatment assessment, the thoroughness of the literature search (including non-English language trials), an analysis of results by trial length, sensitivity analysis assessing sponsorship of trials, and the assessment of publication bias.

The findings of this meta-analysis should be interpreted with caution, given the indication of publication bias. We did not undertake a thorough search of unpublished studies because these are notoriously difficult to find, and debate continues about whether they should be included in meta-analyses since they are not peer reviewed.[80]

A consistent weakness of the studies reviewed was the lack of reporting of the method of allocation concealment. There is growing evidence that reports of randomised trials with inadequate allocation concealment (e.g. once generated, the random numbers are kept in a central location – central randomisation), compared with studies where this information is well reported, result, on average, in an overestimate of the intervention effect by 30%.[18,25]

How much pharmacological therapy differs from treatment with exercise alone is not known. In a recent meta-analysis by Brandsma and colleagues[2] on the effect of walking exercise in patients with intermittent claudication, the percentage of improvement in walking distance or time ranged from 28% to 210% [mean 105%, standard deviation (SD) 55.8%].

Table VII. Secondary outcomes

Outcome/drug	No. of studies (no. of patients[a])	No. of events (no. of patient-years)		No. of reported improvements (total no. of patients)	
		treatment	placebo	treatment	placebo
Mortality					
Pentoxifylline	7 (479)	1 (59)	2 (59)		
Ticlopidine	4 (850)	28 (405)	36 (416)		
Myocardial infarction					
Ketanserin	2 (257)	1 (71)	3 (75)		
Pentoxifylline	8 (559)	4 (65)	3 (66)		
Ticlopidine	3 (803)	1 (263)	7 (274)		
Stroke					
Ticlopidine	2 (647)	2 (228)	7 (237)		
Arrythmia/angina pectoris					
Levocarnitine	2 (496)	2 (111)	2 (118)		
Ketanserin	2 (243)	0 (52)	2 (55)		
Pentoxifylline	2 (479)	3 (59)	0 (59)		
Required surgery					
Ketanserin	2 (257)	1 (71)	9 (75)		
Naftidrofuryl	5 (489)	10 (65)	19 (57)		
Pentoxifylline	4 (170)	7 (14)	7 (14)		
Suloctidil	3 (101)	3 (23)	3 (24)		
Ticlopidine	4 (894)	8 (370)	19 (379)		
Improvement in quality of life					
Ketanserin	1 (35)			6 (17)	5 (18)
Naftidrofuryl	1 (94)			29 (52)	8 (42)
Pentoxifylline	2 (154)			40 (77)	38 (77)
Suloctidil	1 (30)			15 (15)	3 (15)

a Confined to studies that explicitly reported the secondary outcome.

3.2 Research Implications

Although many trials have been conducted on medical therapy for intermittent claudication, the synthesis of the results of these trials is difficult because of heterogeneity in research design and reporting. It would be ideal if researchers in the field could agree on which primary and secondary outcomes should be measured and how they should be measured. This is particularly true for measuring the primary outcome. A standardised effect size should be established. Too often we had to derive the effect size, which was time consuming and decreased the precision of the meta-analytic results.

Table VIII. Adverse events that were reported in more than 1 study

Adverse events/drug	No. of studies (no. of patients)	No. of events (no. of patient-years)	
		treatment	placebo
Gastrointestinal			
Levocarnitine	3 (516)	4 (112)	6 (119)
Ginkgo biloba	2 (75)	2 (16)	0 (18)
Ketanserin	3 (277)	9 (77)	6 (73)
Naftidrofuryl	5 (533)	23 (108)	12 (103)
Pentoxifylline	4 (336)	36 (52)	20 (52)
Ticlopidine	3 (803)	222 (263)	74 (274)
Dizziness			
Ketanserin	4 (298)	20 (75)	6 (80)

Future trials should also have standardised reporting of adverse outcomes and adverse effects to enable more than anecdotal information to be gleaned in these areas. More thorough and consistent reporting of trial results, by the use of reporting guidelines such as the CONSORT statement,[81] would greatly improve the reliability of future meta-analyses.

In the light of the Brandsma meta-analysis[2] showing a consistently beneficial effect of an exercise prescription for people with intermittent claudication, a head-to-head trial comparing medical therapy with exercise is indicated.

3.3 Clinical Implications

Although medical therapy is statistically more effective than placebo in the treatment of intermittent claudication, the results are modest; treated patients will be able to walk, on average, 60m further with therapy than without, and only about half of that added distance will be pain free. It should also be noted that these results are based on treadmill measurements; whether patients would be able to walk the same distance in their activities of daily living is uncertain, as irregular paving, kerb heights and hills may affect the generalisability of these findings.

We have elected not to propose an algorithm regarding the medical treatment of intermittent claudication. Our meta-analysis presents a comprehensive, up-to-date review of the pharmacological management for the symptoms of intermittent claudication. However, an effective algorithm needs to incorporate the global disease management of the patient, including disease process, possible lipid management, quality of life and cost, among other issues.

In conclusion, although medical therapy, especially pentoxifylline, appears to be moderately effective, lifestyle counselling, such as the need for smoking cessation and regular physical activity, should continue to play a major therapeutic role in the treatment of intermittent claudication.

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