Alpha lipoic acid for symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials
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CRD summary
The review concluded that intravenous alpha lipoic acid led to clinically and statistically significant short-term improvements in peripheral diabetic neuropathy (nerve dysfunction). Oral administration resulted in statistical but not clinically significantly improvements. Given possible publication bias, the small number of available trials and the possibility of weaknesses in the statistical analysis, the reliability of the authors' conclusions is unclear.

Authors' objectives
To evaluate the effectiveness of oral or intravenous alpha lipoic acid compared with placebo for symptomatic peripheral diabetic neuropathy.

Searching
MEDLINE and EMBASE were searched up to November 2010 for articles published in any language. Search terms were reported. References of retrieved articles were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared intravenous or oral alpha lipoic acid with placebo, in patients with diabetes mellitus and with peripheral neuropathic pain, were eligible for inclusion. Trials had to use the total symptom score (that evaluated pain, burning, paraesthesia and numbness) as an outcome measure. Trials had to report sufficient data to enable calculation of the standard error. Unpublished trials and conference proceedings were excluded.

Included trials evaluated alpha lipoic acid in daily doses that ranged from 100mg to 1,800mg. Intravenous alpha lipoic acid was administered for three weeks. Oral therapy ranged from three weeks to six months. The age of included patients ranged from 18 years to 74 years. Most included patients had diabetes mellitus type 2.

Three reviewers independently selected the studies for review. Disagreements were resolved by consensus.

Assessment of study quality
The quality of included trials was assessed using the Dutch Cochrane Centre guidelines. This is an eight-item checklist measuring randomisation, allocation concealment, blinding, comparability of groups at baseline, follow-up of at least 80%, and use of intention-to-treat analysis.

Three reviewers independently assessed the quality of included studies.

Data extraction
The mean and standard deviation symptom score change was extracted for each group and used to calculate mean differences with 95% confidence intervals (CI). Trial authors were contacted for further data, where necessary.

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

Methods of synthesis
Standardised mean differences were calculated using the Mantel-Haenszel method. Where there was evidence of significant statistical heterogeneity, a random-effects model was used; in the absence of significant statistical heterogeneity, a fixed-effect model was used. Individual trials were weighted using the inverse variance method. Statistical heterogeneity was assessed using $I^2$. Subgroup analyses were carried out for intravenous and oral administration of alpha lipoic acid.

Results of the review
Four RCTs (585 patients) were included in the review. All trials had randomisation, allocation concealment, blinding of
participants, blinding of doctors, comparable groups at baseline, follow-up of at least 80%, and use of intention-to-treat analyses. None of the trials had blinding of investigators.

Alpha lipoic acid was associated with a significant reduction in total symptom scores (SMD -2.26 95% CI -3.12 to -1.41; four RCTs). There was evidence of significant statistical heterogeneity ($I^2=74\%$). Both oral (SMD -1.78 95% CI -2.45 to -1.10; two RCTs) and intravenous (SMD -2.81 95% CI -4.16 to -1.46; two RCTs) administration were associated with significant reductions in total symptom scores. There was evidence of significant statistical heterogeneity for intravenous administration ($I^2=81\%$) but not for oral administration of alpha lipoic acid ($I^2=0\%$).

The results of individual trials were also discussed to address issues of clinical significance and dosage.

**Cost information**
The cost of alpha lipoic acid at a dose of 600mg was from 17.15 and 75 euros (EUR) per month in the Netherlands. This compared with costs from EUR 3.41 to 71.71 per month for other treatments of neuropathic pain in diabetes.

**Authors' conclusions**
Intravenous alpha lipoic acid led to clinically and statistically significant short-term improvements in peripheral diabetic neuropathy. Oral administration resulted in statistically but not clinically significantly improvements.

**CRD commentary**
The review addressed a clear question with well-defined inclusion criteria. Only two databases were searched, so relevant trials may have been missed. The search was restricted to published articles, so publication bias could not be ruled out. As there were no language restrictions, the risk of language bias was small. Appropriate steps were taken during the study selection and quality assessment stages to minimise the risk of reviewer error and bias. It was unclear whether similar steps were taken during the data extraction process.

The quality of included trials was assessed using an appropriate tool and the results showed good quality. There were no conflicts of interest in the current review, but all included trials received funding from a manufacturer of alpha lipoic acid. It was unclear whether suitable steps were taken in the meta-analysis to enable multiple intervention groups with the same comparator group to be entered into the meta-analysis. There was evidence of significant statistical heterogeneity for two of the analyses, so it may not have been appropriate to combine the trials in a meta-analysis. Only a small number of trials with relatively few patients were available for meta-analysis, which potentially undermined the strength of the results.

Given the possibility of publication bias, the small number of available trials and the possibility of weaknesses in the statistical analysis, the reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**
**Practice:** The authors stated that intravenous lipoic acid should be considered as treatment for diabetic patients with peripheral neuropathy who did not respond to normal therapy.

**Research:** The authors stated that further long-term research was needed to evaluate both intravenous and oral alpha lipoic therapy using a suitable neuropathic pain scale.

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**Bibliographic details**

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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.