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[Intervention Review]

Alpha-lipoic acid for diabetic peripheral neuropathy

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ABSTRACT

Background

Diabetic peripheral neuropathy (DPN) is a frequent complication in people living with type 1 or type 2 diabetes. There is currently no effective treatment for DPN. Although alpha-lipoic acid (ALA, also known as thioctic acid) is widely used, there is no consensus about its benefits and harms.

Objectives

To assess the effects of alpha-lipoic acid as a disease-modifying agent in people with diabetic peripheral neuropathy.

Search methods

On 11 September 2022, we searched the Cochrane Neuromuscular Specialised Register, CENTRAL, MEDLINE, Embase, and two clinical trials registers. We also searched the reference lists of the included studies and relevant review articles for additional references not identified by the electronic searches.

Selection criteria

We included randomised clinical trials (RCTs) that compared ALA with placebo in adults (aged 18 years or older) and that applied the study interventions for at least six months. There were no language restrictions.

Data collection and analysis

We used standard methods expected by Cochrane. The primary outcome was change in neuropathy symptoms expressed as changes in the Total Symptom Score (TSS) at six months after randomisation. Secondary outcomes were change in neuropathy symptoms at six to 12 months and at 12 to 24 months, change in impairment, change in any validated quality of life total score, complications of DPN, and adverse events. We assessed the certainty of the evidence using GRADE.

Main results

Our analysis incorporated three trials involving 816 participants. Two studies included people with type 1 or type 2 diabetes, while one study included only people with type 2 diabetes. The duration of treatment was between six months and 48 months. We judged all studies at high risk of overall bias due to attrition.

ALA compared with placebo probably has little or no effect on neuropathy symptoms measured by TSS (lower score is better) after six months (mean difference (MD) −0.16 points, 95% confidence interval (CI) −0.83 to 0.51; 1 study, 330 participants; moderate-certainty evidence). The CI of this effect estimate did not contain the minimal clinically important difference (MCID) of 0.97 points. ALA compared

with placebo may have little or no effect on impairment measured by the Neuropathy Impairment Score-Lower Limbs (NIS-LL; lower score is better) after six months (MD −1.02 points, 95% CI −2.93 to 0.89; 1 study, 245 participants; low-certainty evidence). However, we cannot rule out a significant benefit, because the lower limit of the CI surpassed the MCID of 2 points. There is probably little or no difference between ALA and placebo in terms of adverse events leading to cessation of treatment within six months (risk ratio (RR) 1.48, 95% CI 0.50 to 4.35; 3 studies, 1090 participants; moderate-certainty evidence).

No studies reported quality of life or complications associated with DPN.

Authors' conclusions

Our analysis suggests that ALA probably has little or no effect on neuropathy symptoms or adverse events at six months, and may have little or no effect on impairment at six months. All the studies were at high risk of attrition bias. Therefore, future RCTs should ensure complete follow-up and transparent reporting of any participants missing from the analyses.

PLAIN LANGUAGE SUMMARY

Is alpha-lipoic acid (a natural antioxidant) better than no treatment or dummy treatment for nerve damage in people with diabetes?

Key messages

• We found that alpha-lipoic acid treatment compared with placebo (dummy treatment) probably has little or no effect on the symptoms of nerve damage and may have little or no effect on impairment after six months of treatment.
• There is probably little or no difference between alpha-lipoic acid and placebo in the occurrence of unwanted effects that cause people to stop using treatment.
• We found no studies to help us answer whether alpha-lipoic acid treatment can improve quality of life or complications of nerve damage (ulceration, amputation, or both) in people with diabetes.

What is diabetic peripheral neuropathy?

People with diabetes have too much sugar in their blood because their pancreas cannot make any insulin (type 1 diabetes) or cannot make enough insulin (type 2 diabetes). Diabetes is one of the most common non-communicable diseases (diseases not spread by infection), and it is becoming more common every year. People with both type 1 and type 2 diabetes develop complications.

High blood sugar can decrease blood flow in the blood vessels that supply the nerves, resulting in nerve damage (diabetic peripheral neuropathy). The main symptom of this condition is pain. Other symptoms include tingling, a burning sensation, numbness, shooting or sharp aches, and even extreme sensitivity to clothes touching the skin. These symptoms are caused by direct nerve damage, which is different from typical pain caused by injury or tissue damage. For this reason, usual painkiller medicines do not alleviate pain caused by peripheral neuropathy. People with this condition can also experience weakness, loss of reflexes, or loss of sensation (together known as impairment), which can disrupt normal functions such as walking.

How is diabetic peripheral neuropathy treated?

Medicines used to treat depression or epilepsy may improve symptoms of diabetic peripheral neuropathy. Some studies have suggested that alpha-lipoic acid (an antioxidant made naturally in the body) may help because of its presumed anti-inflammatory effects.

What did we want to find out?

We wanted to find out if alpha-lipoic acid was better than no treatment or placebo (dummy treatment) for improving symptoms of diabetic peripheral neuropathy, impairment, quality of life, and complications of diabetic peripheral neuropathy (ulceration, amputation, or both) in people with type 1 or type 2 diabetes. We also wanted to know if alpha-lipoic acid had any unwanted effects.

What did we do?

We searched for studies that investigated alpha-lipoic acid treatment compared to no treatment or placebo for at least six months. We analysed and summarised the results of the trials and rated our confidence in the findings.

What did we find?

We found three studies that analysed 816 adults with type 1 and type 2 diabetes. The participants received either alpha-lipoic acid or placebo. The dose of alpha-lipoic acid ranged from 600 mg/day to 1800 mg/day.

Alpha-lipoic acid compared to placebo probably has little or no effect on symptoms of diabetic peripheral neuropathy and may have little or no effect on impairment after six months of treatment. There is probably little or no difference between alpha-lipoic acid and placebo in terms of unwanted effects that cause people to stop treatment.

No studies measured the effect of alpha-lipoic acid treatment on quality of life or complications of peripheral neuropathy.

Until alpha-lipoic acid is proven effective, there is no rationale for comparing it with active treatments.

What are the limitations of the evidence?

We are moderately confident in the evidence on symptoms and unwanted effects because in all three studies, the investigators lost contact with many participants before the end of treatment (loss to follow-up). We have little confidence in the evidence on impairment, because of loss to follow-up and because the result was very imprecise.

How up-to-date is this evidence?

The evidence is current to 11 September 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Alpha-lipoic acid compared to placebo for diabetic peripheral neuropathy

Alpha-lipoic acid compared to placebo for diabetic peripheral neuropathy

Patient or population: people with DPN
Setting: outpatients
Intervention: ALA
Comparison: placebo

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Comments
				Risk with placebo	Risk difference with ALA	
Change in neuropathy symptoms Assessed with: TSS (0 to 14.64, lower is better) Follow-up: 6 months	330 (1 RCT)	⊕⊕⊕⊖ **Moderate**[a]	—	The mean change was 3.78 points lower	**MD 0.16 points lower** (0.83 lower to 0.51 higher)	ALA compared to placebo probably has little or no effect on neuropathy symptoms after 6 months. The 95% CI did not contain the MCID of 0.97 points (Bastyr 2005).
Change in impairment Assessed with: NIS-LL (0 to 88, lower is better) Follow-up: 6 months	245 (1 RCT)	⊕⊕⊖⊖ **Low**[b]	—	The mean change was 3.37 points lower	**MD 1.02 points lower** (2.93 lower to 0.89 higher)	ALA compared to placebo may have little or no effect on impairment after 6 months. However, the lower 95% CI limit surpasses the MCID of 2 points (Dyck 1991; Peripheral Nerve Society 1995), so we cannot rule out a beneficial effect.
Change in any validated quality of life score	—	—	—	—	—	No studies reported this outcome.
Complications of DPN	—	—	—	—	—	No studies reported this outcome.
Adverse events leading to cessation of treatment Follow-up: 6 months	1090 (3 RCTs)	⊕⊕⊕⊖ **Moderate**[c]	**RR 1.48** (0.50 to 4.35)	**Study population**		There is probably little or no difference between alpha-lipoic acid and placebo probably results in little or no difference in adverse events at 6 months.
				2 per 1000	1 more per 1000 (1 fewer to 7 more)	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ALA: alpha-lipoic acid; **CI:** confidence interval; **DPN:** diabetic peripheral neuropathy; **MCID**: minimal clinically important difference; **MD**: mean difference; **NIS-LL:** Neuropathy Impairment Score-Lower Limbs **RCT**: randomised clinical trial; **RR:** risk ratio; **TSS:** Total Symptom Score.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once for risk of bias (attrition bias).
[b]Downgraded once for risk of bias (attrition bias) and once for imprecision (95% CI contains the MCID).
[c]Downgraded once for risk of bias (attrition bias).

BACKGROUND

Description of the condition

Epidemiology of diabetes mellitus and diabetic polyneuropathy

Diabetes mellitus is one of the most common non-communicable diseases and a leading public health concern. Chronic hyperglycaemia arises from two main conditions: insufficient insulin production, known as type 1 diabetes (previously insulin-dependent diabetes); and insulin resistance, known as type 2 diabetes (previously non-insulin dependent diabetes; WHO 1999). As reported in the 9th edition of the International Diabetes Federation Diabetes Atlas, nearly half a billion people worldwide were living with diabetes in 2019. Projections estimate a 25% increase in prevalence by 2030 and a 51% increase by 2045 (Saeedi 2019). People with both types of diabetes can develop multisystem chronic complications, with diabetic neuropathies being the most frequent (IDF 2021; WHO 2016). These are classified clinically as either diffuse or atypical (e.g. mononeuropathies, radiculopathies, or polyradiculopathies; Pop-Busui 2017). Both the sensorimotor and autonomic nervous systems can be affected by diffuse disease. Sensorimotor polyneuropathy disease can involve either large or small nerve fibres, is usually predominantly sensory, and is often painful (Edwards 2008).

Across the spectrum of nervous system involvement, distal symmetric polyneuropathy (referred to as diabetic peripheral neuropathy (DPN) in this review) is the most common form, accounting for up to 75% of diabetic neuropathies (Bansal 2006). The estimated prevalence in the diabetic population ranges from 8% to 54% (Feldman 2019), and the four-year cumulative incidence ranges from 66% to 74%, increasing with age and disease duration (Pop-Busui 2013).

DPN is a major cause of morbidity and is the primary cause of non-traumatic amputations. It is also associated with considerable physical disability, altered quality of life, and increased mortality (Boulton 2005; Tesfaye 2011).

Regular screening for DPN signs and symptoms is crucial to identify the disease in its earliest stages and intervene promptly, preventing the development of complications (Pop-Busui 2017).

Clinical manifestations of diabetic polyneuropathy

From a clinical perspective, DPN is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (Bansal 2006; Boulton 1998). DPN may be asymptomatic and insidious at onset. It may be sensory or motor and may affect small or large fibres, or both (Bansal 2006).

The most common symptom of DPN is neuropathic pain caused by involvement of small fibres, which occurs in up to 50% of people with DPN and is the most frequent reason for seeking medical care (Bredfeldt 2015; Tesfaye 2011). Painful symptoms are varied and include tingling, burning sensations, paraesthesia, shooting or lancinating pains, aching, and allodynia, defined as pain elicited by normally innocuous stimuli, such as contact with clothing (Tesfaye 2011). Involvement of large fibres manifests as painless paraesthesia with vibration impairment, touch and pressure sensations, and loss of ankle reflex, with the possibility of sensory ataxia in advanced stages (Bansal 2006).

DPN complications are also a major threat to the general well-being and quality of life of people with diabetes. Sensory loss, along with retinopathy and vestibular dysfunction, increases the risk of falls two- to three-fold in people with versus people without DPN (Agrawal 2010). People with DPN are also seven times more likely to develop foot ulcerations (Amin 2016). This further predisposed them to active or passive soft tissue infection, which can progress to bone infection and subsequent lower extremity amputation (Kim 2013). DPN, peripheral vascular disease, and soft tissue and bone deformity are serious complications that make diabetes the leading cause of lower extremity amputation (Callaghan 2012a).

DPN symptoms are usually assessed using patient-reported outcome measures that quantify discomfort, sleep disturbances, and quality of life (Bredfeldt 2015).

Pathophysiology of diabetic polyneuropathy

DPN primarily involves sensory and autonomic axons, and to a lesser extent, motor axons (Feldman 2019). Substantial experimental data support the idea that DPN affects the entire neuron, from the perikaryon to the distal terminals (Feldman 2019). However, the pathophysiology of DPN is not fully understood and is likely multifactorial, encompassing genetic, environmental, behavioural, metabolic, neurotrophic, and vascular factors (Chen 2013; Xu 2013). Oxidative stress, whether it arises from an overproduction of free radicals, a deficiency in antioxidant protection, or both, is believed to play a crucial role in the disease's pathogenesis (Low 1997). While good glycaemic control can lower the risk of DPN development, it is not always possible to achieve and is typically insufficient to halt the progression of DPN (Chen 2013; DCCT 1993; Duckworth 2009; Tesfaye 2011).

The pathophysiology of DPN can primarily be described as a neural dysfunction resulting from the interplay of reduced blood flow to nerves (due to hyperglycaemia) and increased oxidative stress, which induces local inflammatory reactions through reactive oxygen species (ROS; Brownlee 2005). Prolonged hyperglycaemia can activate multiple pathways simultaneously, leading to:

- activation of polyol and protein kinase pathways, which leads to reduced nicotinamide adenine dinucleotide phosphate (NADPH) and subsequent depletion of glutathione and nitric oxide (Feldman 1997; Uehara 2004);
- stimulation of angiogenesis via the vascular endothelial growth factor pathway;
- induction of basement membrane thickening and endothelial proliferation (through transforming growth factor-beta (TGF-β) and nuclear factor-kappa B (NFkB)), which cause altered capillary permeability and local hypoxia;
- activation of the hexosamine pathway and diversion of fructose-6-phosphate from the glycolytic pathway; and
- modification of gene expression for glucose transporters and glucokinase (Kolm-Litty 1998).

Generation of ROS and advanced glycosylation end-products activate the same NFkB pathway, which increases oxidative stress and further depletes NADPH. Oxidative stress also induces the activation of poly(adenosine diphosphate-ribose) polymerase, resulting in further nicotinamide adenine dinucleotide

depletion, a positive feedback loop activation of the protein kinase pathway, and increased inflammation (Vinik 2004). All these pathways promote mitochondrial dysfunction, leading to apoptosis, axonal degeneration, and eventual axonal death. Local proinflammatory cytokines, induced by oxidative stress, promote macrophage recruitment, leading to subsequent glial failure, myelin breakdown, and impaired nerve regeneration (Wang 2006). The overpowered antioxidant response allows the progression of a vast injury cascade initiated by ROS, which is accentuated by loss of adenosine triphosphate (ATP) production and neuronal dysfunction (Fernyhough 2015). Neuronal oxidative/nitrosative stress can also stimulate numerous downstream kinases and transcriptional factors, triggering a feed-forward loop of injury (Stavniichuk 2014) and the release of cytokines and chemokines (Feldman 2017). Existing inflammation and immune responses are further stimulated, enhancing cellular oxidative/nitrosative stress, and leading to increased neuronal injury (Vincent 2013). These pathways primarily affect axons, while Schwann cells, exhibiting a much stronger innate antioxidant response, are at least partially protected against ROS damage (Feldman 2017).

The clinical consequences of this hyperglycaemia-induced inflammatory and oxidative state include axonal dystrophy, decreased nerve conduction velocity, diminished neurovascular flow, and, ultimately, small and large fibre neuropathy (Edwards 2008; Feldman 2017).

Management of diabetic polyneuropathy

For the current management of DPN, there are three major treatment strategies: causal therapy (which includes lifestyle changes, intensive glucose and metabolic syndrome control, and overall cardiovascular risk reduction; DCCT 1995; Elafros 2022), pathogenesis-oriented therapy, and symptomatic-directed therapy (Ziegler 2021a).

DPN guidelines issued by the American Diabetes Association (Pop-Busui 2017), International Diabetes Foundation (Ibrahim 2017), American Academy of Neurology (Price 2022), and German Diabetes Association (Ziegler 2021b) all recommend the use of tricyclic antidepressants (Lunn 2014; Saarto 2007), serotonin-noradrenaline reuptake inhibitors (e.g. duloxetine or venlafaxine; Allen 2014), and anticonvulsants (e.g. gabapentin or pregabalin) as first- or second-line treatments for painful DPN. Opioids and opioid-like drugs (e.g. tramadol) are recommended as second- or third-line treatments (Snedecor 2014; Tesfaye 2011; Ziegler 2006).

Regarding pathogenesis-oriented therapy, recommendations are less consistent across the guidelines, primarily due to a lack of sufficient high-quality clinical data supporting the use of medications that target the inflammatory and oxidative stress mechanisms involved in the polyol, hexosamine, protein kinase C, and advanced glycation end product pathways (Ziegler 2022). Two guidelines mention the use of alpha-lipoic acid (ALA) to target the inflammatory pathways in DPN (Allen 2014; Ibrahim 2017; Ziegler 2021b), while others do not (Pop-Busui 2017; Price 2022).

Description of the intervention

ALA, or thioctic acid, is a natural thiol often used as a dietary supplement. It is believed to have potent antioxidant properties and metal-chelating functions, with capacity to regenerate endogenous antioxidants and stimulate glucose uptake (Rochette 2015). The therapeutic use of ALA has been explored in various clinical scenarios, including cardiovascular diseases and diabetic complications such as DPN. Clinical trials have used different methods of administration (intravenous or oral), different doses (from 200 mg/day to 1800 mg/day), and different durations of treatment. Recommendations for maintenance therapy indicate a daily oral dose of 600 mg (Ziegler 2022).

How the intervention might work

ALA, acting as a scavenger of ROS, possesses antioxidant properties that could potentially interrupt the oxidative stress-inflammation pathways triggered in DPN. Thus, it could prove beneficial for both the prevention and treatment of DPN (Rochette 2015).

Early in-vitro studies indicated that both ALA and its reduced form, dihydrolipoic acid (DHLA), are capable of scavenging ROS, including hydroxyl radicals, hypochlorous acid, and singlet oxygen (Packer 1995). In vivo studies have also suggested that ALA can mitigate oxidative stress (Marangon 1999), contribute to the restoration of endogenous cellular antioxidant levels, decrease proinflammatory pathways (Petersen 2008), and potentially facilitate the regeneration of vitamins C and E (Rochette 2015).

The potential benefits of ALA for individuals with diabetes may extend beyond its antioxidant and anti-inflammatory effects. It might also be instrumental in restoring glucose availability, enhancing insulin-stimulated glucose transport, and increasing non-oxidative and oxidative glucose metabolism in insulin-resistant muscle cells (Khanna 1999; Streeper 1997).

Why it is important to do this review

As DPN is highly prevalent among people with diabetes and is associated with considerable morbidity and quality of life impairment, it is critical to prevent and treat this condition effectively and promptly. Although ALA is frequently used for DPN, there is currently no established universal consensus on its usage (Ziegler 2022). Several published Cochrane reviews have assessed the effects of other treatments for DPN, such as aldose reductase inhibitors (Chalk 2007), Chinese herbal medicine (Chen 2013), enhanced glucose control (Callaghan 2012b), and acetyl-L-carnitine (Rolim 2019), but none have synthesised the evidence on ALA. If proven to be effective and safe, this drug could serve as a cost-effective component in the long-term management of DPN.

OBJECTIVES

To assess the effects of alpha-lipoic acid as a disease-modifying agent in people with diabetic peripheral neuropathy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs) and quasi-RCTs that compared ALA with placebo or no treatment for a minimum duration of six months were eligible for inclusion in this review. There were no restrictions on publication status or language.

Types of participants

We included studies involving adults (aged 18 years and older) with type 1 or type 2 diabetes mellitus and established DPN,

regardless of participant sex or study setting. For this Cochrane review, we defined DPN as the "presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after excluding other causes" (Boulton 1998). DPN typically presents as a length-dependent and symmetrical sensorimotor polyneuropathy (Tesfaye 2010). Asymptomatic neuropathy may be detected through abnormal nerve conduction tests, which provide an objective – albeit indirect – semi-quantitative indication of the condition (Tesfaye 2010). Therefore, we included studies that used clinical or electrophysiological criteria (or both) for DPN diagnosis.

Where studies included people younger and older than 18 years, and we were unable to obtain separate data for eligible participants, we included all participants, under the assumption that age would not influence the effect of ALA on DPN.

Types of interventions

We included studies that administered ALA orally or intravenously, at any dose, for at least six months. Eligible comparators were placebo or no treatment. Studies that used co-interventions were eligible if these interventions were equally applied across all groups.

Types of outcome measures

We included studies that measured at least one of the following outcomes.

Primary outcomes

- Change in neuropathy symptoms, expressed as change in Total Symptom Score (TSS) or other validated symptom score at six months after randomisation.

Secondary outcomes

- Change in neuropathy symptoms, expressed as change in TSS or other validated symptom score at six to 12 months and at 12 to 24 months after randomisation.
- Change in impairment, as measured by validated metrics, at six months, six to 12 months, and 12 to 24 months after randomisation. Validated scores include the Medical Research Council (MRC) sum score, the Neuropathy Impairment Score (NIS), the Neuropathy Disability Score (NDS; an impairment score), and the Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score.
- Change in any validated quality of life total score at six months after randomisation
- Complications of DPN, including the number of participants with foot ulceration, amputation, or both at any stage after treatment
- Adverse events, categorised as follows
  - Any adverse event
  - Adverse events leading to cessation of treatment
  - Serious adverse events (i.e. any event that was life-threatening or required prolonged hospitalisation)

Search methods for identification of studies

Electronic searches

On 12 March 2018 and 11 September 2022, the Information Specialist of Cochrane Neuromuscular searched the following databases.

- Cochrane Neuromuscular Specialised Register via the Cochrane Register of Studies (CRS-Web; Appendix 1)
- Cochrane Central Register of Controlled Trials (CENTRAL) via CRS-Web (Issue 1, 2018 for the first search, and Issue 3, 2022 for the updated search; Appendix 2)
- MEDLINE via Ovid SP (1946 to 11 September 2022; Appendix 3)
- Embase via Ovid SP (1974 to Week 37 2022; Appendix 4)

In March 2018 and September 2022, we also searched the following trial registries.

- US National Institutes of Health Ongoing Trials Registry ClinicalTrials.gov (clinicaltrials.gov; Appendix 5)
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; trialsearch.who.int; Appendix 6)

There were no restrictions on language, date, or status of publication.

Searching other resources

We conducted a thorough literature search by reviewing the reference lists of all included primary studies, as well as those of pertinent review articles. This was to ensure that we captured any additional references that might have been overlooked in the electronic searches. Given the comprehensiveness of our search strategy, we considered it unnecessary to reach out to individuals or organisations for further information.

Data collection and analysis

Selection of studies

Two review authors (CB and CD) independently reviewed the titles and abstracts of references identified through electronic searches (minus duplicates). We retrieved the full-text articles of all potentially suitable studies, and another two review authors (AP and FF) independently assessed them using a standardised inclusion form. We resolved any disagreements regarding study relevance through discussion or by consulting a third review author (CB), if necessary. To avoid duplication of data, we consolidated multiple reports of the same study, ensuring that each unique study was the unit of interest. For transparency and thoroughness, we compiled a Characteristics of excluded studies table and created a PRISMA diagram (Moher 2009).

Data extraction and management

Two review authors (AP and FF) independently extracted pertinent information concerning the study design and setting, population, interventions, outcomes, sources of funding, and any declared conflicts of interest of the trial investigators, using Covidence software (Covidence). The two review authors compared their findings and resolved any disagreements through discussion. As a testament to the consistency of our process, there was no need to involve a third review author. We contacted the authors of two included studies for additional clarifications, but we received no response.

Assessment of risk of bias in included studies

Two review authors (AP and FF) independently evaluated the risk of bias of the included studies using the Cochrane risk of bias tool RoB 1, which covers the following domains (Higgins 2017).

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessors
- Incomplete outcome data
- Selective outcome reporting
- Other potential sources of bias

For the last domain, we determined whether studies were conducted in a single centre or by a single investigator (Mallik 2014). We classified each study at low, high, or unclear risk of bias in each domain, and we populated a risk of bias table with our findings. We then provided a narrative description of the overall risk of bias for each study, based on whether any of the domains were deemed to have a high risk of bias.

Measures of treatment effect

In our analysis, we calculated mean differences (MDs) with 95% confidence intervals (CIs) for homogeneous continuous outcome measures. Where studies used different scales to measure the same outcome, we calculated the standardised mean difference (SMD) with its 95% CI. For our dichotomous outcomes (adverse events), we used risk ratios (RRs) with 95% CIs. The scales used in our analysis all had the same directional interpretation: a lower score indicated less severity of symptoms or impairment. Thus, a negative change was indicative of an improvement in symptoms or impairment.

Unit of analysis issues

All included studies were parallel-group randomised trials.

Two trials had three arms. We combined the sample sizes, means and standard deviations (SDs) across the two treatment arms of Reljanovic 1999 using the method described in section 6.5.2.10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We did not include one arm of Ziegler 1999 in any meta-analysis, because the participants received both intravenous ALA (for the first three weeks) and oral placebo (for the remaining six months), and we could not categorise the intervention as either treatment or placebo (due to the possible residual effect of the intravenous ALA).

Had we included any studies that used no treatment as a control, we would have combined data from comparisons with placebo and no treatment groups in a single analysis.

Dealing with missing data

We recorded dropout rates and included them in the risk of bias table. For continuous data, we performed an available case analysis. When interpreting the results of the review, we considered the potential impact of missing data (Higgins 2017). If SDs were missing, we calculated them from other measures such as P values, standard errors (SEs), and the limits of CIs. This procedure ensures that all available data are utilised effectively while also accounting for the potential bias introduced by missing data.

Assessment of heterogeneity

First, we examined the trials to determine whether there were clinical reasons for heterogeneity. For assessing statistical heterogeneity across trials, we used the Chi^2 test and I^2 statistic. We evaluated heterogeneity in meta-analyses with at least three studies.

Assessment of reporting biases

Had we included at least 10 studies in any meta-analysis, we would have evaluated publication bias by creating a funnel plot and performing the Egger test (Egger 1997). We searched for unpublished trials on trial registration databases.

Data synthesis

We calculated the pooled treatment effects using the Cochrane software Review Manager 5 (RevMan 2014). We used a fixed-effect model and performed a sensitivity analysis with the random-effects model.

Subgroup analysis and investigation of heterogeneity

We hypothesised that response to treatment might differ according to disease duration (long-standing DPN less likely to improve), age (older participants less likely to improve), severity of the disease, types of diabetes (as their pathogenesis is different), and the presence of pain. We also expected that the route of administration may influence bioavailability and lead to different effects.

However, we could not perform any subgroup analyses because the sample sizes were small, and the information from the included studies was insufficient.

Sensitivity analysis

We did not perform any sensitivity analysis according to risk of bias because all the studies were at high risk of bias. We did not perform a sensitivity analysis with the random-effects model because either the outcomes included only one study, or there was no heterogeneity.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the five GRADE considerations (risk of bias, inconsistency, indirectness, imprecision, and publication bias) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022). We downgraded the certainty rating by one or two levels for limitations related to each consideration, up to a maximum of three levels for all considerations. Three review authors independently assessed the certainty of the evidence and resolved differences in opinion through discussion.

We included the following outcome measures in the summary of findings table.

- Change in neuropathy symptoms at six months after randomisation
- Change in impairment at six months after randomisation
- Change in any validated quality of life total score at six months after randomisation
- Complications of DPN
- Adverse events leading to cessation of treatment

RESULTS

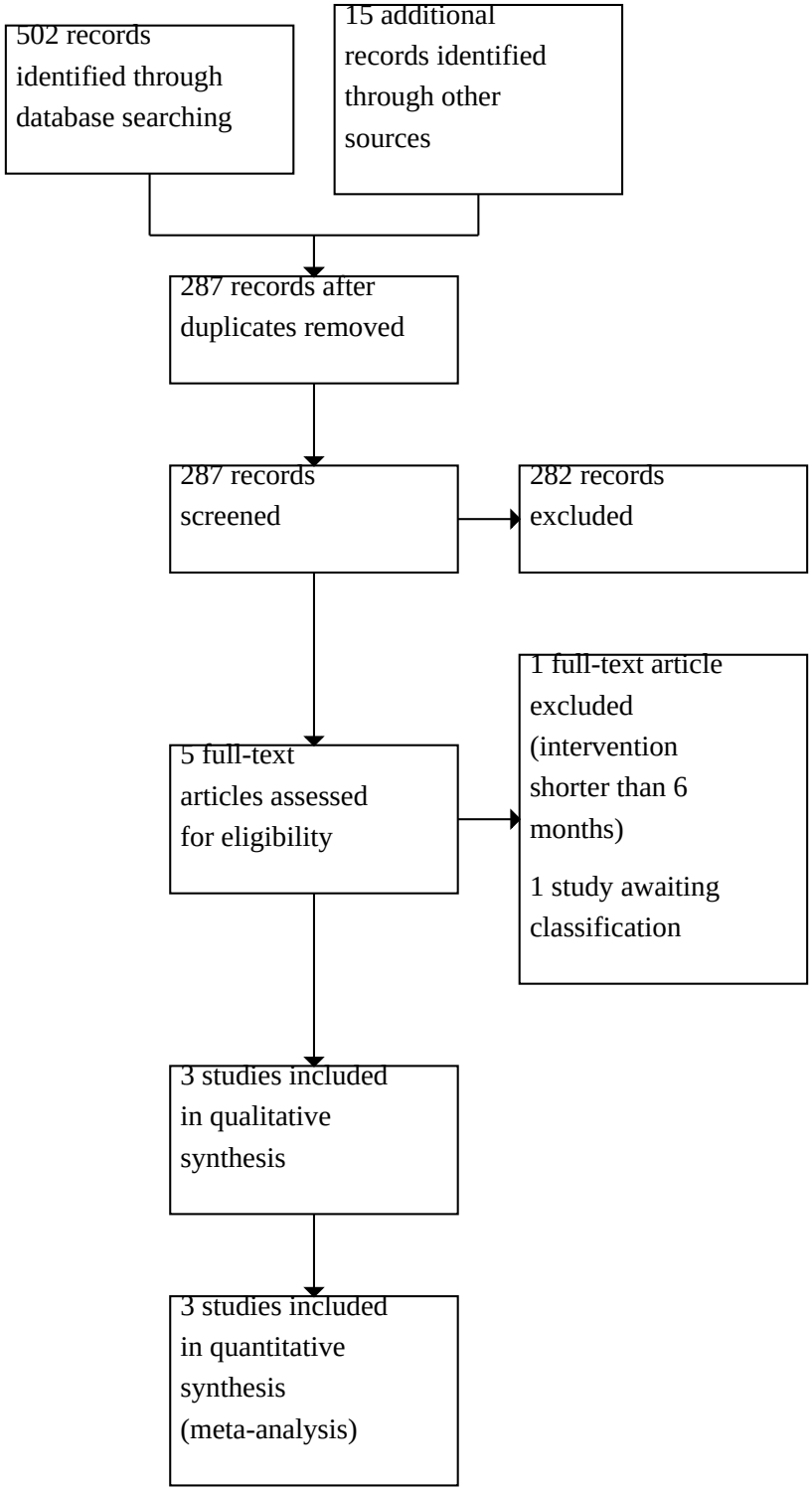
Description of studies

Results of the search

Our searches identified 517 references, of which 230 were duplicates. Of the remaining 287 references, we excluded 282 based on their titles and abstracts (not RCTs or quasi-RCTS, treatment duration shorter than six months, or control intervention other than placebo or no treatment). We assessed five full-text articles, excluding one (Medvedeva 2006). For one of the four remaining studies, we found some discrepancies between the content of a conference abstract and the later full-text article (El Nahas 2020). We were unable to obtain the trial data from the trialists, so we decided to list this study as awaiting classification. We included three studies in our qualitative and quantitative synthesis (Reljanovic 1999; Ziegler 1999; Ziegler 2011).

Figure 1 illustrates the study selection process in a PRISMA diagram.

Figure 1. Study flow diagram.



Included studies

All three included studies were placebo-controlled, parallel-group RCTs. Two studies had three arms (Reljanovic 1999; Ziegler 1999), and one study had two arms (Ziegler 2011).

Two studies had two phases of treatment (Reljanovic 1999; Ziegler 1999). In Reljanovic 1999, participants in the two ALA groups (600 mg/day and 1200 mg/day) received intravenous ALA for five days and then oral ALA for 24 months. The three arms in Ziegler 1999 were intravenous ALA 600 mg/day for three weeks followed by oral ALA 1800 mg/day for six months, intravenous ALA 600 mg/day for three weeks followed by oral placebo for six months, and intravenous placebo for three weeks followed by oral placebo for six months. We did not consider data from the second arm because the treatment with ALA lasted less than six months. In Ziegler 2011, participants were randomised to oral ALA 600 mg/day or oral placebo for four years.

From the three studies, we analysed a total of 816 adults who received either ALA or placebo for at least six months. Two studies included people with type 1 or type 2 diabetes (Reljanovic 1999; Ziegler 2011), while one study included only people with type 2 diabetes (Ziegler 1999). All trial participants had symptomatic DPN as determined by clinical and electrophysiological examinations.

The age range at trial inclusion was 18 to 60 years in Reljanovic 1999, 18 to 65 years in Ziegler 1999, and 18 to 64 years in Ziegler 2011. The participants' mean age was 57.8 (SD 9.7) years in Reljanovic 1999, 56.9 (SD 6.3) years in Ziegler 1999, and 53.6 (SD 7.9 years) in Ziegler 2011.

Reljanovic 1999 had mostly female participants (56.9%), Ziegler 2011 had mostly male participants (66.5%), and the distribution of the sexes was equal in Ziegler 1999.

Two studies assessed change in symptoms, both using the TSS (Ziegler 1999; Ziegler 2011). The TSS scale ranges from 0 to 14.64 points, with higher scores indicating worse symptoms. The minimal clinically important difference (MCID) is 0.97 points (Bastyr 2005).

All studies assessed change in impairment. Ziegler 1999 and Ziegler 2011 used the NIS and the Lower Limbs subscale of the NIS (NIS-LL), while Reljanovic 1999 used the NDS, developed by Young and colleagues (Young 1993). We decided to analyse the NIS-LL data from Ziegler 1999 and Ziegler 2011, for three reasons. First, DPN predominantly impacts the lower limbs. Second, we combined data from Ziegler 2011 (which used the NIS/NIS-LL) and Reljanovic 1999 (which used the NDS) in Analysis 1.4, and since the NDS focusses on the lower limbs, it is more similar to the NIS-LL than to the NIS. Third, the intervention effects were similar for the NIS and the NIS-LL, suggesting these scales may be interchangeable in this context. The NIS-LL scale ranges from 0 to 88 points, with higher scores indicating more significant impairment; the MCID is considered to be 2 points (Dyck 1991; Peripheral Nerve Society 1995). The NDS ranges from 0 to 10 points, with higher scores representing worse impairment. In the analysis that combined different scales, we calculated the SMD. By distribution-based statistical methods, the MCID is universally equivalent to 0.5 × SD (Norman 2003), which implies that 0.5 is the MCID of outcomes expressed as SMDs.

All three studies assessed adverse events.

In addition, the included studies measured nerve conduction velocities, nerve or compound muscle action potentials, the Neuropathy Symptoms and Change score, the cooling detection threshold, or the heat pain response slope.

Two studies reported glycosylated haemoglobin levels (Reljanovic 1999; Ziegler 1999).

The Characteristics of included studies table provides details of all included studies.

Excluded studies

We excluded one study during full-text review because the duration of treatment was shorter than six months (Medvedeva 2006; see the Characteristics of excluded studies table).

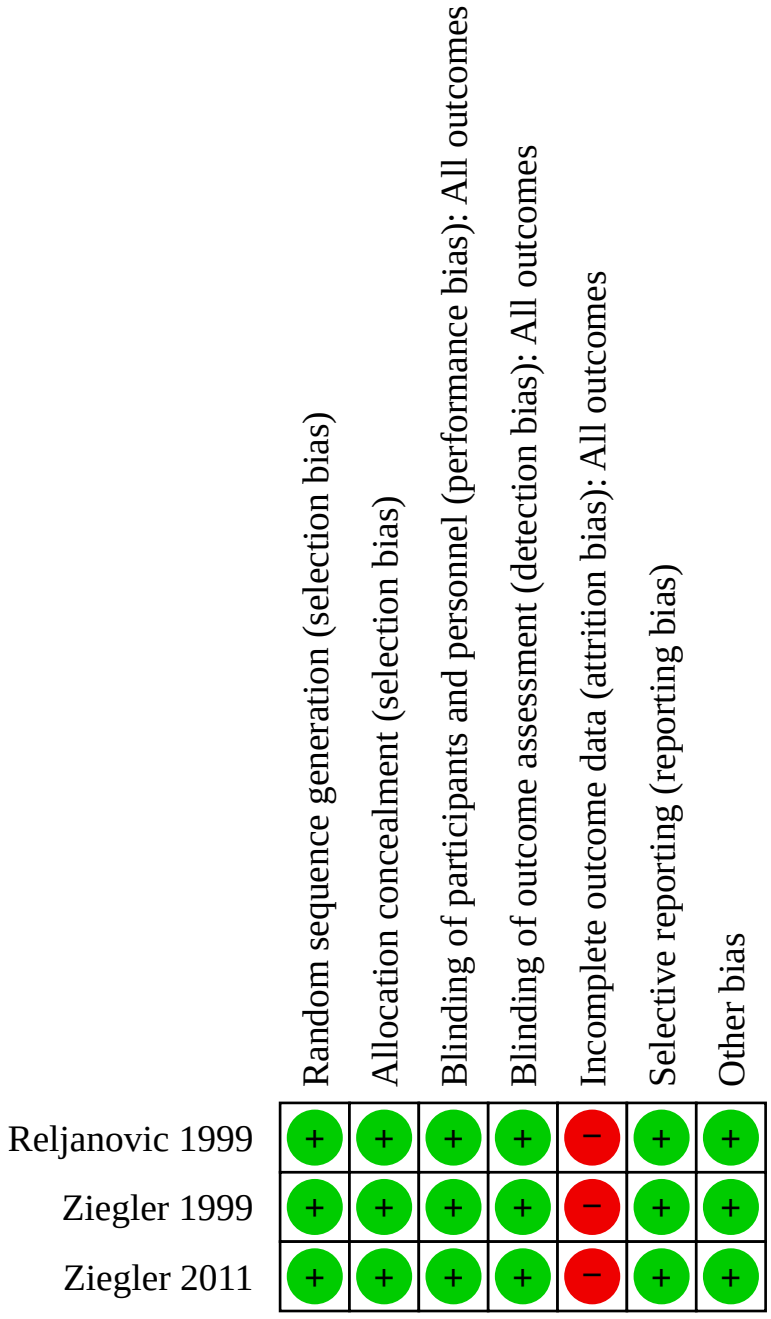
Studies awaiting classification

El Nahas 2020 compared oral ALA 600 mg twice daily with placebo over six months in people with type 2 diabetes.

Risk of bias in included studies

The overall risk of bias was high for all three studies because of attrition rates ranging from 25% to 43% (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies were multicentric and used a central computerised randomisation list. Only Ziegler 2011 specified that "a randomization list was generated by the biostatistics department of the manufacturer of the study drug, at distance of the centers the study took place", and "the random allocation was balanced using an undisclosed block size of six". Still, using the current tools, we considered all the studies at low risk of bias regarding allocation.

Blinding

We assessed the risk of bias related to blinding for each outcome separately. We considered all three studies at low risk of performance bias because they used a placebo, and because the publications indicated that participants and investigators were blinded. The level of detail on randomisation and blinding procedures in these studies is consistent with the standards of that period.

We judged all three studies at low risk of detection bias, as all investigators were blinded to treatment allocation. Ziegler 2011 clearly stated that assessors were blinded, and procedures were in place to decode the individual blinded treatment if necessary. In Ziegler 1999, specific additives in the placebo made it similar in appearance to the active medication.

Although all studies had symptom-based scores as the primary outcome, they were probably assessed objectively.

Incomplete outcome data

We judged all three studies at high risk of attrition bias.

In Reljanovic 1999, although the study initially included 299 participants in an intention-to-treat (ITT) analysis as stated in the protocol, a high attrition rate of 43% (130 participants) was allowed. Furthermore, many participants with outlying electrophysiological results were excluded from the analysis, so that only 65 participants' results were presented.

In Ziegler 1999, although data were presented for the primary outcome (change in TSS) at seven months in an ITT analysis for 503/516 randomised participants, the study authors mentioned a 25% withdrawal rate across all groups and provided no explanation regarding the handling of missing data. Additionally, for the secondary outcomes, data were analysed for only a subset of participants (364 for NIS and 368 for NIS-LL) without any explanation.

In Ziegler 2011, while only 6/460 randomised participants were excluded from the analysis, there were high discontinuation rates of 41% in the treatment arm and 42% in the placebo arm over the four-year study period. The publication did not mention how many outcome measurements were based on the last observation carried forward (LOCF) method ("mean of weeks 191 and 192 or last available value after randomization"). Even in the best-case scenario of conducting an ITT analysis with complete outcome data, the high attrition rates would have likely diluted the potential benefits of ALA, resulting in insufficient statistical power to detect any effect.

Selective reporting

We judged all three studies at low risk of reporting bias.

Reljanovic 1999 aimed to investigate changes in various outcomes related to neuropathy. The publication reported all specified outcomes at the designated time points. Ziegler 1999 focused on measuring changes in TSS and NIS at specific time intervals. Results for these outcomes were reported as initially proposed. Although we could not access the protocols for Reljanovic 1999 or Ziegler 1999, the reported outcomes in these studies align with those typically examined in DPN treatment studies.

Ziegler 2011 had a registered study protocol and reported the results of all prespecified outcomes at both the two- and four-year time points. The publication reported some additional outcomes that were not prespecified in the study protocol, but none were included in our review.

Other potential sources of bias

We found no other sources of bias for any study. Pharmaceutical companies sponsored all studies, but we did not consider this a source of bias. All studies were multicentric and had multiple investigators.

Effects of interventions

See: **Summary of findings 1** Alpha-lipoic acid compared to placebo for diabetic peripheral neuropathy

Alpha-lipoic acid versus placebo

Primary outcome

Change in neuropathy symptoms at six months

Only Ziegler 1999 reported change in neuropathy symptoms at six months. ALA compared with placebo probably has little or no effect on neuropathy symptoms as assessed by TSS at six months (MD −0.16 points, 95% CI −0.83 to 0.51; 330 participants; moderate-certainty evidence; Analysis 1.1). The 95% CI was narrow and did not contain the MCID. We downgraded the certainty of the evidence by one level for attrition bias.

Secondary outcomes

Change in neuropathy symptoms at six to 12 months and 12 to 24 months

Only Ziegler 2011 reported change in neuropathy symptoms beyond six months (at 24 months). ALA compared with placebo probably has little or no effect on neuropathy symptoms as assessed by TSS at 24 months (MD −0.23 points, 95% CI −0.67 to 0.21; 421 participants; moderate-certainty evidence; Analysis 1.2). The 95% CI was narrow and did not contain the MCID. We downgraded the certainty of the evidence by one level for attrition bias.

Change in impairment at six months, six to 12 months, and 12 to 24 months

One study assessed impairment at six months using the NIS-LL (Ziegler 1999). Two studies assessed impairment at 24 months; Reljanovic 1999 used the NDS and Ziegler 2011 used the NIS-LL.

ALA compared with placebo may have little or no effect on impairment as measured by the NIS-LL at six months (MD −1.02 points, 95% CI −2.93 to 0.89 points; 1 study, 245 participants; low-certainty evidence; Analysis 1.3). We downgraded the certainty of the evidence by one level for attrition bias and by one level for imprecision. The lower limit of the 95% CI surpasses the MCID (2 points), so we cannot rule out a beneficial effect.

ALA compared with placebo probably has little or no effect on impairment at 24 months (SMD −0.07 SDs, 95% CI −0.24 to 0.11; I^2 = 0%, P = 0.39; 2 studies, 486 participants; moderate-certainty evidence; Analysis 1.4). We downgraded the certainty of the evidence by one level for attrition bias. The 95% CIs did not include

the statistical MCID (0.5), which means the possibility of a clinically significant difference is very low.

Change in any validated quality of life total score at six months

No studies reported quality of life.

Complications of diabetic peripheral neuropathy

No studies reported complications of DPN.

Adverse events

All three studies reported adverse events leading to cessation of treatment. There is probably little or no difference between ALA and placebo in the risk of adverse events leading to cessation of treatment (RR 1.48, 95% CI 0.50 to 4.35; I^2 = 0, P = 0.69; 3 studies, 1090 participants; moderate-certainty evidence; Analysis 1.5). The number of participants forReljanovic 1999 should have been the 169 participants who completed the 24 months of follow-up rather than the 65 analysed for the other outcomes. However, the whole cohort was included in the adverse events analysis. We downgraded the certainty of the evidence by one level for attrition bias.

No studies recorded all types of adverse event or serious adverse events.

DISCUSSION

Summary of main results

This review included three studies with a total of 1089 participants. From the three studies, we analysed 816 adults who received either ALA or placebo for at least six months.

All three studies were prospective, double-blind, placebo-controlled RCTs with parallel-group design. Two studies (395 participants) had a three-arm protocol, and one study (421 participants) had two arms. The studies used different doses of ALA; the minimum dose was 600 mg once daily. Two studies had an initial intravenous regimen of ALA versus placebo for up to three weeks, followed by an oral regimen of ALA versus placebo for up to 24 months. Two studies included both type 1 and type 2 diabetes, and one study included only type 2 diabetes.

ALA 600 mg three times daily compared to placebo probably has little or no effect on neuropathy symptoms after six months, and ALA 600 mg once daily compared to placebo probably has little or no effect on neuropathy symptoms after 24 months. We identified only one study for each time frame. The certainty of the evidence for both outcomes was moderate (downgraded for attrition bias).

ALA 600 mg once daily compared to placebo may have little or no effect on impairment after six months; however, the 95% CI was wide and included the MCID of the NIS-LL. Only one study reported this outcome. The certainty of the evidence was low (downgraded for attrition bias and imprecision).

Two studies assessed impairment at 24 months using different scales: the NIS-LL and the NDS. Neither study found a clinically significant improvement with ALA. The certainty of the evidence was moderate (downgraded for attrition bias).

We planned to evaluate the impact of ALA treatment on quality of life and the progression of DPN to foot ulceration, amputation, or both. However, no studies reported these outcomes.

All three studies reported adverse events. Data from 1090 participants indicated little or no difference between ALA and placebo in adverse events leading to the cessation of treatment at six months after randomisation. The certainty of the evidence was moderate (downgraded for attrition bias).

Overall completeness and applicability of evidence

We included only three studies assessing the benefits and harms of long-term treatment (more than six months) of DPN with ALA compared to placebo, because most existing studies have a much shorter treatment time. Although all the studies were randomised and double-blinded and included people of both sexes with a wide age interval (18 to 65 years) from multiple centres, different outcomes of interest were reported in only one or two studies.

We found data for symptom improvement, impairment, and adverse events. We did not assess the impact of ALA treatment on quality of life because no studies used a validated quality of life tool. In addition, no studies reported the occurrence of complications (foot ulceration, amputation, or both).

A notable limitation arises from the inconsistent reporting of outcomes across studies, as well as the different time frames the study authors selected for their analysis. This may have reduced the robustness of our conclusions. Only one study reported our primary outcome (change in neuropathy symptoms at six months), while another study reported change in neuropathy symptoms at 24 months. Similarly, one study reported our secondary outcome change in impairment at six months (using the NIS-LL), while two studies reported change in impairment at 24 months (using the NIS-LL and NDS). Concerning harm, the studies only provided data for adverse events leading to treatment cessation, but not all types of adverse events or serious adverse events.

The doses of ALA varied from 600 mg per day to 1800 mg per day, and the route of administration was either oral or intravenous followed by oral. We were unable to perform any subgroup analyses to determine whether the response to treatment varied according to factors like type of diabetes, duration or severity of the disease, age, or route of administration.

Quality of the evidence

Using the GRADE approach, we rated the certainty of evidence as moderate for the primary outcome (change in symptoms at six months) and for all secondary outcomes except change in impairment at six months, which we rated as low.

We downgraded the certainty of evidence for all outcomes because of attrition bias. Ziegler 1999 had an attrition rate of 25%. Ziegler 2011 mentions an attrition rate of 41% for the treatment group and 42% for the placebo groups during the four-year study period; the study authors performed an ITT analysis at 24 months, but did not report the discontinuation status at that time. Reljanovic 1999 started with 299 participants but presented results for only 65 participants.

We also downgraded the certainty of the evidence for change in impairment because of imprecision, because the CI was very wide and contained the MCID.

Overall, we assume that the quality of the included studies limits the robustness of our conclusions.

Potential biases in the review process

This review is the first to cover ALA in diabetic neuropathy for a more extended period (at least six months). The review team is mixed, with three members new to the Cochrane review methodology and two experienced members. We received help with the search strategy from a Cochrane expert. This should, in our opinion, minimise selection risk.

We consider that the review questions are clearly stated and should not induce bias in the study selection process. They were predefined in the published Cochrane protocol and presented following the *Cochrane Handbook for Systematic Reviews of Interventions* and PRISMA. All predefined outcomes from the review protocol are discussed in the review.

We selected outcomes that answer patient-relevant questions following PICO recommendations. We included subjective, patient-reported outcomes (symptom scores) influencing the quality of life. No studies reported objective outcomes like complications (ulcerations or amputations, or both), and this could lead to potential bias in study synthesis.

The selection criteria excluded many trials, mainly because of their duration (a few weeks in most cases). We consider that this selection process induces no bias since outcomes of DPN should focus on the long-term evolution to be clinically meaningful, and the agreement between the review authors concerning the selection of the studies was high.

We identified one study that had identical results to a previous conference paper except for the stated time of development of the study (El Nahas 2020). We contacted the study authors and the publisher for clarification, but the study authors refused to share the study data, so we listed the study as awaiting classification. We felt that this action would not induce any bias.

As with all reviews that include few trials, ours could lack sensitivity for events with infrequent occurrence, such as adverse events.

Agreements and disagreements with other studies or reviews

We identified several published systematic reviews reporting the effect of ALA on DPN.

Han 2012 conducted a similar meta-analysis that included studies from Chinese biological medicine alongside CENTRAL, MEDLINE, and Embase. The intervention was intravenous ALA. Their primary outcomes were 'benefit', median motor and sensory conduction velocities, and peroneal nerve sensory and motor conduction velocities. Secondary outcomes included the occurrence of adverse events. Of 138 studies screened, the authors of Han 2012 retrieved 24 full-text articles (18 in Chinese and six in English) and included 15 studies (all in Chinese). The intervention in all 15 studies was ALA combined with another treatment (methylcobalamin in eight studies, prostaglandins in four, vitamin B1 in one, cilostazol in one, and gingko leaves injection in one). The duration of the intervention ranged from 14 days to 28 days, with a mean of 21 days. There was significant heterogeneity for each of the outcomes presented. The stated limitations were related to the overall poor methodology of the included trials, most of which did not provide details of the study design, randomisation, or allocation. Although the authors of Han 2012 stated that rigorous studies are needed, they concluded that short-term ALA treatment is generally safe and can improve both symptoms and nerve conduction speeds. No studies included in Han 2012 met our inclusion criteria because of the short duration of the interventions.

Another published review evaluated intravenous ALA treatment (minimum three weeks) and included only studies from the German VIATRIS repository (Ziegler 2004). Like Han 2012, Ziegler 2004 concluded that intravenous ALA is effective for improving symptoms and nerve conduction speeds.

We identified only one systematic review published since 2020 that evaluated ALA for DPN (Abubaker 2022). Secondary outcomes included adverse effects of the interventions. There were no inclusion criteria regarding length of treatment, but the included studies had to evaluate standalone ALA treatment and report pain or symptom scores. Eight studies were included, totalling 1500 participants. Two of the included studies were also in our review (Reljanovic 1999; Ziegler 1999), and one was the study we listed as awaiting classification (El Nahas 2020). Of the four remaining studies, one evaluated ALA in fibromyalgia and not in DPN (Gilron 2021). The authors of Abubaker 2022 considered all the studies to be of "high quality", stating as their risk of bias assessment tool the Critical Appraisal Skills Programme (CASP) appraisal tool. They concluded that ALA is safe and tolerable and may reduce symptoms, but that there is limited evidence to support its efficacy. The results of our review also suggest that ALA is safe, but we found no convincing evidence of a beneficial effect. In addition, we considered the studies included in our review to be at high overall risk of bias.

AUTHORS' CONCLUSIONS

Implications for practice

For patients

Treatment with alpha-lipoic acid (ALA) probably has little or no effect on neuropathy symptoms after six months of therapy or on functional impairment after 24 months of therapy in people with diabetic peripheral neuropathy (DPN). ALA may have little or no effect on functional impairment after six months of therapy. ALA probably has no adverse effects that would lead to treatment cessation within six months.

We found no studies assessing the impact of ALA treatment on quality of life or on the complications of DPN (foot ulceration, amputation, or both).

For clinicians

There was moderate-certainty evidence from one study that ALA treatment has little or no effect on DPN symptoms (Total Symptom Score; TSS) after six months of treatment, and moderate-certainty evidence from another study that ALA treatment has little or no effect on DPN symptoms (TSS) after 24 months of treatment.

There was low-certainty evidence from one study that ALA treatment compared with placebo has little or no effect on impairment assessed by the Neuropathy Impairment Score-Lower Limbs (NIS-LL) after six months of treatment. There was moderate-certainty evidence from two studies using different scales (NIS-LL and Neuropathy Disability Score) that ALA treatment compared with placebo has little or no effect on impairment after 24 months of treatment.

There were no data on the impact of ALA treatment on quality of life or DPN complications (foot ulceration, amputation, or both).

There was moderate-certainty evidence from three studies of little or no difference between ALA and placebo in terms of adverse events that would lead to cessation of treatment after six months.

For policymakers and funders

There is moderate-certainty data that ALA has little or no effect on symptoms of DPN.

There is low- and moderate-certainty data that ALA has little or no effect on impairment.

There are no data on the effect of ALA on quality of life or DPN complications.

Implications for research

We found only three randomised clinical trials assessing the efficacy of long-term treatment (more than six months) of DPN with ALA compared to placebo. All were at high risk of attrition bias; therefore, future RCTs should ensure complete follow-up and transparent reporting of any participants missing in the analyses. Studies should also measure symptoms, impairment, and quality of life using validated scales. Other important outcomes are complications of DPN (foot ulceration, amputation, or both) and adverse effects.

Intensive glycaemic control is considered the primary approach for preventing DPN, and haemoglobin A1C (HbA1C) is widely recognised as the most reliable biomarker for assessing glycaemic control. It is important to note that ALA is not expected to directly affect HbA1C levels, and only limited evidence suggests its potential as an insulin sensitiser. In the included studies, no significant variation was observed in HbA1C levels between baseline and end of follow-up in the intervention or control groups. However, future studies may assess the role of glycaemic control as a modifier of the potential effect of ALA.

Until ALA is proven effective, there is no rationale for comparing it with active treatments.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Colin Chalk, Department of Neurology & Neurosurgery, McGill University, Montreal, Canada
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Luisa M Fernandez Mauleffinch, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Julia Turner, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Jennifer Hilgart, Cochrane (methods); Douglas M Salzwedel, Information Specialist, Cochrane Hypertension (search); Robert Wyllie (consumer); Professor Richard Hughes, King's College London (clinical). Two additional peer reviewers provided clinical peer review but chose not to be publicly acknowledged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Reljanovic 1999

Study characteristics	
Methods	Prospective, double-blind, multicentre, 3-arm parallel-group, randomised study
Participants	**Number:** 299 randomised, 65 analysed **Age:** mean 57.8 (SD 9.7) years **Sex:** 56.9% women **Inclusion criteria** • Type 1 and Type 2 diabetes • Age 18-60 years • Polyneuropathy (clinical and electrophysiological diagnosis)
Interventions	**EG1:** ALA 600 mg/day, IV administration (with trometamol salt solution) for 5 days followed by oral administration for a total of 24 months **EG2:** ALA 1200 mg/day, IV administration (with trometamol salt solution) for 5 days followed by oral administration for a total of 24 months **CG:** placebo
Outcomes	**Primary outcomes** • NDS **Secondary outcomes** • Sural sensory nerve conduction velocity (SNCV) • Sural sensory nerve action potential (SNAP) • Tibial motor nerve conduction velocity (MNCV) • Motor nerve distal latency (MNDL) • Glycosylated haemoglobin (HbA1C)
Funding	Grants from ASTA Medica AG, Frankfurt am Main, Germany
Conflicts of interest	ALA tablets (Thioctacid®) were manufactured by ASTA Medica AG, Frankfurt am Main, Germany.
Notes	299 people were recruited from 32 outpatient centres, but 130 participants were lost for different reasons. From the 169 participants who completed the 24 months' follow-up, another 104 were excluded because of flaws in the electrophysiological assessment, so the analysis included only 65 participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "... patients with symptomatic polyneuropathy were randomly assigned to TA 1200, TA 600 or PLA according to their entry sequence following a central computerized randomization list."

Reljanovic 1999 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "... patients with symptomatic polyneuropathy were randomly assigned to TA 1200, TA 600 or PLA according to their entry sequence following a central computerized randomization list."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both PLA tablets and solutions contained ingredients identical with those containing TA except for the latter. In order to achieve a color similar to the active drug ferrooxide (E 172) was added to the tablets and 0.03 mg of riboflavin to the ampoules." Comment: trial described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Trial described as double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	As treated analysis with substantial departure from randomisation: 299 patients included, 64 analysed.
Selective reporting (reporting bias)	Low risk	No study protocol available, but the published report includes all expected outcomes.
Other bias	Low risk	We found no other sources of bias.

Ziegler 1999

Study characteristics	
Methods	Prospective, double-blind, placebo-controlled, multicentre, 3-arm parallel-group, randomised study
Participants	**Number:** 516 randomised, 503 analysed in the 3 groups (330 participants analysed in the 2 groups of interest, comparing ALA with placebo) **Age:** 56.9 (SD 6.3) years **Sex:** 52.1% women **Inclusion criteria** • Type 2 diabetes and symptomatic peripheral neuropathy • Age 18–65 years • Treatment with diet, oral antidiabetic agents, insulin, or a combination of these • Stable glycaemic control • Evidence of symptomatic symmetrical distal neuropathy (stage 2, i.e. TSS ≥ 4 points and NIS ≥ 2 points)
Interventions	**EG1:** ALA 600 mg IV once daily for 3 weeks followed by ALA 1800 mg daily (3 600-mg tablets) for 6 months **EG2:** ALA 600 mg IV once daily for 3 weeks followed by oral placebo 3 times daily for 6 months (we did not include this group in our review, as it did not fulfil the inclusion criteria concerning duration of treatment) **CG:** placebo IV administration once daily for 3 weeks followed by oral placebo 3 times daily for 6 months
Outcomes	**Primary outcomes**

Ziegler 1999 *(Continued)*

- TSS
- NIS
- NIS-LL

Secondary outcomes

- Glycosylated haemoglobin
- Adverse events

Funding	"This study was supported by ASTA Medica AG, Frankfurt am Main, Germany"
Conflicts of interest	The trometamol salt solution and the tablets containing 600 mg of ALA were manufactured by ASTA Medica AG, Frankfurt am Main, Germany.
Notes	Of the 516 randomised participants, 7 participants from 1 centre were not exposed to treatment, and no efficacy data were available for 6 other participants. Therefore 503 participants were included in the ITT analysis. 34 participants dropped out during the IV treatment period because of lack of efficacy (2; EG1/EG2/CG: 1/1/0), drug intolerance (2: 0/0/2), intercurrent disease (6: 1/1/4), exclusion criteria (19: 7/7/5), noncompliance (5: 1/4/0) and other reasons (7: 2/3/2). 92 participants dropped out during the oral treatment period because of lack of efficacy (24: 8/11/5), drug intolerance (9: 4/1/4), intercurrent disease (15: 4/5/6), exclusion criteria (11: 3/6/2), noncompliance (28: 8/11/9) and other reasons (17: 9/5/3). The total rate of withdrawal was 25% throughout the trial, without significant differences between the 3 studied groups. There were 24 protocol violations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each patient was randomized according to his or her entry sequence following a central computerized randomization list."
Allocation concealment (selection bias)	Low risk	Quote: "Each patient was randomized according to his or her entry sequence following a central computerized randomization list." Comment: the measures for concealment are not fully described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "During the oral phase, tablets containing 600 mg a-lipoic acid or placebo of identical size, appearance, and taste were used. All investigators and participants were blinded to the randomization of the study drug assignments."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "During the oral phase, tablets containing 600 mg a-lipoic acid or placebo of identical size, appearance, and taste were used. All investigators and participants were blinded to the randomization of the study drug assignments."
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition and exclusions reported in each interventional group; total withdrawal rate of 25% during the trial, equal in the 3 arms of the study. For the primary outcome (change in TSS), 503/516 participants were included in the ITT analysis, but there was no mention of missing data or how the study authors dealt with them. For the secondary outcomes (change in NIS and NIS-LL) the study authors analysed data of only 364 participants (NIS) and 368 participants (NIS-LL), without any explanation. Therefore, we consider a high risk of attrition bias for NIS and NIS-LL and an unclear risk of attrition bias for TSS.

Ziegler 1999 *(Continued)*

Selective reporting (reporting bias)	Low risk	No study protocol available, but the published report includes all expected outcomes.
Other bias	Low risk	We found no other sources of bias.

Ziegler 2011

Study characteristics	
Methods	Prospective, double-blind, placebo-controlled, multicentre, 2-arm 1:1 allocation ratio, parallel-group, randomised study
Participants	**Number:** 460 randomised, 421 analysed **Age:** 53.6 (SD 7.9) years **Sex:** 33.5% women **Inclusion criteria** • Type 1 or 2 diabetes and mild-to-moderate distal, symmetrical polyneuropathy attributable to diabetes • Age 18–64 years • With a diabetes duration ≥ 1 year • Stable insulin regimen, weight, diet, and physical activity level
Interventions	**EG:** oral administration once daily of ALA 600 mg (film-coated tablets) for 4 years **CG:** oral placebo tablets once daily for 4 years "The trial consisted of a 2-week screening phase, 6-week placebo run-in phase, 4-year double-blind phase, and 4-week washout phase."
Outcomes	**Primary outcomes** • Composite score including the NIS-LL+7: vibration detection threshold • Peroneal motor nerve conduction velocity (MNCV) • Peroneal motor nerve distal latency • Peroneal compound muscle action potential (CMAP) • Tibial motor nerve distal latency • Sural sensory nerve action potential amplitude • Change in heart rate response to deep breathing (HRDB) **Secondary outcomes** • NIS • NIS-LL • Neuropathy Symptoms and Change (NSC) score • TSS • Cooling detection threshold • Heat pain response slope (0.5–5.0) • Tibial nerve compound CMAP and MNCV • Sural sensory nerve action potential latency, and sensory nerve conduction velocity (SNCV) • Adverse events

Ziegler 2011 *(Continued)*

Funding	No funding source is mentioned. However, MEDA Pharma produced the medication, its Biostatistics department generated the randomisation list, 5 study authors received honoraria/grants from MEDA Pharma, and the other 3 authors were employees of MEDA Pharma.
Conflicts of interest	5 study authors received honoraria or grants from, and 3 authors were employees of the manufacturer of the study drug.
Notes	879 people were assessed for eligibility, of whom 419 were excluded (353 did not meet the inclusion criteria and 91 met the exclusion criteria). 460 participants were randomised: 233 were randomised to ALA (of whom 231 received ALA) and 227 were randomised to placebo, (of whom 225 received placebo). More than 40% of the participants from each group discontinued treatment/placebo. Results for all outcomes at 2 years from randomisation were reported for 421 participants (214 in the ALA group and 207 in the placebo group).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a randomization list was generated by the biostatistics department of the manufacturer of the study drug ..."
Allocation concealment (selection bias)	Low risk	Quote: "a randomization list was generated by the biostatistics department of the manufacturer of the study drug, at distance of the centers the study took place"; "the random allocation was balanced using an undisclosed block size of six."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... matching placebo tablets with increased amounts of cellulose and lactose that were identical in appearance." Comment: trial described as double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigators and the monitor received sealed envelopes to enable decoding the individual blinded treatment in case of emergency."
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 40% of participants discontinued intervention in both groups during the 4-year study. We do not know how many participants were lost before the outcomes at 2 years (our outcome of interest), and how many after the first 2 years. Most participants (454/460) were included in the ITT analysis, but the study authors did not report for how many they managed to measure the outcome, and for how many they used the last observation carried forward ("mean of weeks 191 and 192 or last available value after randomization"). Apparently, the proportion of dropouts and the causes of dropout were equally distributed among the 2 groups.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported (ClinicalTrials.gov ID NCT00977483). The publication also reported outcomes that were not prespecified, which were the only outcomes with statistically significant results. However, these added outcomes were not among the outcomes of our systematic review.
Other bias	Low risk	We identified no other sources of bias.

ALA: alpha-lipoic acid; CG: control group; DPN: diabetic peripheral neuropathy; EG: experimental group; ITT: intention-to-treat; IV: intravenous; NDS: Neuropathy Disability Score; NIS: Neuropathy Impairment Score; NIS-LL: Neuropathy Impairment Score-Lower Limbs; SD: standard deviation; TSS: Total Symptom Score.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Medvedeva 2006	The duration of the intervention and follow-up was 10 days, not compatible with our inclusion criteria.

Characteristics of studies awaiting classification *[ordered by study ID]*

El Nahas 2020

Methods	Prospective, double-blind, placebo-controlled, double-arm randomised study
Participants	200 people with type 2 diabetes and symptomatic peripheral neuropathy
Interventions	**EG:** ALA 600 mg twice daily for 6 months **CG:** placebo for 6 months
Outcomes	**Primary outcomes** • Pain perception evaluated by Neuropathy Symptom Score (NSS) • Pain perception evaluated by VAS **Secondary outcomes** • Vibration perception threshold • NDS
Notes	

ALA: alpha-lipoic acid; CG: control group; EG: experimental group; NDS: Neuropathy Disability Score; VAS: visual analogue scale.

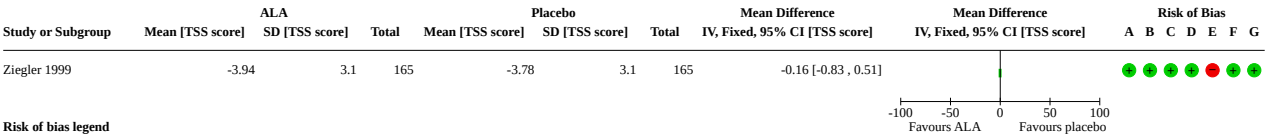
DATA AND ANALYSES

Comparison 1. Alpha-lipoic acid (ALA) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in validated symptom score at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Change in validated symptom score at 24 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Change in impairment score at 6 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.4 Change in impairment score at 24 months	2	486	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.24, 0.11]

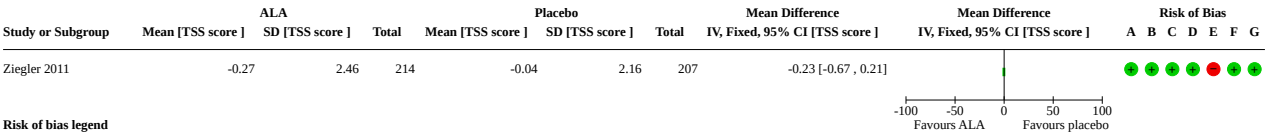
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Adverse events leading to cessation of treatment	3	1090	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.50, 4.35]

Analysis 1.1. Comparison 1: Alpha-lipoic acid (ALA) versus placebo, Outcome 1: Change in validated symptom score at 6 months



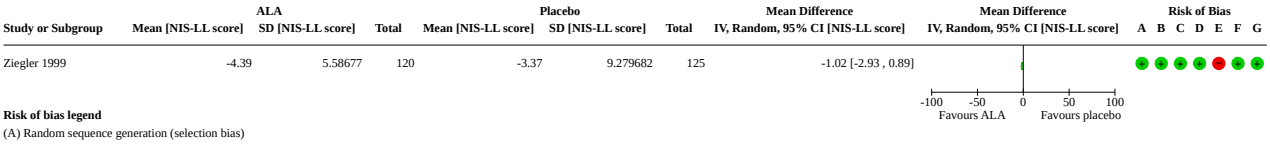
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Alpha-lipoic acid (ALA) versus placebo, Outcome 2: Change in validated symptom score at 24 months



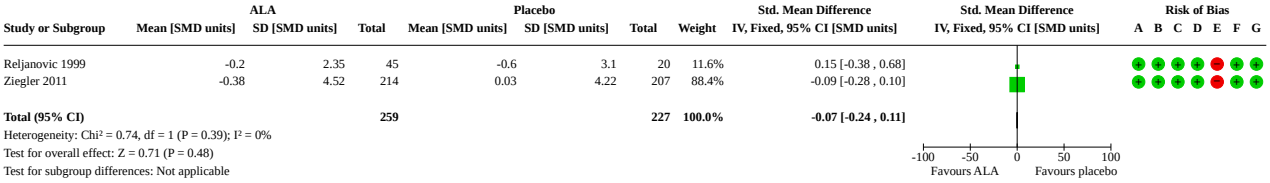
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Alpha-lipoic acid (ALA) versus placebo, Outcome 3: Change in impairment score at 6 months



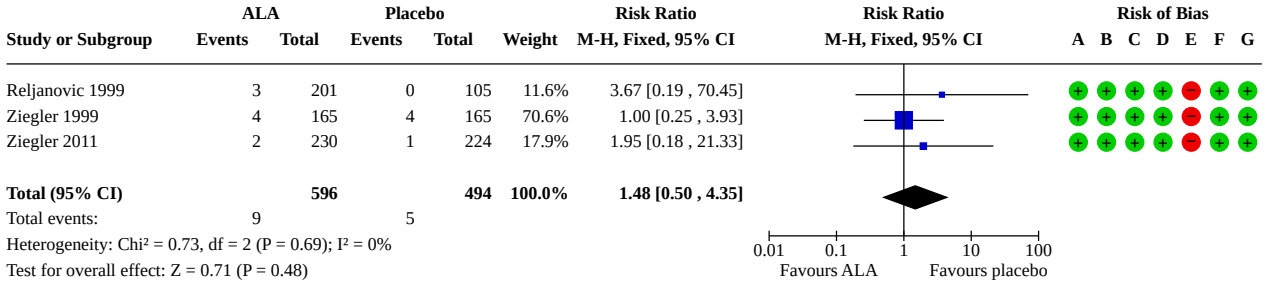
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Alpha-lipoic acid (ALA) versus placebo, Outcome 4: Change in impairment score at 24 months



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Alpha-lipoic acid (ALA) versus placebo, Outcome 5: Adverse events leading to cessation of treatment



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDICES

Appendix 1. Cochrane Neuromuscular Specialised Register (CRS-Web) search strategy

1 MESH DESCRIPTOR Diabetes Mellitus EXPLODE ALL AND INREGISTER 798

2 (diabet*):AB,EH,EMT,KW,KY,MH,TI AND INREGISTER 1524

3 #1 OR #2 1524

4 MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL AND INREGISTER 2070

5 (neuropath* or polyneuropath*):AB,EH,EMT,KW,KY,MH,TI AND INREGISTER 2489

6 #4 OR #5 3466

7 #3 AND #6 1292

8 MESH DESCRIPTOR Thioctic Acid EXPLODE ALL AND INREGISTER 53

9 ("lipoic acid" or "alpha lipoic" or thioctic):AB,EH,EMT,KW,KY,MH,TI AND INREGISTER 62

10 #8 OR #9 87

11 #7 AND #10 49

Appendix 2. Cochrane Central Register of Controlled Trials (CRS-Web) search strategy

1 MESH DESCRIPTOR Diabetes Mellitus EXPLODE ALL AND CENTRAL:TARGET 35204

2 (diabet*):AB,EH,EMT,KW,KY,MH,TI AND CENTRAL:TARGET 103341

3 #1 OR #2 103631

4 MESH DESCRIPTOR Peripheral Nervous System Diseases EXPLODE ALL AND CENTRAL:TARGET 6098

5 (neuropath* or polyneuropath*):AB,EH,EMT,KW,KY,MH,TI AND CENTRAL:TARGET 16341

6 #4 OR #5 19187

7 #3 AND #6 5026

8 MESH DESCRIPTOR Thioctic Acid EXPLODE ALL AND CENTRAL:TARGET 2278

9 ("lipoic acid" or "alpha lipoic" or thioctic):AB,EH,EMT,KW,KY,MH,TI AND CENTRAL:TARGET 832

10 #8 OR #9 2756

11 #7 AND #10 155

12 12/03/2018_TO_27/03/2022:CRSINCENTRAL AND CENTRAL:TARGET 815714

13 #11 AND #12 62

Appendix 3. MEDLINE (Ovid SP) search strategy

Database: Ovid MEDLINE(R) ALL <1946 to March 25, 2022>

1 ((Randomized Controlled Trial or Controlled Clinical Trial).pt. or (Randomi?ed or Placebo or Randomly or Trial or Groups).ab. or Drug Therapy.fs.) not (exp Animals/ not Humans.sh.) (4628636)

2 ((exp Diabetes Mellitus/ or diabet*.mp.) and (exp Peripheral Nervous System Diseases/ or (neuropath* or polyneuropath*).mp.)) or Diabetic Neuropathies/ (31081)

3 Thioctic Acid/ or (lipoic acid or alpha lipoic or thioctic).mp. (6501)

4 1 and 2 and 3 (222)

5 limit 4 to ed=20180309-20221231 (31)

6 limit 4 to dt=20180309-20221231 (40)

7 5 or 6 (45)

Appendix 4. Embase (Ovid SP) search strategy

Database: Embase <1974 to 2022 Week 12>

1 ((crossover-procedure or double-blind procedure or single-blind procedure or randomized controlled trial).sh. or (random* or crossover* or cross over* or placebo* or (doubl* adj blind*) or allocat*).tw,ot. or trial.ti. or controlled clinical trial/) not ((exp animal/ or exp invertebrate/ or animal.hw. or non human/ or nonhuman/) not (human/ or human cell/ or human tissue/ or normal human/)) (2125573)

2 limit 1 to (conference abstracts or embase) (1782354)

3 (exp diabetes mellitus/ or diabet*.mp.) and (peripheral neuropathy/ or (neuropath* or polyneuropath*).mp.) (57802)

4 thioctic acid/ or (lipoic acid or alpha lipoic or thioctic).mp. (10191)

5 2 and 3 and 4 (180)

6 limit 5 to dc=20180310-20221231 (40)

Appendix 5. ClinicalTrials.gov search strategy

Condition or disease: Diabetic Neuropathy OR Diabetic Polyneuropathy OR Diabetic Peripheral Neuropathy OR Diabetic Peripheral Polyneuropathy

Study type: Interventional Studies (Clinical Trials)

Intervention/treatment: Thioctic OR Lipoic

13 Studies found

Appendix 6. WHO ICTRP

(Diabetic Neuropathy OR Diabetic Polyneuropathy OR Diabetic Peripheral Neuropathy OR Diabetic Peripheral Polyneuropathy) AND (Thioctic OR Lipoic)

19 records for 19 trials

HISTORY

Protocol first published: Issue 2, 2018

CONTRIBUTIONS OF AUTHORS

CB, CD, FF, AP and EvE conceived the review.
CB, CD, FF, AP and EvE designed the review.
CB and EvE co-ordinated the review.
CB and CD collected the data for the review.
CD and CB screened the search results.
AP and FF performed the full-text review and CB resolved any discrepancies.
CD and CB extracted data from papers.
CB wrote to the authors of the papers for additional information.
CD obtained and screened data on unpublished studies.
CB managed data for the review.
CB, CD, FF, and AP entered data into RevMan.
CB performed the data analysis.
CB, EvE, and FF interpreted the data.
FF and AP evaluated the risk of bias, and CB and EvE resolved discrepancies.
CB and EvE provided a methodological perspective.
CB, CD, FF, and AP provided a clinical perspective.
CB, CD, FF, and AP wrote the review.
EvE provided general advice on the review.
CB, CD, FF, AP, and EvE created the protocol on which the current review is based.

DECLARATIONS OF INTEREST

CB: none known.
AP: none known.
EvE: none known.
CD: none known.
FLF: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other

  None

External sources

- None, Other

  None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

See Baicus 2018 (protocol).

For consistency with other outcomes, we changed the label of the primary outcome from 'Improvement in neuropathy symptoms' to 'Change in neuropathy symptoms'.

For the secondary outcome 'Change in impairment', one validated scale mentioned in the protocol was the Neuropathy Impairment Score (NIS; Baicus 2018). Two included studies used both the NIS and its subscale Neuropathy Impairment Score-Lower Limbs (NIS-LL; Ziegler 1999; Ziegler 2011), and we chose to use NIS-LL because: 1) diabetic peripheral neuropathy mainly affects lower limbs; 2) for Analysis 1.4, we meta-analysed NIS-LL score with another impairment score, the Neuropathy Disability Score (NDS; Young 1993), which also refers only to lower limbs; and 3) the effects of interventions were similar for both NIS and NIS-LL (Ziegler 1999; Ziegler 2011).

In the summary of findings table, we included 'Adverse events leading to cessation of treatment' instead of 'Any adverse event' because the included studies reported the more specific harms outcome.

We were unable to perform the planned subgroup analysis, because the sample sizes were small, and the information from the included studies was insufficient.

INDEX TERMS

Medical Subject Headings (MeSH)

*Diabetes Mellitus, Type 2 [complications] [drug therapy]; *Diabetic Neuropathies [drug therapy]; Lower Extremity; MEDLINE; *Thioctic Acid [adverse effects]

MeSH check words

Adult; Humans