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Alpha-lipoic acid for diabetic peripheral neuropathy (Protocol)

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[Intervention Protocol]

Alpha-lipoic acid for diabetic peripheral neuropathy

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of ALA as a disease-modifying agent in DPN, looking at clinical indicators and biomarkers of disease (symptoms, neuropathy scores, ulceration, quality of life, and neurophysiological parameters), and adverse events.

BACKGROUND

Description of the condition

Epidemiology of diabetes mellitus and diabetic polyneuropathy

Diabetes mellitus is one of the most common noncommunicable diseases and a leading public health concern. Chronic hyperglycaemia results from insufficient insulin production (type 1 diabetes, formerly called insulin-dependent diabetes) or insulin resistance (type 2 diabetes, formerly non-insulin dependent) (WHO 1999). According to World Health Organization (WHO) estimates, the number of adults living with diabetes has quadrupled between 1980 and 2014 (NCD 2016). People with both types of diabetes develop multisystem complications (WHO 2016), one of the most frequent being diabetic peripheral neuropathy (DPN).

DPN has an estimated prevalence in the diabetic population of between 10% and 100% depending upon the data source and ascertainment methodology (Feldman 2016).

DPN can be classified clinically as either focal or diffuse. Diffuse disease can affect the sensorimotor or the autonomic nervous systems or both. Sensorimotor disease can involve large or small nerve fibres (Edwards 2008), is usually predominantly sensory, and may be painful.

Distal symmetrical sensorimotor polyneuropathy is the most common form of DPN, with a reported prevalence in diabetes mellitus ranging from 28.5% to 45%, increasing with age and disease duration (Harris 1993; Pirart 1977; Young 1993). Distal symmetrical sensorimotor polyneuropathy represents a major cause of morbidity and the leading source of diabetes-related hospitalizations and non-traumatic amputations. It is also accountable for considerable physical disability, altered quality of life, and increased mortality (Boulton 2005; Tesfaye 2011).

Clinical manifestations of DPN

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" (Boulton 1998). DPN may be asymptomatic and insidious at onset. The most common symptom of DPN is neuropathic pain, 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 pain, tingling, burning sensations, paraesthesia, shooting or lancinating pains, aching, and contact pain (allodynia) provoked by clothing (Tesfaye 2011).

DPN complications are also a major threat to the general well-being and quality of life of people with diabetes. Numbness caused by DPN, along with retinopathy and vestibular dysfunction, increase the risk of falls two- to three-fold compared to people without DPN (Agrawal 2010). People with DPN are also seven times more likely to develop foot ulcerations (Amin 2016). Foot ulcerations further predispose 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 disturbance, and quality of life (Bredfeldt 2015).

Pathophysiology of DPN

The pathophysiology of DPN is not fully understood, and very likely to be multifactorial (genetic, environmental, behavioural, metabolic, neurotrophic, and vascular) (Chen 2013; Xu 2013). Oxidative stress generated by excess free radical formation or errors in antioxidant protection, or both, is thought to be important in the pathogenesis (Low 1997). Good glycaemic control reduces the risk of developing DPN, but glycaemic control is not always achievable and is usually not sufficient to halt DPN progression (Chen 2013; DCCT 1993; Duckworth 2009; Tesfaye 2011).

DPN pathophysiology can not only be explained as neural dysfunction caused by the interplay of decreased blood flow to nerves as a result of hyperglycaemia, and increased oxidative stress, which induces local inflammatory reactions through reactive oxygen species (ROS) (Brownlee 2005). Prolonged hyperglycaemia simultaneously activates multiple pathways. It promotes the following.

- Activation of polyol and protein kinase pathways that leads to reduced nicotinamide adenine dinucleotide phosphate (NADPH) and subsequent depletion of glutathione and nitric oxide (Feldman 1997, Uehara 2004).
- Angiogenesis driven by the vascular endothelial growth factor pathway.
- Basement membrane thickening and endothelial proliferation (via transforming growth factor-β and nuclear factor - kappa B), which cause altered capillary permeability and local hypoxia.
- Activation of the hexosamine pathway and shunting of fructose-6-phosphate from the glycolytic pathway.
- Modified gene expression for glucose transporters and glucokinase (Kolm-Litty 1998).

Generation of ROS and advanced glycosylation end-products activates the same NFkB pathway, which increases oxidative stress with additional NADPH depletion. Oxidative stress also induces poly(ADP-ribose) polymerase activation, which sequentially results in supplemental nicotinamide adenine dinucleotide depletion, positive loop activation of the protein kinase pathway, and promotes inflammation (Vinik 2004). All these pathways promote mitochondrial dysfunction, which in turn is followed by apoptosis, axonal degeneration, and axonal death. Local pro-inflammatory cytokines induced by oxidative stress promote macrophage recruitment with subsequent glial failure, myelin breakdown, and impaired nerve regeneration (Wang 2006).

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

Management of DPN

Current management of DPN consists of three therapeutic approaches. The main target is prevention, through control of fasting and postprandial glucose (Callaghan 2012b). Medications that target symptoms and disease-modifying treatments are used in the treatment of people with diagnosed DPN. Symptomatic treatments target pain; they include anticonvulsants, tricyclic antidepressants (Lunn 2014; Saarto 2007), serotonin and noradrenaline reuptake inhibitors (Allen 2014), opioids and opioid-like drugs (Snedecor 2014; Tesfaye 2011; Ziegler 2006), systemic local anaesthetics (Challapalli 2005), nonsteroidal anti-inflammatory agents (Boulton 2005; Snedecor 2014; Tesfaye 2011), and non-drug therapies such as transcutaneous electrical nerve stimulation, pulsed radiofrequency sympathectomy (Naderi 2015), and acupuncture (Abuaisha 1998; Zhang 2010).

Disease-modifying treatments aim to prevent, slow, or reverse DPN progression by reduction of oxidative stress and inhibition of the polyol, hexosamine, protein kinase, advanced glycosylation product, and poly(ADP-ribose) polymerase pathways.

Description of the intervention

Alpha-lipoic acid (ALA) is a natural thiol used as a dietary supplement. ALA has presumed potent antioxidant properties, metal-chelating functions, and is able to regenerate endogenous antioxidants and stimulate glucose uptake (Rochette 2015). The therapeutic use of ALA has therefore been investigated in different clin-

ical scenarios, including cardiovascular diseases and diabetic complications, such as DPN. Clinical trials have used different forms of administration and treatment durations. ALA dosage ranges from 200 mg/day to 1800 mg/day, administered intravenously or orally.

How the intervention might work

ALA acts as a scavenger of ROS and has antioxidant properties that could block the oxidative stress-inflammation pathways activated in DPN. It could therefore be useful both in prevention and treatment of DPN (Rochette 2015).

Early in vitro studies showed that ALA and its reduced form, dihydrolipoic acid (DHLA), scavenge ROS, including hydroxyl radicals, hypochlorous acid, and singlet oxygen (Packer 1995). In vivo studies also indicated that ALA decreases oxidative stress (Marangon 1999), participates in restoring endogenous cellular antioxidant levels and reducing pro-inflammatory pathways (Petersen 2008), and may influence the regeneration of vitamins C and E (Rochette 2015).

The benefit of ALA in people with diabetes could range beyond antioxidant and anti-inflammatory effects. The therapeutic properties of ALA might include the ability to restore glucose availability and increase insulin-stimulated glucose transport and non-oxidative and oxidative glucose metabolism in insulin-resistant muscle cells (Khanna 1999; Streeper 1997). ALA has therefore been a candidate for clinical study in DPN.

Why it is important to do this review

DPN is a major public health problem, owing to its prevalence in people with diabetes, related morbidity, and potentially severe impairment in quality of life. Although ALA is widely used for DPN, no consensus about its use in diabetes is established at present. A number of published Cochrane reviews assess the effects of treatments for diabetic peripheral neuropathy (e.g. aldose reductase inhibitors (Chalk 2007), Chinese herbal medicine (Chen 2013), and enhanced glucose control (Callaghan 2012b)), but none investigate the effects of ALA. If effective and safe, ALA could have cost-effective utility in the long-term management of DPN.

OBJECTIVES

To assess the effects of ALA as a disease-modifying agent in DPN, looking at clinical indicators and biomarkers of disease (symptoms, neuropathy scores, ulceration, quality of life, and neurophysiological parameters), and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials (RCTs) and quasi-RCTs that compare ALA with a placebo or with no treatment. We will only consider studies in which the intervention was applied for at least six months. We will consider data from studies published as abstracts and unpublished data where it is derived from completed studies reported in clinical trials registries. We will apply no language restriction.

Types of participants

We will include studies that enrol people with either type 1 or 2 diabetes mellitus and established DPN, who are older than 18 years, and regardless of gender or setting. For the purpose of this Cochrane Review, the definition of DPN will be the "presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (Boulton 1998). This will include typical DPN: sensorimotor polyneuropathy that is length-dependent and symmetrical (Tesfaye 2010). An abnormality of nerve conduction tests alone, detecting an asymptomatic neuropathy in diabetes, appears to be an objective, semi-quantitative (albeit indirect) indication of the condition (Tesfaye 2010). We will thus include participants with a clinical or an electrophysiological diagnosis of diabetic neuropathy, or both.

Types of interventions

We will include oral or intravenous ALA compared to placebo or no treatment, with at least six months' duration of treatment. We will allow co-interventions provided they are provided to all groups equally.

Types of outcome measures

Primary outcomes

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

Secondary outcomes

- Neuropathy symptom improvement expressed as change in TSS, or other validated symptom score at six to 12 months and greater than 12 months to 24 months after randomisation.
- Change in impairment as measured by validated measures such as the Medical Research Council (MRC) sum score, the Neuropathy Impairment Score (NIS), the Neuropathy Disability Score (NDS) (an impairment score), 10 m walk and sensory function quantified by validated tools such as the Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score, at six to 12 months and greater than 12 to 24 months.
- Change in any validated quality of life score - total score - compared to the baseline at six months.
- Complications of DPN, including numbers of participants with foot ulceration, amputation, or both at any stage after treatment.
- Adverse events, divided into 'any adverse event', 'adverse events leading to cessation', and 'serious adverse events' (any event resulting in death, being life-threatening, or requiring prolonged hospitalisation). We will assess adverse events in all included studies of any duration at any time.

Search methods for identification of studies

Electronic searches

The Cochrane Neuromuscular Information Specialist will search the following databases.

- Cochrane Neuromuscular Specialised Register
- Cochrane Central Register of Controlled Trials (CENTRAL).
- MEDLINE (Appendix 1)
- Embase.

We will also conduct a search of the US National Institutes for Health Clinical Trials Registry, ClinicalTrials.gov (www.ClinicalTrials.gov), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; (apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

We will search the EU Clinical Trials register (www.clinicaltrialsregister.eu), and theUS Food and Drug Administration (FDA) (www.fda.gov) and European Medicines Agency (EMA) (www.ema.europa.eu) websites.

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will search reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

Data collection and analysis

Selection of studies

Two review authors (CB and CD) will independently scan the title and abstract of every record identified by the searches to determine the studies to be assessed further for eligibility. They will retrieve full-text reports of all potentially relevant articles. Two review authors (FF and AP) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (CB). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

Data extraction and management

We will extract data concerning details of study design and setting, study population, intervention and outcomes, source(s) of study funding, and any conflicts of interest among investigators using Covidence software (www.covidence.org). Two review authors (FF and AP) will independently extract data and will compare extractions and resolve disputes by discussion. A third review author (CB) will settle the unresolved disputes. If needed, we will contact the authors of included studies for clarification.

Assessment of risk of bias in included studies

Two review authors (CD and AP) will independently perform 'Risk of bias' assessments using the Cochrane 'Risk of bias' tool (Higgins 2011). They will assess studies using the following criteria: the method of randomisation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessors, selective outcome reporting, and incomplete outcome data (completeness of follow-up). Other sources of bias will include being a single-centre trial or single investigator (Mallik 2014). We will grade these items as at low, high, or unclear risk of bias, and we will create a 'Risk of bias' table. A third review author (CB) will resolve any differences in the assessments.

Measures of treatment effect

For homogenous continuous outcome measures, we will use Review Manager 5 (RevMan 5) to calculate the results as mean differences (MDs) with 95% confidence intervals (CIs) (RevMan

2014). Where studies have used different scales to measure the same outcome, we will perform meta-analysis using standardized mean differences (SMDs). To aid interpretation of SMDs and MDs, we will also dichotomise the results into 'clinical improvement' or 'no clinical improvement' (i.e. not improved or worsened) depending on established minimal clinically important difference (MCID) reported in the literature for, for example, the TSS (Bastyr 2005) and INCAT (Merkies 2010; Merkies 2017). For dichotomous outcome measures, we will present the results as risk ratios with 95% CIs. In the absence of established MCIDs or if data are not suitable for dichotomisation, we will convert SMDs to number needed to treat for an additional beneficial effect (Higgins 2011).

Unit of analysis issues

Most studies are likely to be parallel-group randomised trials. Cross-over trials are improbable, as the treatment needs a long time to take effect, the reversibility of any effect is unknown, and the wash-out period for ALA has not been established. In the event of repeated observations on participants, we will define the outcomes based on different periods of follow-up (six months, six to 12 months, and 12 to 24 months).

Where a trial includes multiple treatment arms, we will include only the treatment arms relevant to this review. We will avoid double-counting participants (for example, from a control group in multi-arm trials by combining intervention groups if this makes clinical sense, or by halving the control group (Higgins 2011). We will combine comparisons versus placebo and versus no treatment in a single analysis.

Dealing with missing data

We will collect dropout rates and report them in the 'Risk of bias' table. We will conduct an available cases analysis for continuous data, and we will consider the potential impact of the missing data in the interpretation of the results of the review (Higgins 2011). In the event of missing data we will calculate them from other measures, such as P values, standard errors, T values, and CI. If this is not possible we will include the study in the review but not in meta-analyses.

Assessment of heterogeneity

Clinical and methodological heterogeneity is likely to produce statistical heterogeneity. First, we will examine the trials in order to see if there are clinical reasons for heterogeneity. For assessing heterogeneity across trials we will use the Chi² test and I² statistic. We will not employ simple thresholds to diagnose heterogeneity, but will use the rough guide to interpretation described in the *Cochrane Handbook for Systematic Reviews of Interventions:* 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity (Higgins 2011). If we find heterogeneity, we will attempt to explore possible reasons for it, for example by undertaking sensitivity analyses by repeating the calculation after omitting the trials which have low scores on individual quality items. In the event of heterogeneity being identified, we will carry out subgroup analyses (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Where more than 10 studies are included in any one analysis, we will investigate potential small study biases using a funnel plot and Egger test (Egger 1997). We will search for unpublished trials on trial registration databases, and the FDA and EMA websites.

Data synthesis

We will calculate the treatment effect from the included clinical trials using the Cochrane statistical software, RevMan 5 (RevMan 2014). We will use a fixed-effect model and perform a sensitivity analysis with the random-effects model.

'Summary of findings' table

We will assess the quality of the evidence using the five GRADE considerations (i.e. study limitations, inconsistency, indirectness, imprecision, and publication bias) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will downgrade the quality rating by one level for each factor, up to a maximum of three levels for all factors. If there are very severe problems for any one factor we will downgrade two levels due to that factor alone. Three review authors will independently assess the quality of the evidence, and resolve differences in opinion through discussion.

We will include the following outcome measures in the 'Summary of findings' table:

- Neuropathy symptom improvement as expressed as change in TSS, or other validated symptom scores at six months after randomisation.
- Change in impairment as measured by validated measures such as the MRC sum score, the Neuropathy Impairment Score (NIS), the Neuropathy Disability Score (NDS) (an impairment score) at six months.
- Change in any validated quality of life score - total score - compared to the baseline at six months.
- Complications of DPN, including the number of participants with foot ulceration, amputation, or both.
- Any adverse event.

As described in Types of outcome measures, we will report MDs when studies use the same scale for an outcome. If they use different scales for an outcome that is conceptually the same, we will

dichotomise the data, i.e. report number of participants improved versus participants not improved or worsened, alongside SMD to aid interpretation.

Subgroup analysis and investigation of heterogeneity

We hypothesise that response to treatment may differ according to disease duration (longstanding DPN less likely to improve), age (older participants less likely to improve), severity of the disease, and type of diabetes, as the pathogeneses are different. We also expect that outcomes will be reported differently in the presence of pain. Route of administration may influence bioavailability and lead to different effects.

Therefore we will perform the following subgroup analyses, when sufficient data are available.

- Painful versus nonpainful neuropathy.
- Type of diabetes (type 1 versus type 2).
- Disease duration ≤ five years, six to 10 years, or greater than 10 years.
- Participants aged ≤ 65 or greater than 65 years.
- Oral versus intravenous administration.

We will use the following outcomes in subgroup analyses.

- Change in TSS or other validated neuropathy symptom score.
- Change in any validated quality of life score.

We will use the formal test for subgroup interactions in RevMan 5 (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² statistic value.

Sensitivity analysis

We will exclude studies at high risk of bias in one or more key domains and studies for which the risk of bias is unclear in one or more key domains in sensitivity analyses (Higgins 2011). We will compare the results of studies with a low risk of bias with the results of all available studies. We will only perform sensitivity analyses if there are at least two studies that are at low risk of bias in the analysis.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice. Our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

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1 randomized controlled trial.pt. (469833)
2 controlled clinical trial.pt. (95075)
3 randomized.ab. (405922)
4 placebo.ab. (192462)
5 drug therapy.fs. (2035863)
6 randomly.ab. (286430)
7 trial.ab. (428193)
8 groups.ab. (1764339)
9 or/1-8 (4191739)
10 exp animals/ not humans.sh. (4[illegible]484)
11 9 not 10 (3613342)
12 exp Diabetes Mellitus/ (38[illegible]80)
13 diabet$.mp. (608134)
14 12 or 13 (609856)
15 exp Peripheral Nervous System Diseases/ (137699)
16 15 or (neuropath$ or p[illegible]neuropath$).mp. (222573)
17 14 and 16 (25606)
18 Diabetic Neuropathies/ ([illegible]3937)
19 17 or 18 ([illegible]5606)
20 Thioctic Acid/ (3831)
21 (lipoic acid or alpha lipoic or thioc*).mp. (25770)
22 20 or 21 ([illegible]770)
23 11 and 19 and [illegible]2 (189)
24 remove duplicates from 23 (168)

CONTRIBUTIONS OF AUTHORS

FF and CB wrote a draft of the protocol; AP, CD, and EvE revised it. All authors approved the protocol. AP entered the protocol into RevMan 5 (RevMan 2014).

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.

External sources

- None, Other.