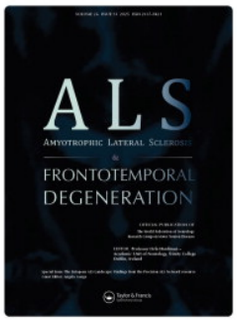

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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ALSUntangled #79: alpha-lipoic acid

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REVIEW ARTICLE

ALSUntangled #79: alpha-lipoic acid

ALAINA GIACOBBE[1]*, JAMES HIANA[1]*, OLIVIA WANG[2]*, MICHAEL BENATAR[3], PAUL WICKS[4], JAVIER MASCIAS CADAVID[5], SARTAJ JHOOTY[6], CHRISTOPHER MCDERMOTT[7], GARY PATTEE[8], TULIO BERTORINI[9], TERRY HEIMAN-PATTERSON[10], DYLAN RATNER[11], PAUL BARKHAUS[12], GREGORY CARTER[13], CARLAYNE JACKSON[14], KEELIE DENSON[15], ANDREW BROWN[3], CARMEL ARMON[16], YUYAO SUN[17], ANDRE NGUYEN[18], RICHARD BEDLACK[1] & XIAOYAN LI[1]

[1]Neurology Department, Duke University, Durham, NC, USA, [2]Cognitive Science, University of Pennsylvania, Philadelphia, PA, USA, [3]Department of Neurology, University of Miami, Miami, FL, USA, [4]Wicks Digital Health, Lichfield, UK, [5]Neurology Department, Hospital Carlos III-La Paz, Madrid, Spain, [6]University of North Carolina, Chapel Hill, NC, USA, [7]Sheffield Institute of Translational Neuroscience, University of Sheffield, Sheffield, UK, [8]Department of Neurology, University of Nebraska Medical Center, Omaha, NE, USA, [9]Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA, [10]Neurology Department, Temple University, Philadelphia, PA, USA, [11]Tulane University, New Orleans, LA, USA, [12]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA, [13]Providence St. Luke's Rehabilitation Medical Center, Spokane, WA, USA, [14]Department of Neurology, UT Health San Antonio, San Antonio, TX, USA, [15]Department of Neurology, Houston Methodist Hospital, Houston, TX, USA, [16]Department of Neurology, Shamir Medical Center, Be'er Ya'akov, Israel, [17]Department of Neurology, University of Kentucky, Lexington, KY, USA, and [18]Duke University, Durham, NC, USA

Abstract

Alpha-lipoic acid (ALA) is a naturally occurring fatty acid. It serves as an essential cofactor for enzymatic reactions in mitochondrial energy production, is a potent antioxidant and has anti-inflammatory effects, which are plausible mechanisms in slowing ALS progression. In ALS preclinical studies, ALA slowed motor function decline and improved survival. There were self-reported cases of improved muscle strength in ALS patients when ALA was taken with numerous additional supplements, making it difficult to discern its efficacy. One small, 6-month open-label study showed improved quality of life, fatigue, and mood after participants took it with B vitamins and amino acids for the first 3 months. So far, no clinical trials have been published in people living with amyotrophic lateral sclerosis (PALS). Given the insufficient clinical data, we cannot endorse ALA and will support more research on its efficacy in slowing ALS progression.

Keywords: *ALS, alpha lipoic acid, oxidative stress, antioxidant, antiinflammation*

ALSUntangled reviews alternative and off-label treatments on behalf of people living with amyotrophic lateral sclerosis (PALS). Here, we review alpha-lipoic acid (ALA) therapy, for which we have had 158 requests (https://www.alsuntangled.com/future-reviews/).

Overview

Alpha-lipoic acid is a naturally occurring fatty acid that can be obtained from dietary sources, and a small amount of ALA is synthesized endogenously in mitochondria. In nature, ALA is enriched in organ meats and a variety of vegetables, including spinach, broccoli, tomato, and brussels sprouts (1,2). ALA can also be found in over-the-counter supplements as a synthetic form. It exists as two optical isomers due to its asymmetrical carbon structure: R-lipoic acid (R-ALA) and S-lipoic acid (S-ALA). The naturally occurring and biologically active form is R-ALA. Commercial ALA is chemically synthesized and usually contains a racemic

Correspondence: Xiaoyan Li, Neurology Department, Duke University, 932 Morreene Rd, Durham, NC, USA. E-mail: Xiaoyan.li266@duke.edu
*These authors contributed equally to this work.

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mixture of R- and S-ALA; some studies suggested the latter might improve the bioavailability of the R-isomer (2,3).

ALA has been studied in metabolic and neurodegenerative diseases as a potential therapeutic. Oral treatment with ALA has been shown to improve symptomatic diabetic polyneuropathy in a randomized, placebo-controlled clinical trial (RCT) (4). Combined treatment with ALA and an antihypertensive medication demonstrated effects in improving vascular endothelial function and reducing inflammation in metabolic syndrome (5). ALA and omega-3 fatty acids treatment was shown to slow down cognitive and function decline in Alzheimer's disease over 12 months in a small-sized RCT trial (6). We caution our readers that alpha linolenic acid (an omega-3 fatty acid) is often abbreviated as ALA as well in the literature, but it is a different product.

In this article, we review oral ALA supplement as a potential treatment for slowing ALS progression.

Mechanistic plausibility

ALA has a few plausible ways to affect ALS pathophysiology. These mechanisms include serving as a cofactor of energy production pathways in mitochondria, directly neutralizing free radicals and regenerating other antioxidants as well as anti-inflammation.

ALA is a cofactor for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, two essential enzymes for generating NADH and FADH through a chain of reactions in the citric acid cycle (TCA) (7). NADH and FADH are ultimately converted to energy-adenosine triphosphate (ATP)-through oxidative-phosphorylation reaction. The role of mitochondrial dysfunction in ALS pathogenesis is multifaceted, and interference with energy production is one of the proposed mechanisms due to the high energy requirement to support motor neuron survival and normal function (8,9). A recent study discovered the introduction of mitochondrial respiratory complex IV mutation in rat motor neurons caused selective motor neuron loss and paralysis (10). Therefore, ALA could theoretically benefit ALS by enhancing mitochondrial energy production.

Reactive oxygen species (ROS) are free radical byproducts generated during chemical reactions in mitochondria. In healthy tissues, ROS are kept at a low level. However, ROS are found to accumulate at higher levels in the bio-fluids of ALS patients (11,12). Oxidative stress occurs when the ROS production overcomes the human body's antioxidant defense system. ROS can then oxidize DNA, RNA, protein, and other essential cellular structures, causing their malfunction. ROS levels increase with aging and play an important role in the development of various neurodegenerative diseases (13). In ALS, ROS was found to induce TDP-43 protein aggregation, and the latter is a pathological hallmark for most ALS (14,15).

ALA and its reduced form dihydrolipoic acid (DHLA) are potent antioxidants that can scavenge a variety of ROS (16). They have also been shown to regenerate other endogenous antioxidants, such as vitamin C, E and glutathione (1). Notably, glutathione is the principal antioxidant in the brain, and its deficiency has been shown to cause neuronal cell dysfunction and has been implicated in several neurodegenerative diseases, including ALS (17,18). ALA's ability to cross the blood brain barrier also makes it an appealing therapeutic agent (19).

Finally, ALA can lower proinflammatory cytokines and chemokines (20). A prospective observational study showed a combined coQ10 and ALA treatment regimen improved chronic COVID-19 syndrome (21).

Given its potential effects on optimizing mitochondrial energy production, anti-oxidative stress and antiinflammation in human studies, ALSUntangled assigned TOE "mechanisms" grade of A.

Pre-clinical

A few studies have directly examined the effects of ALA in ALS disease models. In one study using the G93A SOD1 transgenic rodent model, the mice were fed from 4 weeks of age with a diet supplemented with ALA at a 0.05% concentration (100 mg/kg/day) or a diet without ALA for 19 weeks. The results showed a significantly delayed onset of motor dysfunction in rotarod performance and less weight loss in the treatment group compared to the control group. ALA also moderately improved survival time (22). A second study similarly showed that ALA improved motor function and lifespan in a human G85R SOD1 transgenic drosophila model (23). Further, in a motor neuron cell line carrying the G93A SOD1 gene, adding ALA to the cell culture activated antioxidant functions and improved cellular viability (23).

Because two non-blinded preclinical studies showed survival benefits and protection of motor function by ALA, ALSUntangled assigned TOE "Pre-clinical study" grade of C.

Data in PALS

Cases

In the online community PatientsLikeMe, 112 members report using ALA as a treatment for ALS, with 28 PALS completing 35 treatment evaluations (a few PALS completed more than one evaluations during the treatment course).

The dosage ranged from 100 mg to 600 mg daily. The majority reported "can't tell" about the effectiveness (29/35) or no effect (4/35). One PALS reported slight to moderate effectiveness. Most evaluations reported no side effects (33/35); there were two reports of moderate side effects of headaches and lower blood sugar.

In the online community ALSForum, 21 members reported using ALA as a treatment for ALS, and three of them provided evaluations relevant to ALS progression. One PALS reported increased hand strength after starting a regimen consisting of 12 supplements, including 1200 mg of ALA twice daily and unknown doses of L-serine, GABA, arginine-alpha-ketoglutarate, creatine, coconut oil, cannabis, vitamin E, vitamin D, methylated vitamin B12, fish oil, and acetyl L-carnitine. He was uncertain which supplement was responsible for the improvement or if it resulted from his regular routine of moderate exercise. Another PALS took ALA and acetyl L-carnitine with an unspecified "cocktail of supplements". This individual reported relatively slow progression based on progression mapping data from PatientsLikeMe but was again unsure which component was helping him. A third PALS reported improvements in foot drop and strength after six weeks of taking 750 mg of ALA with 4 g of acetyl-L-carnitine and 8 mg of biotin daily, along with more than 20 other supplements. It remained unclear whether these improvements were transient or long-lasting.

Although several PALS from the ALS community reported therapeutic benefits, we could not confirm their diagnoses nor the improvements. They often took many other supplements concomitantly and were uncertain whether the benefits were attributable to ALA. Therefore, ALSUntangled assigns a TOE "Cases" grade of D (Table 1).

Of potential interest, we found a study of PolyMVA showing improvement of ALS symptoms. PolyMVA is a proprietary blend containing palladium ALA complex, B vitamins, and amino acids. In this open-label prospective study, nine PALS were treated with four teaspoons daily of PolyMVA over 6 months. Based on the study protocol (NCT04557410), each participant received ALA at ~150 mg daily. The study assessed the safety of PolyMVA and its effectiveness in improving fatigue and quality of life (QOL) in PALS, and the results were presented during the 2022 American Academy of Neurology Annual Meeting. At month-1 and month-3, there were significant improvements in QOL, fatigue, and depression. At 6 months, they reported no regression in these outcome measures. PolyMVA was safe and well tolerated during the study. Please note the study has not undergone peer review, but the abstract was published in *Neurology* journal (24).

Table 1. Evidence for alpha-lipoic acid.

	Grade	Explanation
Mechanisms	A	ALA has potential effects on optimizing mitochondrial energy production, oxidative stress and anti-inflammation in human studies.
Pre-clinical	C	Two nonblinded preclinical studies suggested survival benefits and protection of motor function by ALA.
Cases	D	Subjective reports of benefit without validated diagnoses and benefits. Although several PALS from the ALS community reported therapeutic benefits, they often took many other supplements concomitantly and were uncertain whether the benefits were attributable to ALA.
Trials	U	There have been no published trials of ALA in PALS.
Risks	B	ALA was safe and well-tolerated based on self-report from PALS in online forums.

We also found a published case report entitled "Healing of amyotrophic lateral sclerosis: a case report", claiming to show an ALS reversal associated with a combination of chelation therapy and many supplements, including ALA (25). However, this case had a few unusual features that made the ALS diagnosis questionable. There were concerns that his condition might be related to mercury toxicity from the extensive dental amalgam fillings because there were findings of sensory and motor neuropathy on electrodiagnostic study and the patient had an immediate improvement in muscle strength after his dental fillings were removed and before initiating the treatment. The electromyography study at 1.5 years post-treatment was reported as "absence of ALS of the affected muscles" without a detailed description. However, chronic reinnervation changes (enlarged motor unit potentials) on electromyography are expected to persist even after recovery from clinical weakness, as seen in post-poliomyelitis syndrome (26).

Trials

We found one registered clinical trial (NCT04518540): explore neuroprotective effect of lipoic acid in amyotrophic lateral sclerosis. The study was designed to recruit and randomize 150 ALS participants to the lipoic acid group and control group (75 participants per arm). The aims included safety and the efficacy of lipoic acid in delaying disease progression and improving motor and respiratory function and survival. The study was estimated to be completed in October 2022, and results have not been published yet. We reached out to the clinical trial contact and have not received a response.

Since there have been no published trials of ALA in PALS, ALSUntangled assigns a TOE "Trials" grade of U (Table 1).

Dosing, risks, and costs

ALA supplement dosing ranges from 600 to 1800 mg daily. The effect of ALA has been studied in patients with diabetic polyneuropathy at different doses (600 mg, 1200 mg, and 1800 mg daily), and the optimal dose is 600 mg once daily (4). However, there have been no studies on dosing in patients with PALS. It is suggested that the supplement be taken on an empty stomach to improve its absorption (27).

Its short half-life and low bioavailability can limit ALA's therapeutic potential due to rapid hepatic degradation and poor solubility. Some solutions to increase its bioavailability include supplementing with the R-ALA and choosing the liquid over the solid preparation. Oral R-ALA supplement has been proven to cross blood–brain barrier (28). Other preparations have also been tried to improve solubility and bioavailability including preparation with lecithin or encapsulation within nanoparticles (29,30).

Overall, PALS reported ALA is safe and well-tolerated (24) (on PLM and ALSForum). In the diabetic polyneuropathy RCT trial with 227 participants, the low-dose ALA (600 mg daily) group showed comparable adverse events with the placebo group and none of the participants discontinued the study. However, high-dose ALA treatments (1200 mg or 1800 mg daily) led to more adverse events, including nausea, vomiting, and vertigo, and 11–13% participants dropped out of the study.

A month's supply of racemic mixture ALA or R-ALA at 600 mg daily costs approximately $10–$30. However, PolyMVA is sold at ~$360 per 237 mL (https://yourhealthbasket.co.uk/), and a year's supply can cost up to $19,800 (Poly-MVA—Wikipedia).

Because ALA was safe and well-tolerated based on self-report from PALS in online forums, ALSUntangled assigns a TOE "Risks" grade of B (Table 1).

Conclusions

ALA has several plausible mechanisms for slowing ALS progression, including enhancing energy production, reducing oxidative stress as a potent antioxidant and anti-inflammation. Preclinical studies demonstrated better motor function and improved survival. One open-label study suggested improved QOL and fatigue when administered as a palladium lipoic acid complex, but motor function was not assessed. Several PALS in the ALS online community reported improved muscle strength when taking ALA as part of extensive supplement regimens, but most did not. Therefore, it is unclear whether the reported improvement was directly related to ALA. Although one clinical trial was completed in PALS, the result has not been published. ALA was safe and well-tolerated based on self-report from PALS and in clinical trials for other disease conditions at 600 mg daily. Given the above, we cannot endorse ALA as an effective therapy for PALS. We support more research on the efficacy of ALA in slowing ALS progression.

Declaration of interest

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ORCID

Paul Wicks http://orcid.org/0000-0002-2293-9284
Christopher McDermott http://orcid.org/0000-0002-1269-9053

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