Phil. J. Internal Medicine, 47: 211-218, Sept.-Oct., 2009

THE ROLE OF ORAL ALPHA-LIPOIC ACID IN REDUCING THE SYMPTOMS OF DIABETIC NEUROPATHY A META-ANALYSIS

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ABSTRACT

Background: **There are several ways to reduce the complications of diabetes mellitus. Food Supplements are now available and are said to benefit diabetic patients. It has been proven that intravenous alpha-lipoic acid improves sensory symptoms of diabetic neuropathy.**

Objective: **The objective of this study is to assess the efficacy of oral alpha-lipoic acid in reducing the symptoms of diabetic neuropathy.**

Research Design and Methods: **Searches using the Medline database of the National Institute of Medicine at Pubmed, Cochrane, Ovid and other medical and non-medical search engines using search terms "oral alpha-lipoic acid", "AND", "diabetic neuropathy", "RCT", and "meta-analysis".**

Statistical Analysis: **Statistical analysis was done using the Review Manager 4.2**

Results: **Two published randomized, double-blind, placebo-controlled studies by Ruhnau *et al* in 1999 and Ziegler in 2006 showed the effectiveness of oral lipoic acid in reducing the symptoms of diabetic neuropathy using the total symptom score questionnaire (TSS).**

Ruhnau *et al*., published a randomized, double-blind, placebo-controlled study using 24 subjects with symptoms of diabetic neuropathy. They were given 600mg alpha-lipoic acid T.I.D. or placebo for 3 weeks. Baseline and endpoint TSS was compared, study showed that oral alpha-lipoic acid reduces neuropathic symptoms.

Ziegler *et al*., published a randomized controlled study using 181 diabetic patients who were given daily oral doses of 600mg, 1200mg, 1800mg or placebo for 5 weeks after a week placebo. The primary outcome measure was the change from baseline of the TSS. The study showed that oral treatment with ALA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP.

Conclusion: **Since oral preparation is effective, cheaper and with better compliance rate, oral treatment is an option in the treatment of diabetic neuropathy.**

INTRODUCTION

The worldwide prevalence of Diabetes Mellitus has risen dramatically over the past 2 decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030.[11] Diabetes mellitus is a chronic disease and medical and non-medical treatment should be emphasized to prevent short-term and long-term diabetes-related problems.

Diabetes is the leading known cause of peripheral neuropathy in developed countries, and conversely, neuropathy is recognized as the most common complication and the greatest source of morbidity and mortality among diabetes patients. It is estimated that the prevalence of neuropathy in diabetes patients is approximately 20%. Diabetic neuropathy is implicated in 50-75% of non-traumatic amputations. It is a disabling complication, hence, prevention is generally emphasized.

Neuropathies are characterized by a progressive loss of nerve fibers that can be documented non-invasively by several tests of nerve function including electromyography, nerve conduction studies, quantitative sensory testing, and autonomic function tests. Diabetic neuropathy is clinically defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes.

Strict glycemic control is needed to reduce

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the risk of long term diabetic complication, which includes retinopathy, nephropathy, cardiomyopathy, coronary artery disease, peripheral vascular disease, stroke, coronary artery stenosis, myonecrosis, encephalopathy and peripheral neuropathy.

Diabetes Mellitus is indeed, one chronic disease that requires aggressive pharmacologic and non-pharmacological intervention to better achieve glycemic control. Non-phamacologic intervention includes patient education, dietetic support, sensible exercise, self monitoring of blood glucose with the goal of keeping both short-term and long-term blood glucose within normal limits. However, pharmacological management is of prime importance in order to avoid both the acute and chronic complications of the disease. Recently, supplemental therapy has been incorporated in the practice of some clinicians to treat complications like neuropathy.

One of the supplemental therapy used in the treatment of neuropathy is Alpha-Lipoic Acid, also called Thioctic acid. It is an organic compound, consisting of carboxylic acid and a cyclic disulfide. There are 2 forms, the R and S enantiomer. Only the R-enantiomer is biologically significant. It is essential for aerobic life and a common dietary supplement. It is an effective antioxidant, since it is able to scavenge free radicals in vitro. However, little or no evidence show that it is also effective in vivo. The relatively good scavenging activity of alpha-lipoic acid is due to the strained conformation of the 5-membered ring in the intramolecular disulfide. Alpha-lipoic acid has also been shown to increase cellular uptake of glucose by recruiting the glucose transporter GLUT 4 to the cell membrane suggesting its importance in diabetes.

In 2003, a meta-analysis was published by Ziegler *et al*[1], to assess the possible benefit of intravenous alpha-lipoic acid in improving neuropathic symptoms. Intravenous alpha-lipoic acid improved or reduced symptoms of diabetic polyneuropathy in all trials. Four trials (ALADIN I, ALADIN II, SYDNEY, NATHAN II) comprised 1258 patients (alpha lipoic acid n= 716 and placebo n= 542) were used. Selection was based on the following criteria: published, double-blind, placebo-controlled, parallel group trial using alpha-lipoic acid infusion of 600mg IV per day for 3 weeks except for weekends, in diabetic patients with positive sensory symptoms of polyneuropathy which were scored by the Total Symptom Score (TSS) in the feet on a daily basis. The primary end point was the comparison of the differences in TSS from baseline to the end of intravenous treatment. The results of this meta-analysis showed a statistically significant effect size for intravenous with placebo, and concluded that intravenous alpha-lipoic acid improves or reduces sensory symptoms of diabetic neuropathy.

Objectives

The primary aim of this meta-analysis is to review the randomized controlled trials that determine the efficacy oral alpha-lipoic acid in improving the sensory symptoms of diabetic neuropathy.

Search strategy

A. Searches of electronic database: MEDLINE at Pubmed, Cochrane, Ovid were carried out using the following search strategy:
   1. randomized controlled trial
   2. Diabetic Neuropathy (MESH)
   3. oral alpha-lipoic acid (MESH)
   4. Total Symptom Score (MESH)

B. Review of textbooks in Medicine (Harrison's 17th edition) and Endocrinology (William's Textbook of Endocrinology)

C. Review of References of Retrieved Articles

Selection criteria

A. Types of Studies

Included in this meta-analysis are randomized-controlled, double-blinded trials that compare oral alpha-lipoic acid versus placebo on the total symptom score (TSS).

B. Types of Participants

All patients in the two studies fulfilled the criteria for having diabetes with symptoms of neuropathy described as pain, burning, paresthesiae, and numbness.

C. Types of Interventions

Study group: oral alpha-lipoic acid (600mg, 1200mg, 1800mg)
Control group: placebo

D. Types of Outcome Measures

The primary endpoint of this meta-analysis was to determine the effect of oral alpha-lipoic acid treatment in the total symptom score (TSS) in patients with symptoms of diabetic neuropathy.

Data Collection and Analysis

Internet searches using the Medline database of the National Institute of Medicine at Pubmed, Cochrane, Ovid and other medical and non-medical search

engines using search terms “oral alpha-lipoic acid”, “AND”, “diabetic neuropathy”, “RCT”, and “meta-analysis”. Biographical links from journals taken were reviewed. Full text articles were acquired from the internet and printed journals. Manual literature searches and cross references were also done.

Statistical analysis was done using Review Manager Version 4.2. Meta-analysis was done by entering data of the studies and the results were presented graphically and analyzed accordingly.

MATERIALS AND METHODS

Selection of the Trials

References of the journal articles searched were checked for other relevant articles. Copies of previously published reviews on the topic were obtained and checked for references to the studies. Consultation with clinical experts was also done regarding significant articles on this topic.

Trials selected were published in English language and restricted only to diabetic patients with symptoms of neuropathy. Cross-references, review articles, citations of the clinical trials obtained from computer search were examined. The articles obtained were independently reviewed. Journals that fulfilled the study’s objectives were retrieved and evaluated.

Inclusion Studies

Included in this meta-analysis are two randomized-controlled trials done by Ziegler *et al* in 2006, wherein 181 subjects with diabetic neuropathy were randomly assigned in receiving oral alpha-lipoic acid versus placebo, and by Ruhnau *et al* in 1999, wherein 24 subjects with diabetic neuropathy were also randomly assigned in receiving oral alpha-lipoic acid versus placebo. (Table I)

Inclusion Criteria

Studies included in this meta-analysis used a study population randomized to receive oral alpha-lipoic acid or placebo for diabetic patients with neuropathic symptoms.

Participants included were those diagnosed to have diabetic neuropathy at the start of the study. Participants should present with any of the neuropathic symptoms such as pain, burning sensation, paresthesias and numbness.

Present therapies are directed at improving symptoms of diabetic neuropathy. Improvement or efficacy of intervention is defined as a decrease in the total symptom score or TSS (Appendix A), meaning decrease in symptoms of diabetic neuropathy. This meta-analysis aims to study and evaluate the efficacy of oral alpha-lipoic acid in reducing the symptoms of diabetic neuropathy. (Table II)

Exclusion Criteria

Participants treated with intravenous alpha-lipoic acid instead of oral alpha-lipoic acid were excluded from the meta-analysis. In a study done by Ziegler D., Gries FA[10] in 1997, favoring alpha-lipoic acid versus placebo, 328 patients with diabetic neuropathy were randomly assigned to treatment using alpha-lipoic acid versus placebo. However, intravenous form of alpha-lipoic acid was used instead of oral and was thus excluded from this meta-analysis. In another study by Ametov, *et al.*[2], 120 subjects were enrolled and results showed a statistically significant outcome favoring alpha-lipoic acid – improvement from baseline total symptom score by 5.7 points in the group treated with alpha-lipoic acid. However, interventions used was also intravenous versus

Table I. Characteristics of Included Trials

STUDY ID	METHODS	PARTICIPANTS	INTERVENTION	OUTCOME	QUALITY
Ziegler et al. Diabetes Care 2006; 29: 2365-2370	Randomized, double-blind placebo-controlled trial comparison of oral ALA or placebo	181 participants	oral ALA 600mg (n=45), 1200mg (n=47), 1800mg (n=46) OD ; Placebo (n=43)	Mean reduction in total symptom score (TSS)	B
Ruhnau et al. British Diabetic Association. Diabetic Medicine 1999; 16: 1040-1043	Randomized, double-blind comparison of oral ALA or placebo	24 participants	oral ALA 600 mg TID (n=12) and Placebo (n=12)	Mean reduction in total symptom score (TSS)	A

placebo. In the study conducted by Ziegler, Hanefield *et al.*[3] in 1999, intravenous treatment was followed by oral alpha-lipoic acid and this was compared to placebo. Similarly, this study was excluded due to the presence of a confounder (intravenous treatment).

Table II. Inclusion and Exclusion Criteria of Included Sudy

Study ID	Inclusion Criteria	Exclusion Criteria
Ziegler et al. Diabetes Care 2006; 29: 2365-2370	age between 18 and 74 yrs, diabetes (type 1 or 2) as defined by American Diabetes Association criteria, duration of diabetes >/= 1 year, HbA1c <10%, symptomatic DSP attributable to diabetes, TSS >7.5 points, Neuropathy Impairment Score (NIS) subscore for lower limbs (NIS_{LL}) >/= 2 points, and pain sensation according to the pain prick test absetnt or decreased	Confounding neurologic disease or neuropathy, myopathy of any cause; peripheral vascular disease severe enough to cause intermittent claudication, ischemic ulcers or limb ischemia; hepatic or renal disease; antioxidant therapy or pentoxyphylline within the last month; use of >/= 50mg ALA ot use of gamma linolenic acid containing substances within the last 3 months.
Ruhnau et al. British Diabetic Association. Diabetic Medicine 1999; 16: 1040-1043	Age between 18 and 79 years, with type 2 diabetes treated with diet, oral anti-diabetic agents and/ or insulin, evidence of distal symmetrical polyneuropathy (reduced/absent ankle reflexes, reduced vibration, thermal,tactile, pin-prick, and/or position sensation) with at least moderate severity of one or more of the typical symptos (pain, burning, paresthesiae, numbness) in the feet, equivalent to 4 or more points in the total symprom score.	asymmetrical neuropathy of the trunk and proximal lower limbs, presence of foot ulcers, peripheral vascualr disease (nonpalpable foot pulses, intermittent clausication), myopathy, causes of neuropathy other than diabetes and significant neurological diseases, participation in a study of any investigational drug for neuropathy within the last 3 months before the study, use of antioxidants or vitamin B within 1 month before the study, severe concomitant diseases, pregnancy, lactation, or child bearing age without birth control devices

Participants with neuropathic symptoms caused by other variables other than diabetes mellitus were likewise excluded.

Studies which utilized testing other than the total symptom score were excluded from the study. In the study published in Deutsche Kardial Autonome Neuropathie Studie by Ziegler *et al*, oral dose of 800mg alpha-lipoic acid versus placebo was used, however, heart rate variability was measured as an outcome instead of the neuropathy total symptom score. In another study by Reljanovic *et al.*[7], intravenous alpha-lipoic acid was used instead of oral and Neuropathy Disability Score, Sensory Nerve Conduction Velocity (SNCV), Sensory Nerve Action Potential (SNAP), Motor Nerve Conduction Velocity (MNCV), Motor Nerve Distal Latency (MNDL) were used instead of the Total Symptom Score (TSS) Questionnaire. These were the reasons for exclusion.

There were 2 open-labeled studies, Tankova et al.9 and Hahm et al.10, which also favored oral alpha-lipoic acid in diabetic neuropathy but were excluded in the study.

Quality of Trials

The included trials were assessed for potential bias. Randomization, concealment, follow-up and intention to treat analysis were ensured. The primary validity criteria used were the presence of randomization, adequate concealment, and complete and adequate follow-up. Based on the quality scale, the trials were graded as A (no bias), B (low risk for bias), and C (high risk for bias). Only studies classified as A or B were included. The methodological quality of the studies is good (grade A and B). All of them had adequate concealment. (Tables III and IV)

Table III: Quality Scale for Meta-Analytic Reviews

Study Title: Effects of 3 weeks oral treatment with the antioxidant thioctic acid (alpha-lipoic acid) in symptomatic diabetic polyneuropathy (Ruhnau et al.)

Subtle Bias	Frank Bias
Were there attempts at allocation concealment? Comments: identical placebo tablets	Were the groups being compared balanced in terms of known determinants of outcome?
[X]Y [ ]N [ ]NS	Comments:
	[X]Y [ ]N [ ]NS
Was the physician caring for the patient blinded regarding treatment?	Were the two groups treated equally in terms of other medication received, frequency of follow-up and general quality of care?
Comments:	Comments: aside from the treatment, there were no difference in the two groups
[X]Y [ ]N [ ]NS	[X]Y [ ]N [ ]NS
Was an intention to treat analysis conducted?	Are the drop-out rates between the groups comparable?
Comments:	Comments: a total of 2 patients dropped out from the study of Ruhnau et al (1 in treatment and 1 in placebo)
[X]Y [ ]N [ ]NS	[X]Y [ ]N [ ]NS
Were the persons making an outcome assessment blinded regarding treatment?	Are the outcomes detection methods used similar in both groups?
Comments:	Comments: evaluation of symptoms were measured using the total symptom score (TSS) questionnaire
[X]Y [ ]N [ ]NS	
Reviewer: Kristine Catherine L. Tan M.D. Date: October 2008 Overall score: A	[X]Y [ ]N [ ]NS

Table IV: Quality Scale for Meta-Analytic Reviews

Study Title: Oral Treatment With Alpha-Lipoic Acid Improves Symptomatic Diabetic Polyneuropathy	
Subtle Bias	Frank Bias
Were there attempts at allocation concealment? Comments: [X]Y [ ]N [ ]NS	Were the groups being compared balanced in terms of known determinants of outcome? Comments: [X]Y [ ]N [ ]NS
Was the physician caring for the patient blinded regarding treatment? Comments: [X]Y [ ]N [ ]NS	Were the two groups treated equally in terms of other medication received, frequency of follow-up and general quality of care? Comments: aside from the treatment, there were not difference in the two groups [X]Y [ ]N [ ]NS
Was an intention to treat analysis conducted? Comments: [X]Y [ ]N [ ]NS	Are the drop-out rates between the groups comparable? Comments: a total of 15 patients dropped out (1 in placebo; 6 in ALA 1200; 8 in ALA1800) [ ]Y [X]N [ ]NS
Were the persons making an outcome assessment blinded regarding treatment? Comments: identical placebo tablets was used [X]Y [ ]N [ ]NS	Are the outcomes detection methods used similar in both groups? Comments: evaluation of symptoms were measured using the total symptom score (TSS) questionnaire [X]Y [ ]N [ ]NS
Reviewers: Kristine Catherine L. Tan, M.D. Date: October 2008 Overall score: B	

RESULTS

Figure 1 shows the mean change in total symptom score (TSS) for all patients. The point estimate was noted at -1.87 with a 95% cl between -2.81 to -0.93. Test for heterogeneity was significant, with P-value of <0.90. The overall effect was significant with a P-value <0.0001, in favor of oral alpha-lipoic acid.

DISCUSSION

Diabetic neuropathy is one of the more important long term complications of diabetes mellitus. Neuropathy is characterized by microvascular injury involving small blood vessels supplying peripheral nerves. It presents as numbness and tingling of extremities, dysesthesia (decreased or loss of sensation to a body part), diarrhea, erectile dysfunction, urinary incontinence, impotence, facial, mouth and eyelid drooping, vision changes and dizziness, muscle weakness, dysphagia, speech impairment, fasciculation, anorgasmia, burning or electric stabbing pains.

It has been suggested that hyperglycemia is the primary risk factor in the development of diabetic neuropathies. Persistent hyperglycemia (or glucose toxicity) or insulin deficiency may precipitate metabolic or vascular events. These include alteration of the polyol or sorbitol pathway, abnormalities in the lipid metabolism, deficiencies of di-homo-y-linolenic acid (GLA) and N-acetyl-L-carnitine, glycation or AGE formation, increased oxidative stress, and diabetes mellitus- induced growth factor defects. Hyperglycemia also generates free radicals primarily by increasing flux through the mitochondrial electron transport chain. Formation of the advanced glycation end products (AGE) and interaction with the AGE receptor may also lead to the generation of the reactive oxygen species (ROS). It has been investigated that oxidative stress resulting from enhanced free-radical formation and/or defects in

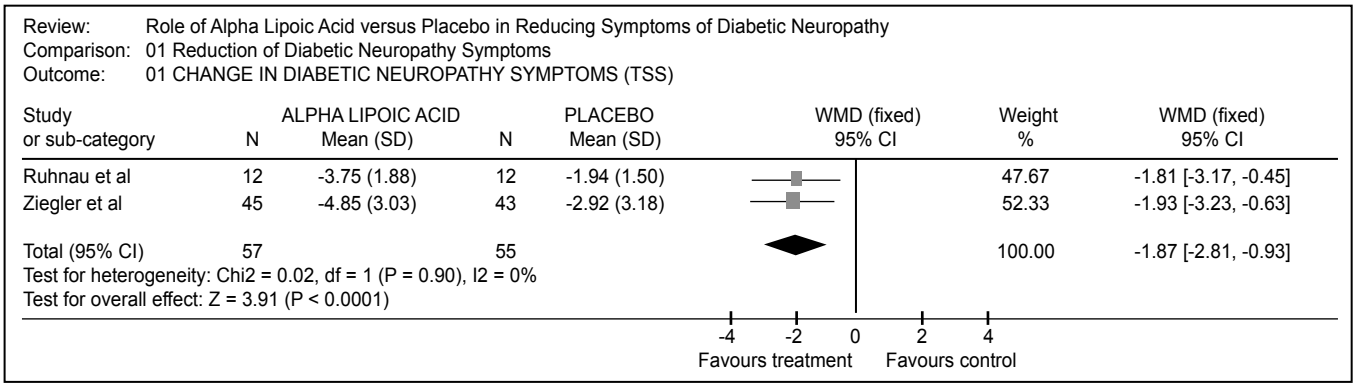

Figure 1: Effect of Oral ALA versus Placebo on Symptoms of Diabetic Neuropathy

antioxidant defense may induce neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction.[11] Recent investigations showed that alpha-lipoic acid diminish increased oxidative stress. It has been shown to neutralize free radicals in both fatty and watery regions of cells, unlike Vitamin C which is only water soluble and Vitamin E which is fat soluble. It directly recycles and extends the lifespan of Vitamin C, glutathione Coenzyme Q10, and indirectly renews Vitamin E. It is considered an ideal antioxidant since it is able to fulfill several criteria: absorption from the diet, conversion in cells and tissues into usable forms, and low toxicity.

A meta-analysis done in 2003 by Ziegler *et al.*[1], showed the efficacy of intravenous alpha-lipoic acid in reducing symptoms of diabetic neuropathy. However, intravenous administration is not only time consuming, it limits the access of therapy for the general diabetic population. In a study done by Teichert *et al.*[12], results showed that alpha-lipoic acid orally administered for the treatment of symptomatic neuropathy is readily and nearly completely absorbed. The study also pointed out that biliary excretion, further electrochemically inactive degradation products and complete utilization of alpha-lipoic acid as a primary substrate in the endogenous metabolism should be considered. Alpha lipoic-acid is found in animal and plant sources, such as kidneys, heart, liver meats, spinach, brocolli, and potatoes. It is suggested that it should be taken on an empty stomach for maximum absorption.

This paper focuses on the importance of oral alpha-lipoic acid not only because oral preparation is less time consuming, but more importantly it has better compliance rate compared to intravenous form and acceptable bioavailability.

In 1999, Ruhnau *et al.*[4], published a randomized, double-blind, placebo-controlled study involving 24 subjects with symptoms of diabetic neuropathy, they were given 600mg/tablet formulation of alpha-lipoic acid T.I.D. or placebo for 3 weeks. Baseline and endpoint Total Symptom Score (TSS), Hamburg Pain Adjective List (HAPL), and Neuropathy Disability Score (NDS) were compared. Study showed that alpha-lipoic acid 600mg/tablet T.I.D. Reduces neuropathic symptoms.

Later in 2006, Ziegler, *et al*[5], published a randomized controlled study using 181 diabetic patients who were given once daily oral doses of 600mg, 1200mg, 1800mg or placebo for 5 weeks after a week placebo. The primary outcome measure was the change from baseline of the Total Symptom Score (TSS), including stabbing pain, burning pain, paresthesia and asleep numbness of feet. Secondary endpoints included individual symptoms of Total Symptom Score (TSS), Neuropathy Symptoms and Change (NSC), Neuropathy impairment score (NIS) and patient's global assessment of efficacy. Study showed that oral treatment with ALA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP. An oral dose of 600mg once daily appears to provide optimum risk-to-benefit ratio.

Safety analysis was also performed. In the study done by Ruhnau *et al.*[4], no adverse effects were noted. While in the study done by Ziegler *et al.*[5], rate of adverse effects were noted to increase with escalating doses. These adverse effects are as follows: nausea 0,6 (13%), 10 (21%), and 22 (48%); vomiting 0,1 (2%), 2 (4%), and 12 (26%); vertigo 0,2 (4%0, 2 (4%), and 5 (11%). Fifteen patients (8%) dropped out from the study of Ziegler *et al.* Due to adverse effects.

Based on the analysis of the two available RCTs used in this study, studies showed that oral alpha-lipoic acid versus placebo is effective in reducing the symptoms of diabetic neuropathy.

Until the present, there are only 2 RCTs available regarding the role of oral alpha-lipoic acid in reducing the symptoms of diabetic neuropathy. This study could be a starting point for further research regarding this condition. Experts in endocrinology have been trying to come up with an effective supplemental treatment to reduce the complications of diabetes mellitus. Antioxidants such as Alpha-lipoic acid has gained considerable amount of acceptance from specialists in reducing symptoms of diabetic neuropathy.

REVIEWERS' CONCLUSIONS

A. Implications for Practice:

Diabetes mellitus is a chronic disorder which may produce many complications if not controlled. Diabetes mellitus is a genetic disorder that affects approximately 16 million people. Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetes patients. It is estimated that the prevalence of neuropathy in diabetes patients is approximately 20%. Diabetic neuropathy is implicated in 50-75% of nontraumatic amputations. Diabetic neuropathy can be a disabling complication, hence, prevention should be emphasized.

It has been claimed that intravenous alpha-lipoic acid reduces the symptoms of diabetic neuropathy. A meta-analysis by Ziegler et al[1], has shown that Intravenous alpha-lipoic acid reduces symptoms of diabetic neuropathy using the Total Symptom Score (TSS), Neuropathy Impairment Score (NIS), Neuropathy Impairment Score of the lower limbs (NIS-LL).

This study would like to introduce the efficacy of oral alpha-lipoic acid vs. intravenous. Treatment is not only cheaper but assures better compliance rate compared to intravenous form.

B. Implications for Research:

Until the present, there are only 2 RCTs available regarding the role of oral alpha-lipoic acid in reducing the symptoms of diabetic neuropathy. This study could be a starting point for further research regarding this topic. Experts in endocrinology have been trying to come up with an effective supplemental treatment to reduce the complications of diabetes mellitus. Antioxidants such as Alpha lipoic acid has gained considerable amount of acceptance from specialists in reducing symptoms of diabetic neuropathy.

ACKNOWLEDGEMENTS

The author would like to extend her gratitude to Dr. Gentry Dee, who unselfishly taught us everything he could about doing a meta-analysis and continued to review the progress of our papers; to Abbott Company for teaching us to use the Revman; to Dra. Gwen Dy-Agra, who endlessly checked and gave constructive criticisms regarding our papers

Potential Conflict of Interest

The author is not involved with any company or organization concerned with Alpha-lipoic Acid.

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APPENDIX A:

TOTAL SYMPTOM SCORE QUESTIONNAIRE

Subjective Peripheral Neuropathy Screen Questionnaire

Full name:_____ Date _____

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

1.	Do you ever have legs and/or feet that feel numb?	❑ Yes	❑ No
2.	Do you ever have any burning pain in your legs and/or feet?	❑ Yes	❑ No
3.	Are your feet too sensitive to touch?	❑ Yes	❑ No
4.	Do you get muscle cramps in your legs and/or feet?	❑ Yes	❑ No
5.	Do you ever have any prickling or tingling feelings in your legs or feet?	❑ Yes	❑ No
6.	Does it hurt at night or when the covers touch your skin?	❑ Yes	❑ No
7.	When you get into the tub or shower, are you unable able to tell the hot water from the cold water?	❑ Yes	❑ No
8.	Do you ever have any sharp, stabbing, shooting pain in your feet or legs?	❑ Yes	❑ No
9.	Have you experienced an asleep feeling or loss of sensation in your legs or feet?	❑ Yes	❑ No
10.	Do you feel weak when you walk?	❑ Yes	❑ No
11.	Are your symptoms worse at night?	❑ Yes	❑ No
12.	Do your legs and/or feet hurt when you walk?	❑ Yes	❑ No
13.	Are you unable to sense your feet when you walk?	❑ Yes	❑ No
14.	Is the skin on your feet so dry that it cracks open?	❑ Yes	❑ No
15.	Have you ever had electric shock-like pain in your feet or legs?	❑ Yes	❑ No