Alpha-Lipoic Acid: Safe and Effective

Arthur J. Berkson, M.D.

Diplomate, American Board of Family Medicine

Diplomate, American Board of Integrative Medicine

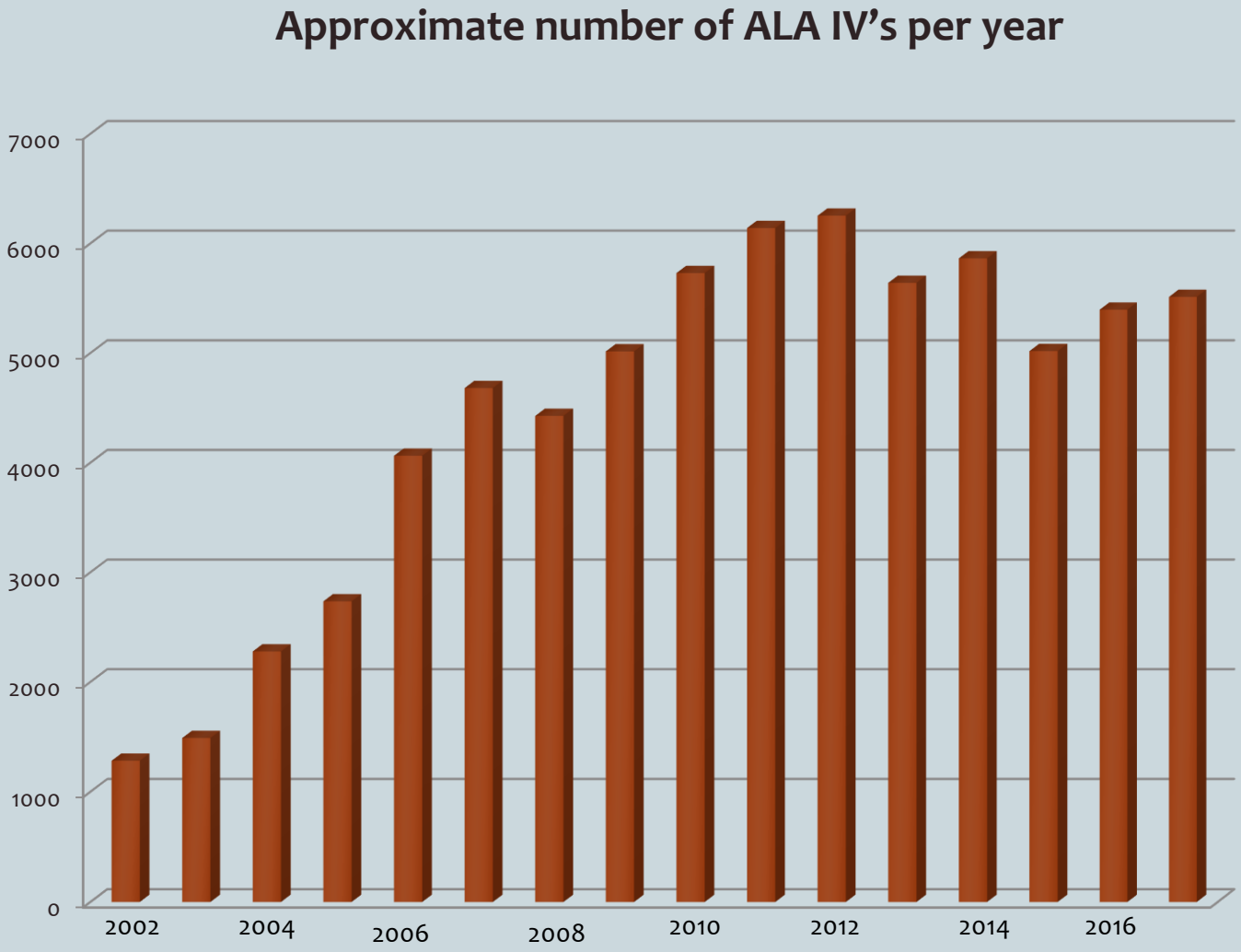
Integrative Medical Center of New Mexico

Las Cruces, NM

Intravenous Alpha-Lipoic Acid: Essential in the Treatment of Diabetic Neuropathy

- FDA:
  - Safe ("do not appear to be significant adverse effects associated with its use")
  - Effective ("ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy")
- There really is no available equivalent treatment in terms of safety and efficacy
- There are promising uses that can be subjects of future controlled studies
- IV ALA is safe, effective, and stable
- Case reports

Approximate Number of ALA IV's given at IMCNM



Approximate total number of ALA IV's given since 2002:

75,360

Number of serious adverse events:

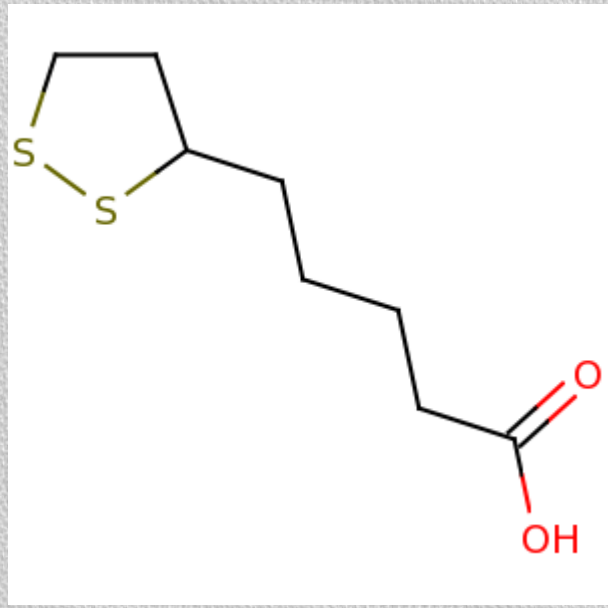
0

We do see episodes of hypoglycemia, headaches, sleepiness

Alpha-Lipoic Acid

Structure and Functions

- Some Functions:
  - Water- and fat-soluble antioxidant[1]
  - Recycles other antioxidants[1]
  - Cofactor in aerobic ATP production in mitochondria[2]
  - Heavy metal chelator[3]
  - Insulin mimetic[2] and reduces insulin resistance[4]
  - Inhibits nf kappa-B activation[5]



1. Moura FA, et al. Lipoic Acid: its antioxidant and anti-inflammatory role and clinical applications. Curr Top Med Chem. 2015;15(5):458-83
2. Rochette L, et al. Alpha-Lipoic Acid: molecular mechanisms and therapeutic potential in diabetes. Can J Physiol Pharmacol. 2015 Dec;93(12):1021-7.
3. Rochette L, et al.Direct and indirect antioxidant properties of alpha-lipoic acid and therapeutic potential. Mol Nutr Food Res.2013 Jan;57(1):114-25.
4. Akbari, et al. The effects of alpha-lipoic acid supplementation on glucose control and lipid profiles among patients with metabolic diseases: A systemic review and meta-analysis of randomized controlled trials. Metabolism. 2018 July 7.
5. Ying, et al. Evidence that alpha-lipoic acid inhibits NF-kB activation independent of its antioxidant function. Inflamm Res. 2011 Mar;60(3):219-25.

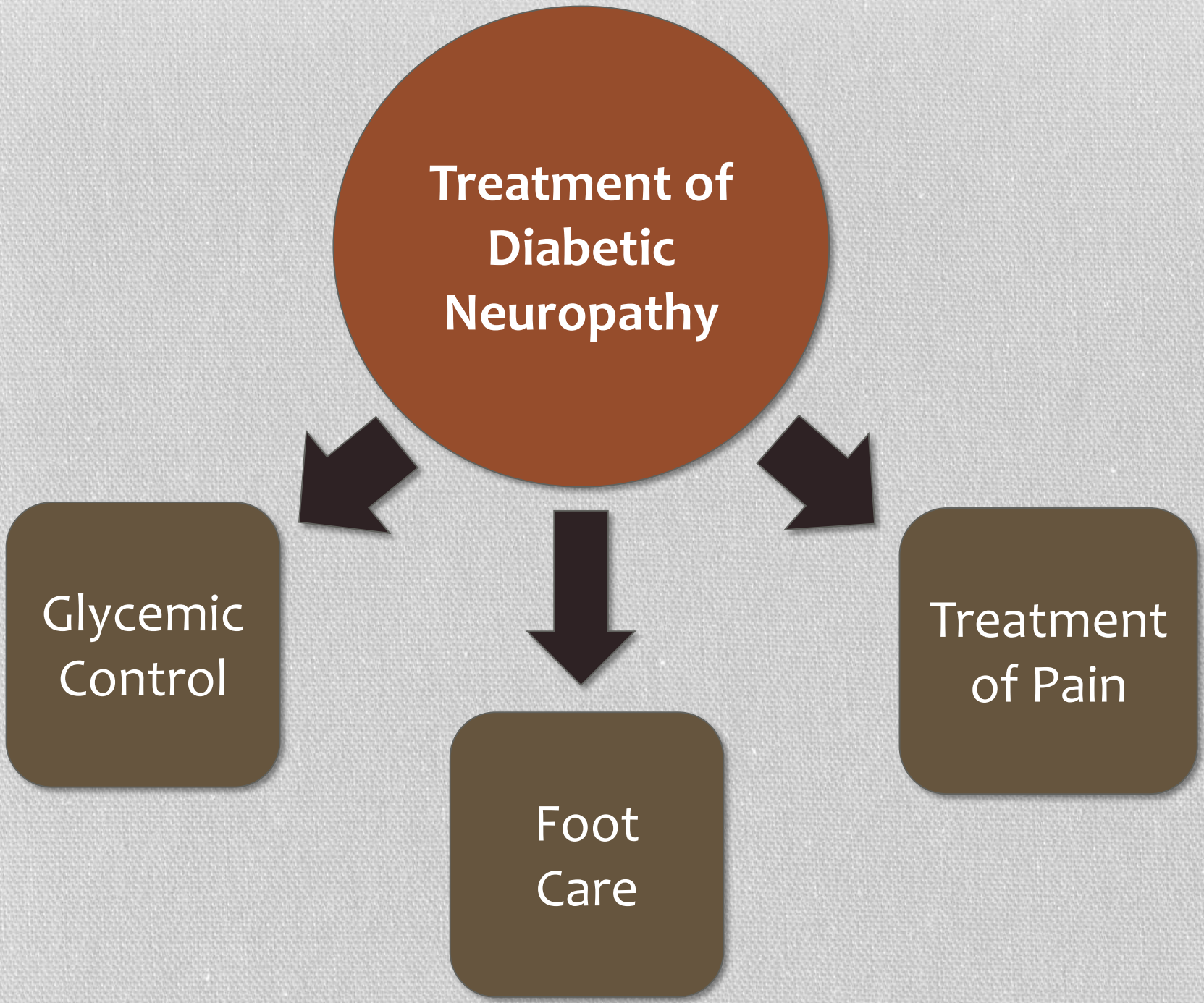
Partial List of Diseases in the Literature

- Metabolic
  - Diabetes Mellitus, Insulin Resistance
  - Weight Loss, Kwashiorkor
  - Osteoporosis, PCOS
- Diabetic Complications
  - Diabetic Peripheral and Autonomic Neuropathy, Nephropathy, and Retinopathy
- Neurological
  - MS, Alzheimer's Disease
  - Migraine Prophylaxis, Sciatica, Burning Mouth Syndrome, CTS
  - Chemotherapy Induced Neuropathy
- Ophthalmological
  - Age-Related Macular Degeneration, Cataract Protection, Glaucoma
- Immune/ID
  - HIV/AIDS
- Hepatology
  - Hepatitis C, Acute Hepatic Necrosis
- Cardiovascular
  - Hypertension, Ischemia Reperfusion Injury
  - Erectile Dysfunction
- Dermatological
  - Wound Healing, Photoaging

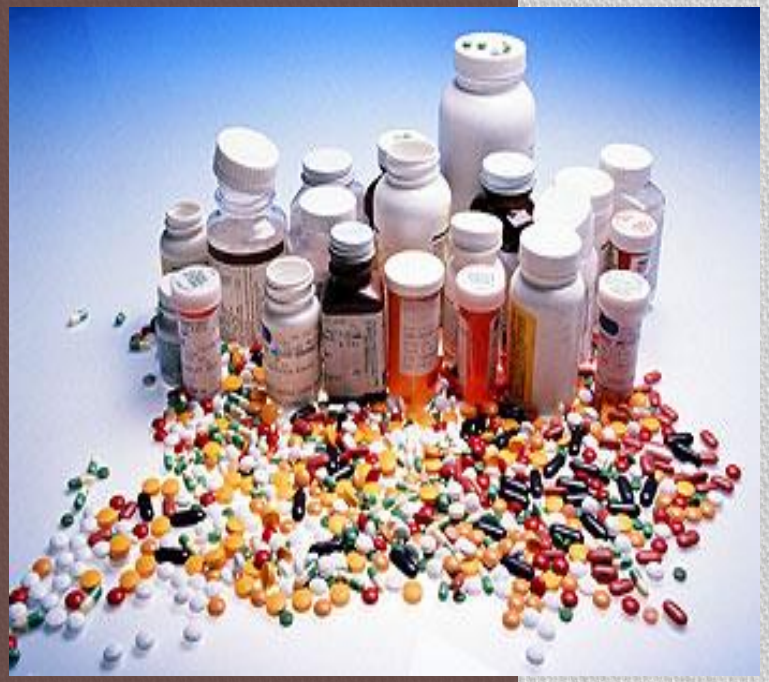
Intravenous Alpha-Lipoic Acid

- **Best evidence**
  - Diabetic Neuropathy[1]

1. Ziegler, D.; Nowak, H.; Kempler, P.; Vargha, P. & Low, P. (2004). Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha lipoic acid: a meta-analysis. *Diabet Med*, vol.24, no.2, (February 2004), pp.114-121, ISSN 1464-5491.


Treatment of Diabetic Neuropathy
Glycemic Control
Foot Care
Treatment of Pain

Treatment Options in Diabetic Neuropathy



- **Strong Evidence:**
  - Pregabalin*
- **Moderate Evidence:**
  - Gabapentin
  - Sodium valproate
  - Amitriptyline
  - Duloxetine*
  - Venlafaxine
  - Dextromethorphan
  - Morphine Sulfate
  - Oxycodone
  - Tramadol
  - Tapentadol**
  - Capsaicin
  - Isosorbide Dinitrate Spray
- **Possibly effective:**
  - Lidocaine

*FDA Approved Treatment
**FDA Approved After Release of Guidelines

Source:
AAN Summary of Evidenced-based Guidelines for CLINICIANS- Treatment of Painful Diabetic Neuropathy, ©2011

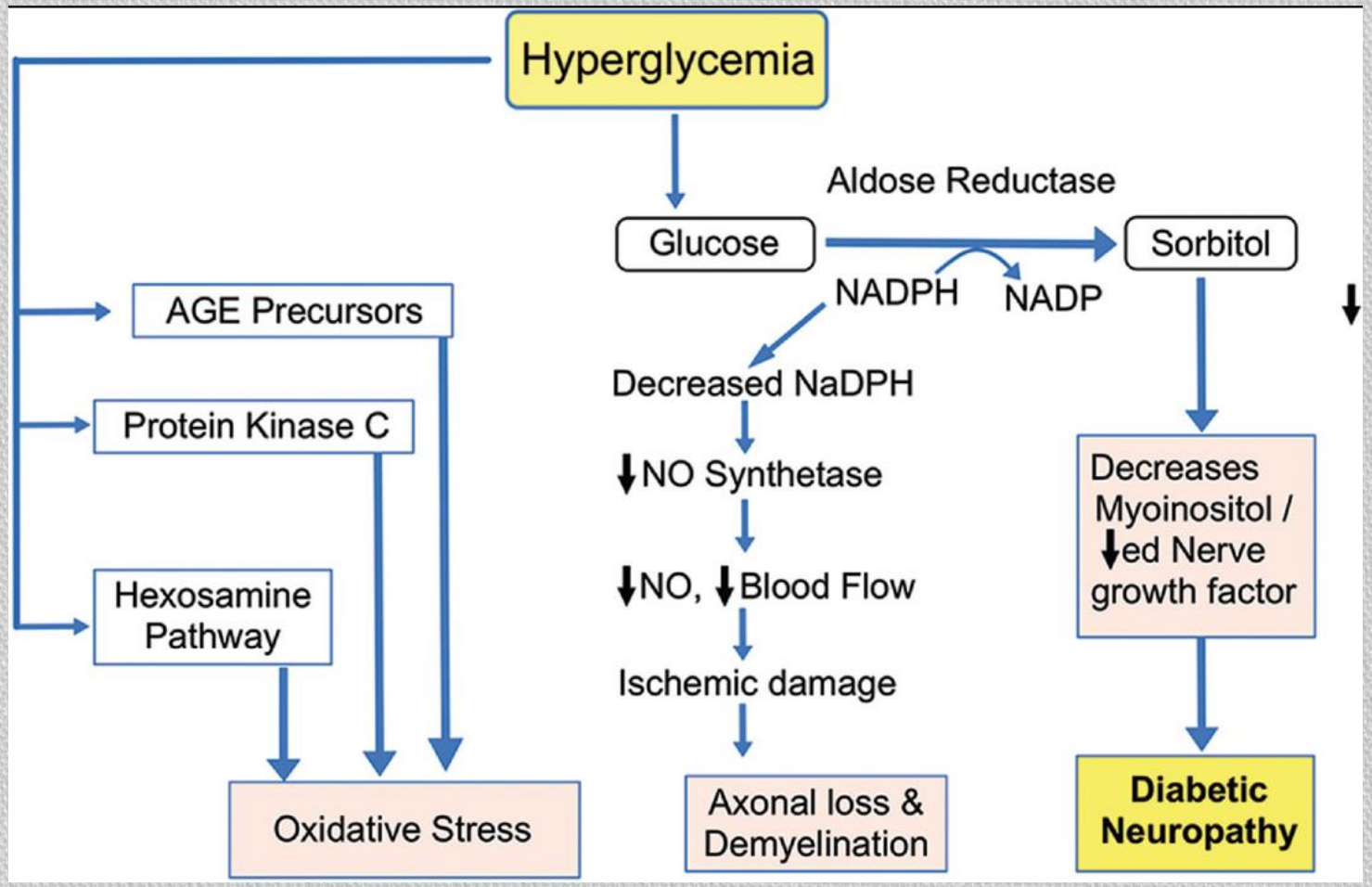
What do all these treatments for diabetic neuropathy have in common?

What do all these treatments for diabetic neuropathy have in common?

They all change perception of pain. They don't treat the underlying cause of the pain.

Why not treat the cause?

Pathophysiology Diabetic Peripheral Neuropathy

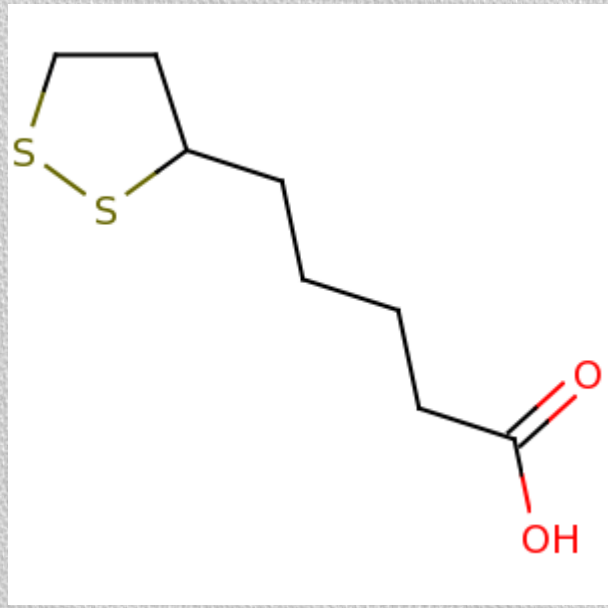


Source: Kapoor N, et al. Approach to diabetic neuropathy. *Current Medical Issues*. 2017; 15(3):189-199

Alpha-Lipoic Acid

Structure and Functions

- Some Pertinent Functions:
  - Water- and fat-soluble antioxidant[1]
  - Recycles other antioxidants[1]
  - Cofactor in aerobic ATP production in mitochondria[2]
  - Heavy metal chelator[3]
  - Insulin mimetic[2] and reduces insulin resistance[4]
  - Inhibits NF kappa-B activation[5]



1. Moura FA, et al. Lipoic Acid: its antioxidant and anti-inflammatory role and clinical applications. Curr Top Med Chem. 2015;15(5):458-83
2. Rochette L, et al. Alpha-Lipoic Acid: molecular mechanisms and therapeutic potential in diabetes. Can J Physiol Pharmacol. 2015 Dec;93(12):1021-7.
3. Rochette L, et al.Direct and indirect antioxidant properties of alpha-lipoic acid and therapeutic potential. Mol Nutr Food Res.2013 Jan;57(1):114-25.
4. Akbari, et al. The effects of alpha lipoic acid supplementation on glucose control and lipid profiles among patients with metabolic diseases: A systemic review and meta-analysis of randomized controlled trials. Metabolism. 2018 July 7.
5. Ying, et al. Evidence that alpha-lipoic acid inhibits NF-kB activation independent of its antioxidant function. Inflamm Res. 2011 Mar;60(3):219-25.

RCTs of Intravenous ALA in DM Neuropathy

ALADIN I (N=328)

- 3 wk IV ALA v. placebo

- ***Results:***
  - **Total symptom score (TSS)** in feet decreased from baseline to day 19:
    - 58.6% in ALA 1,200 mg (p=0.003 vs. placebo), 63.5% in ALA 600 mg (p<0.0001 vs. placebo)
    - 38.4% in placebo
  - **Response rate** (improvement in TSS≥30%)
    - 70.8% in ALA 1,200 mg , 82.5% in ALA 600 mg (p=0.002 vs. placebo)
    - 57.6% in placebo

"…intravenous treatment with alpha-lipoic acid using a dose of 600mg/day over 3 weeks is superior to placebo in reducing symptoms of diabetic peripheral neuropathy, without causing significant adverse reactions."

1. Ziegler D, et al. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial. Diabetologia. 1995 Dec; 38(12):1425-33.

RCTs of Intravenous ALA in DM Neuropathy

ALADIN III (N=509)

Cross over ALA IVx3wk + POx6mo vs. IV + PO placebo vs. placebo IV + placebo oral

Key results:

- **Total Symptom Score:**
  - No significant difference vs. placebo
- **Neuropathy Improvement Score at day 19:**
  - Decreased by 4.34 in ALA vs. 3.49 in placebo (p=0.016)
  - Decreased in lower extremities by 3.32 in ALA vs. 2.79 in placebo (p=0.055)

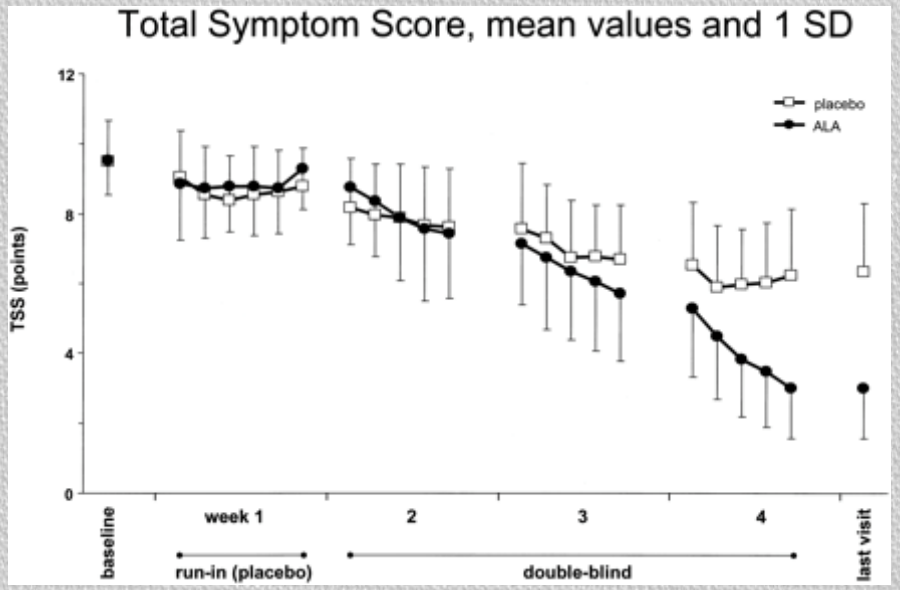
"…this treatment was associated with a favorable effect on neuropathic deficits without causing significant adverse reactions."

Ziegler D, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). Diabetes Care 1999 Aug; 22(8):1296-1301.

RCTs of Intravenous ALA in DM Neuropathy

SYDNEY3 (N=120)

3 wk IV x14 over 3 wk vs. placebo



Key Results:

- **Total Symptom Score** (14.64 max score)
  - Decreased by 5.7 points in ALA group vs. 1.8 points in placebo (p=<0.001)
- **Neuropathy Improvement Score**
  - Improved by 2.7 points in ALA group vs. 1.2 points in placebo (p<0.001)

"Intravenous racemic ALA, a potent antioxidant, rapidly and to a significant and meaningful degree, improved such positive neuropathic sensory symptoms as pain and several other neuropathic endpoints. This improvement of symptoms was attributed to improved nerve pathology…"

- Ametov, et al. The Sensory Symptoms of Diabetic Polyneuropathy Are Improved With Alpha-Lipoic Acid. Diabetes Care. 2003 Mar;26(3):770-6.

Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis

Ziegler, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabetic Medicine*. 2004 Feb;21(2):114-21.

Study:

- Randomized, double-blind, placebo-controlled trials
- 600 mg IV ALA/d x 3 wk (15 treatments)
- 4 trials
- n=1258
- **Evaluated:**
  - Total Symptom Score
  - Neuropathy Impairment Score

Results:

- 24.1% decrease in TSS compared to placebo ($p<0.05$)
- 16% decrease in NIS (didn't meet significance)
- Responder rate for ALA 52.7% vs. 36.9% placebo ($p<0.05$)
- No difference in adverse event rate

Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis

Ziegler, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis. *Diabetic Medicine*. 2004 Feb;21(2):114-21.

"The results of this meta-analysis (n=1258) provide evidence that treatment with alpha-lipoic acid (600 mg/day i.v.) over 3 weeks is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy."

Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy

Rom J Intern Med. 2004;42(2):457-64.

Alpha-lipoic acid in the treatment of autonomic diabetic neuropathy (controlled, randomized, open-label study).

Tankova T[1], Koev D, Dakovska L.

⊕ **Author information**

Abstract

AIM: to evaluate the effect of alpha-lipoic acid in autonomic diabetic neuropathy in a controlled, randomized, open-label study.

MATERIAL AND METHODS: 46 patients with type 1 diabetes and different forms of autonomic neuropathy, of mean age 38.1 +/- 12.5 years and mean duration of diabetes 16.8 +/- 8.9 years were treated with alpha-lipoic acid for 10 days 600mg daily iv, thereafter one film tablet of 600mg daily for 50 days. 29 type 1 diabetic patients with autonomic diabetic neuropathy, of mean age 40.2 +/- 9.3 years and mean duration of diabetes 15.4 +/- 7.9 years served as a control group. We have followed-up patients' complaints, Ewing's tests, laboratory parameters of oxidative stress.

RESULTS: There was a significant improvement after treatment in the score for severity of cardiovascular autonomic neuropathy--from 6.43 +/- 0.9 to 4.24 +/- 1.8 ($p<0.001$), while in the control group it worsened from 6.18 +/- 1.3 to 6.52 +/- 0.9 ($p>0.1$). We found improvement in the Valsalva manoeuvre after treatment - from 1.05 +/- 0.04 to 1.13 +/- 0.08 ($p<0.001$); in the deep-breathing test -from 3.4 +/- 2.8 to 10.4 +/- 5.7 ($p<0.001$); and in the lying-to-standing test--from 0.99 +/- 0.01 to 1.01 +/- 0.02 ($p>0.1$), while in the control group there was no improvement. There was a beneficial effect of treatment on the change of systolic blood pressure at the lying-to-standing test--from 22.7 +/- 11.5 to 9.8 +/- 7.9 ($p<0.001$), while in the control group the change was 20.5 +/- 11.1 mmHg and 19.7 +/- 12.9 mmHg ($p>0.1$), respectively. We found improvement in diabetic enteropathy in six patients; in the complaints of dizziness, instability upon standing in six patients; in neuropathic edema of the lower extremities in four patients and in erectile dysfunction in four patients after treatment, while in the control group no change was reported in the symptoms and signs of autonomic neuropathy by the end of the follow-up period. There were changes in the laboratory parameters of oxidative stress after therapy--total serum antioxidant capacity increased from 20.42 +/- 1.8 to 22.96 +/- 2.3 microgH2O2/ml/min ($p<0.05$), serum SOD activity - from 269.8 +/- 31.1 to 319.8 +/- 29.IU/l ($p=0.02$) and erythrocyte SOD--from 0.89 +/- 0.10 to 1.11 +/- 0.09 U/gHb ($p=0.04$).

CONCLUSION: Our results demonstrate that alpha-lipoic acid (Thiogamma) appears to be an effective drug in the treatment of the different forms of autonomic diabetic neuropathy.

"… alpha-lipoic acid (Thiogamma) appears to be an effective drug in the treatment of different forms of autonomic neuropathy."

How does oral ALA affect diabetic neuropathy in the real world?

- J Diabetes Complications. 2009 May-Jun;23(3):174-7. doi: 10.1016/j.jdiacomp.2008.02.002. Epub 2008 Apr 9.

  Switching from pathogenetic treatment with alpha-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients.

- Ruessmann HJ German Society of outpatient diabetes centres AND (Arbeitsgemeinschaft niedergelassener diabetologisch tätiger Arzte e.V.)

Study results:

- 293 patients switched from oral ALA to gabapentin or no treatment
- Untreated group developed symptoms within 2 wks
- Gabapentin group: 45% stopped treatment due to side effects
  - 55% nonresponders to gabapentin and changed to another drug
- Daily cost lower for ALA
- Outpatient visits doubled when switched off ALA

How does oral ALA affect diabetic neuropathy in the real world?

- J Diabetes Complications. 2009 May-Jun;23(3):174-7. doi: 10.1016/j.jdiacomp.2008.02.002. Epub 2008 Apr 9.
  Switching from pathogenetic treatment with alpha-lipoic acid to gabapentin and other analgesics in painful diabetic neuropathy: a real-world study in outpatients.
  Ruessmann HJ German Society of outpatient diabetes centres AND (Arbeitsgemeinschaft niedergelassener diabetologisch tätiger Arzte e.V.)

"In conclusion, switching from long-term treatment with alpha-lipoic acid to central analgesic drugs such as gabapentin in painful diabetic neuropathy was associated with considerably higher rates of side effects, frequencies of outpatient visits, and daily costs of treatment."

FDA Report: Response

Don't take my word, look at the FDA report…

Safety:

- "There has been extensive literature reporting clinical evaluation of ALA, and there do not appear to be significant adverse effects associated with its use."

Efficacy:

- "ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy."
- "No trial has shown ALA to improve diabetic autonomic neuropathy."

  See 2004 Tankova study

FDA Report: Response

Concerns:

- "A search of the British Pharmacopoeia, the European Pharmacopoeia, and the Japanese Pharmacopoea did not show any monograph listings for alpha-lipoic acid."
  - Intravenous ALA is a known pharmaceutical drug in Germany
  - Intravenous ALA is a recently approved pharmaceutical drug in Colombia

Stability of ALA in Aqueous Solution

1) Studies of IV ALA

- Experience with IV ALA in studies since the 1970's
- Multiple studies of ALA as an IV preparation (acknowledged in FDA report)
- Presence of IV ALA as a prescription drug in Germany and Colombia

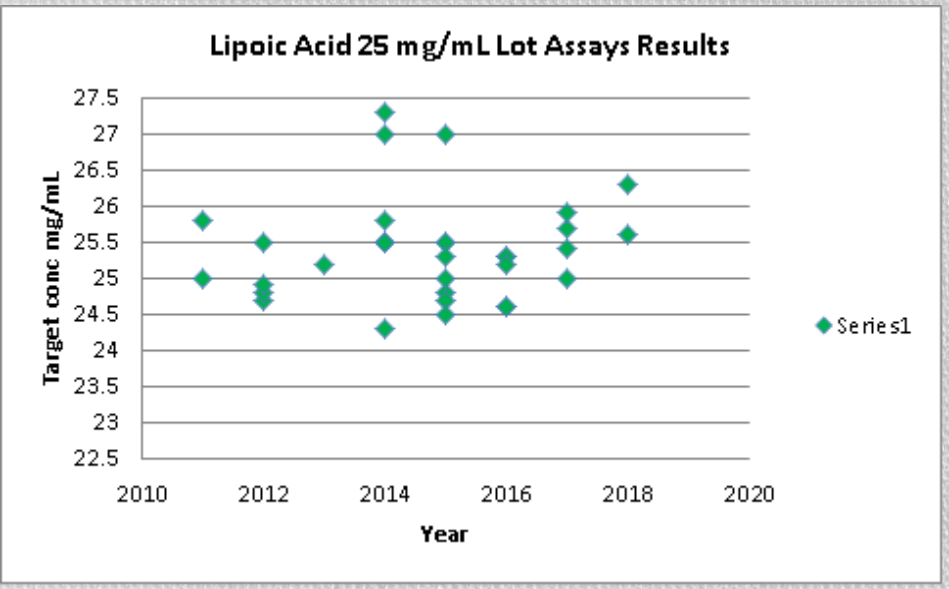
2) Data

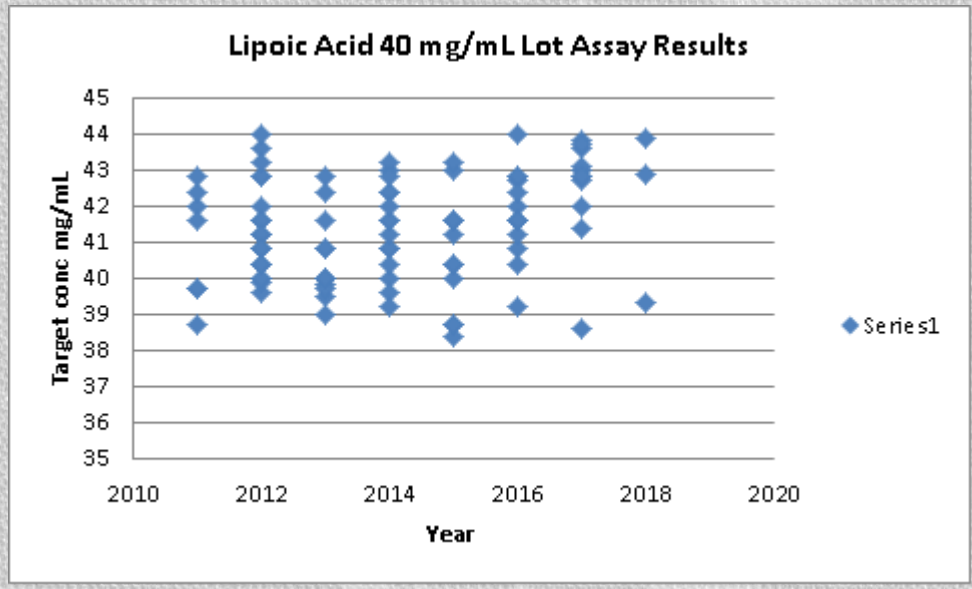
- Extensive testing for appearance, particulate matter, pH, potency, sterility, integrity, and preservative effectiveness and concentration in multidose vials
- Response by pharmacists

3) FDA Statement

- "The aqueous formulations are likely to be much more unstable than the solid dosage forms."
- "Due to lack of precise stability information supporting solution forms of ALA, the stability of the solution cannot be determined. Therefore, the stability of the liquid formulations of the drug substance is still of concern."
- No citation

Historical Potency Assay Data from McGuff





MCPS's formulations of 25 mg/mL and 40 mg/mL have been verified by numerous HPLC potency assays.

McGuff CPS's Lipoic Acid Injection Stability Study

Data / Results Table for Stability Study			
Characteristic	Test Method	Result at T_o	Result at T_{BUD}
Date of study initiation / conclusion		March 16, 2015	September 3, 2015
Study drug Lot Number		15B3101:082615	
Number of samples placed into inverted storage [Room temperature]			27
Appearance, Seal	Visual	Passed	Passed
Appearance, Vial	Visual	Passed	Passed
Appearance, Product	Visual	Yellow	Yellow
Foreign Matter, Visible Particulate	Per Pharmacy Procedure or Current USP <790>	No visible ppt	No visible ppt
pH	Per Pharmacy Procedure	7.1	7.5
Assay	[USP <621> HPLC, USP<851> Spectrophotometry]	38.4 mg/mL	38.7 mg/mL
Sterility	Current USP Chapter <71>	Sterile	Sterile
Or, in lieu of Sterility Container/Closure Integrity	BTS Method # CM413 (dye ingress)	NA	CCI post BUD for Lot 17H5611 – Passed -
Sterility test Method Suitability Test	Current USP Chapter <71>	Lot 14G4311 - Passed -	NA
Preservative Effectiveness (for Multi Dose Vials)	Antimicrobial Effectiveness current USP <51>	Meets USP	NA
Preservative concentration (for Multi Dose Vials)	Current USP Chapter <341>	Benzyl alcohol 1.03 %	Benzyl alcohol 1.2 %

At the Integrative Medical Center of New Mexico, we treat diabetic neuropathies (and other conditions) with IV ALA every day.

We need to be on our patients' team

Where do we stand?

Alpha-Lipoic Acid

- FDA:
  - Safe ("do not appear to be significant adverse effects associated with its use")
  - Effective ("ALA appears to show symptom improvement with treatment for several weeks in the treatment of diabetic neuropathy")
- There really is no available equivalent treatment in terms of safety and efficacy
- There are promising uses that can be subjects of future controlled studies
- IV ALA is safe, effective, and stable

- Stand up for our patients, our friends, our families, ourselves
- Follow the science
- Continue to allow for the compounding of ALA in the oral and IV forms