Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Mijnhout GS, Kollen BJ,et al.
Title	Alpha Lipoic Acid for Symptomatic Peripheral Neuropathy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Trials
PMID	22331979
Citation	Int J Endocrinol. 2012;2012:456279. doi: 10.1155/2012/456279
Other information if relevant	

Methods	
Aim of study	To evaluate the effectiveness of alpha lipoic acid as a treatment of painful diabetic peripheral neuropathy
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Patients with diabetes mellitus and peripheral neuropathic pain
Intervention being evaluated	Alpha lipoic acid (ALA) intravenously ALA orally
Comparison or control intervention	Placebo

Outcomes	- Total symptom score (TSS) for neuropathic symptoms - TSS asks the patient to assess the intensity (absent, mild, moderate, severe) and frequency (now and then, often, continuous) of four symptoms (pain, burning, paresthesia, numbness) - The TSS has a minimum score of 0 for no symptoms and a maximum score of 14.66 for the highest level of each symptom - A 30% change in the TSS is considered to be clinically meaningful, or a change of at least 2 points in a patient who had a starting score of at least 4 points - Mean change scores on the TSS were used as the main outcome of treatment
Study types	Randomized clinical trials only

Study selection	
Search date of literature review	November 2010
Databases in literature search	MEDLINE, EMBASE
How authors assessed study quality (risk of bias and other considerations	- Randomization - Concealment of allocation - Blinding of patients, doctors, and investigators - Baseline comparability of groups - Followup of at least 80% of patients - Intention to treat analysis of outcome
Additional information if relevant	The RCTs were primarily performed by a single German research group, but recruited patients in Germany, Israel, Russia, and Croatia

Results	
Number of studies screened	- 242 studies were screened on the basis of abstracts and title
Number of studies selected for analysis of results	- 10 studies were selected for more detailed attention - 4 studies were excluded for not meeting the inclusion criteria - 2 additional studies were excluded for methodological limitations - 4 studies were included in the meta-analysis - 2 of the studies investigated intravenous ALA - 2 of the studies investigated oral ALA

Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc)	- The authors used I^2 as a criterion for judging heterogeneity, where a value of >30% was judged to be heterogeneous, prompting the use of a random effects model for pooling the data
Quality of studies as assessed by authors	Most of the studies were rated satisfactory on the methodological criteria, except that no study met the criterion of blinded investigators
Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	- For the TSS, pooling of oral and IV ALA studies was heterogeneous, with an I^2 of 74%, and the pooled mean difference in TSS change scores was 2.26 points for ALA over placebo - The pooled effect size was greater for IV ALA (2.81 points with a 95% confidence interval 1.46 to 4.16) than for oral ALA (1.78 points with a 95% CI 1.10 to 2.45) - The IV studies were heterogeneous with I^2 of 81%, while the oral studies were homogeneous with I^2 of 0
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	
Additional information if relevant	- A single author (Ziegler 2006) published a single article which had three dosing levels of ALA versus placebo: 600 mg, 1200 mg, and 1800 mg; these were handled in the meta-analysis as three separate trials with the same comparison group of placebo patients - The three doses of ALA had nearly identical effect sizes in terms of reduction in TSS - The 2 studies of IV ALA had a length of 3 weeks; one of the studies of oral ALA had a length of 3 weeks, and one of the oral studies had a length of 5 weeks

Conclusions	
Key conclusions of study authors	- ALA causes a statistically significant decrease in neuropathic pain when administered in daily doses of 600 mg for three to five weeks - Although the studies of IV ALA had a clinically important effect on the main outcome of the TSS, the clinical importance of oral ALA was less clear, because the reduction in TSS was less than the 30% threshold considered to be clinically relevant - The studies were all sponsored by industry, and the several of the authors had ties to the manufacturer - The studies are all very short term, and need to be longer in the future
Additional information if relevant	

Comments by DOWC staff

- The authors mention most of the limitations of the available studies, especially the short duration and the sponsorship by the manufacturer of ALA
- Although the between-group differences between oral ALA and placebo are less than 2 points, which was one of the criteria used as an indicator of clinical relevance, the ALA groups had fairly large changes in the TSS of about 4.5 points on a scale of 1 to 14.64
- The finding that the effect size of IVALA is greater than for the oral route is difficult to interpret, but may support the hypothesis that there is some biological activity of ALA
- The meta-analysis of the oral route of administration shows a forest plot (Table 6) with four study entries; however, three of these represent different ALA doses from the same clinical trial, and this can be a factor in the absence of heterogeneity in the analysis

Assessment by DOWC staff	

Overall assessment as suitability of evidence for the guideline ☐ High quality ☒ Adequate ☐ Inadequate	Adequate meta-analysis showing that there is some evidence that alpha-lipoic acid at a dose of 600 mg per day may reduce the symptoms of painful diabetic neuropathy in the short term of three to five weeks. The effect of the intravenous route appears to be greater than that of the oral route, but the oral route may have a clinically relevant effect
If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Ziegler D, Ametov A, et al., Oral treatment with α-lipoic acid improves symptomatic diabetic polyneuropathy. Diabetes Care, vol. 29, no. 11, pp. 2365–2370, 2006.