REVIEW ARTICLE

A Comprehensive Review of Safety, Efficacy, and Indications for the Use of Alpha-Lipoic Acid and Acetyl-L-Carnitine in Neuropathic Pain

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Abstract

The debilitating, chronic symptoms of neuropathic pain result in decreased quality of life, depressed mood, and anxiety in patients suffering from neuropathic pain. Despite hundreds of dollars in monthly treatment-related costs, more than half of the patients report inadequate pain relief. Traditional first-line agents are expensive and may have disruptive side effects.

Given the disease burden of neuropathic pain, many patients turn to over-the-counter supplements. Here we review two supplements, alpha-lipoic acid (ALA), also known as thioctic acid, and acetyl-L-carnitine (ALC), and data of treatment outcomes from the available literature suggest comparable efficacy to currently available pharmaceuticals for the treatment of neuropathic pain.

Meta-analysis of randomized controlled trials demonstrates that ALA can significantly improve neuropathic pain and nerve conduction velocity. ALA has been evaluated in the treatment of multiple sources of neuropathic pain, including chemotherapy-induced peripheral neuropathy, entrapment neuropathies, radicular nerve pain, and burning mouth syndrome. Common dose-dependent side effects include nausea, vomiting, and vertigo. Cost analysis from June 2022 indicates that a clinically effective dose (600 mg/day) of ALA costs patients $14.40 monthly. Two randomized control trials demonstrate that ALC exhibits neuroprotective effects, can regenerate nerves, and improve vibratory perception in the early stages of DPN. In terms of adverse reactions, no significant differences were observed between treatment and placebo groups, implying that ALC is generally well-tolerated. Cost analysis from June 2022 indicates that a clinically effective dose of ALC (2000 mg/day) costs patients $27.60 monthly.

Comparable efficacy in clinical trials, minimal side effects, and lower monthly costs suggest that ALA and ALC should be considered among the accepted first-line treatment options for neuropathic pain.

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Introduction

Approximately 15.7% of US adults suffer from neuropathic pain mostly due to diabetic peripheral neuropathy (DPN), followed by post-herpetic neuralgia and trigeminal neuralgia.[1,2] Neuropathic pain results from nerve damage caused by lesions in the nervous system (e.g., surgery, trauma, thalamic strokes, etc.) or damage secondary to disease or toxins (e.g., diabetes, alcohol, chemotherapy, herpes zoster, etc.).[1,3,4] Patients experience chronic and maladaptive pain that persists even with treatment.[3] The most recent estimate of annual healthcare costs associated with diabetic neuropathy was $10.9 billion in the United States, with patients paying hundreds of dollars in prescription medication every month.[3,5] Traditionally, first-line agents for neuropathic pain have been tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, calcium channel blockers, and topical lidocaine.[3,6] From Table 1, the number needed to treat (NNT) for the first-line agents range from 1.3 for lacosamide to 8.7 for mirogabalin. Thus, even with medications, less than 50% of patients report adequate pain relief and many generally experience side effects that range from mild to severe. Additionally, these first-line agents on average cost anywhere from $29.43 to $844.87 monthly, with the majority of medication costs in the upper ranges (Table 1). Many patients are simultaneously prescribed several medications to treat their pain, which further increases monthly costs for patients.[1] As a direct result of their pain, patients have reported sleep disturbances, impaired activities of daily living, depressed mood, anxiety, and overall diminished quality of life.[3,4] Many also experience decreased work productivity, changes in employment status, or early retirement.[1] To alleviate the concomitant symptoms, approximately half of the patients are further prescribed medications (i.e., antidepressants, sedatives, and analgesics) to treat anxiety,

Table 1. A Comparison of Medications Available to Treat Neuropathic Pain Based on Number Needed to Treat (NNT), defined as the Number of Patients that are Needed to Provide One Patient With At Least 50% Pain Relief

Drug or Drug Class	Mechanism or Drug Class	No. Needed to Treat (95% CI)	Cost/ month ($)	Cost/ unit ($)	Oral Dose	Common Adverse Effects
ALA[57]	Antioxidant	2.7 (1.8-5.8)	14.40	0.24	300 mg BID	Nausea, vomiting, vertigo, headache
ALC		NA	27.60	0.23	500 mg QID	Headache, facial paresthesia, nausea
Anticonvulsants meta-analysis[57,58]	-	2.7 (2.2-3.8)	-	-	-	-
Phenytoin[57,59]	Anticonvulsants	2.1 (1.5-3.6)	38.56	0.43	100 mg TID	Gingival hyperplasia, nystagmus, slurred speech, somnolence
Carbamazepine[57,60]		2.3 (NA)	80.36	0.89	200 mg TID	Hepatic toxicity, dizziness, somnolence, nausea
Valproic Acid[61]		7.0 (NA)	85.04	1.42	500 mg BID	Tremor, nausea, headache, fatigue, vomiting, weakness, dizziness
Lacosamide[62]		1.3 (1.1-1.5)	844.87	14.08	200 mg BID	Dizziness, headache, diplopia, nausea
Oxcarbazepine[63]		6 (3-114)	151.89	2.53	600 mg BID	Hyponatremia, abdominal pain, ataxia, dizziness, fatigue, diplopia, nystagmus
Lamotrigine[64]		3.3 (1.7-59.3)	61.87	1.03	100 mg BID	Nausea, Rare: pancytopenia, Stevens-Johnson syndrome
Antidepressants meta-analysis[57,58]	-	3.4 (2.6-4.7)	-	-	-	-
Amitriptyline[16,57]	TCA	2.5 (NA)	38.48	0.32	25 mg QID	Somnolence, dizziness, nausea, vomiting, weight gain
Venlafaxine[57]	SNRI	4.5 (NA)	236.82	1.97	150 mg QID	Nausea, somnolence, dry mouth, constipation
Duloxetine[57]		4.9 (3.6-7.6)	208.94	3.48	60 mg QD	Nausea, headache, dry mouth, somnolence, trouble sleeping
Citalopram[57,59]	SSRI	7.7 (NA)	29.43	0.49	20 mg BID	Nausea, dry mouth, somnolence, drowsiness, increased sweating
Paroxetine[57,59]	SSRI	2.9 (NA)	34.38	0.57	20mg BID	Nausea, somnolence, weakness, dizziness, anxiety
Gabapentin[57,59]	Gabapentinoids	3.7 (2.4-8.3)	194.13	2.16	600 mg TID	Dizziness, somnolence, peripheral edema, weakness, dry mouth, constipation
Pregabalin[57]		4.0 (3.3-5.3)	377.55	6.29	300 mg BID	
Mirogabalin[65]		8.7 (5.1-30.5)	279.00	4.65	15 mg BID	Dizziness, weight gain, fatigue
Tramadol[57,59]	Opioid agonist	3.4 (2.3-6.4)	125.33	0.70	50 mg 6 × per day	Dizziness, nausea, constipation, headache, drowsiness
Oxycodone[6]		5.7 (4.0-9.9)	90.96	1.01	10 mg TID	Nausea, constipation, somnolence, dizziness, pruritus, respiratory depression
Oxycodone CR[57,60]		2.6 (NA)	109.63	1.82	20 mg BID, ER	
Lidoderm patches[57]	Sodium channel blockade	4.4 (2.5-17)	990.96	8.26	5%, QID	Bruising, erythema, skin irritation (itchy, dry, peeling)
Capsaicin, 0.025%[57]	Local depletion of substance P	8.1 (4.6-34)	5.32	-	-	Local burning and stinging

Note: This comparison is limited by differences between studies with respect to the quality of the studies, the patient populations studied, the severity of the underlying condition, generally DPN. Prices are based on average retail prices reported by goodrx.com, vitaminshoppe.com, and Japanese Natural Pharmacy prices as of June 2022.

Abbreviations: QD, once a day; BID, twice a day; TID, three times a day; QID, four times a day; NA, none available; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; ALA, alpha-lipoic acid; ALC, acetyl-L-carnitine.

depressed mood, and sleep disturbances.[1] With limited relief from traditional pharmaceuticals, many patients have turned to alternative therapies.[7]

According to the 2021 Consumer Survey on Dietary Supplements, 80% of Americans report using supplements.[7] Although supplements lack the same quality and safety data required of pharmaceuticals, adverse reactions to supplements make up only 1.3% of adverse drug event visits to the emergency department, compared to 21.4% for pharmaceutical drugs.[8,9] While the Food and Drug Administration is tasked with regulating dietary supplements in line with Good Manufacturing Practice regulations, enforcement relies on consumer reporting after products are placed on the market.[10] Further scrutiny of dietary supplement quality and safety may be obtained from independent verification of supplement quality and safety from organizations including the United States Pharmacopeia, National Sanitation Foundation, Consumer Labs, and Natural Products Association. The National Institute of Health provides resources online (i.e., Dietary Supplement Label Database and Dietary Supplement Ingredient Database) to help patients make informed choices.

With the steadily increasing use of supplements each year, it is important for healthcare providers to ask patients about their supplement use, understand and advise patients on safe supplement practices, and be able to provide alternative treatments to prescription drugs.[10] Although there is more limited information about the use of supplements to treat neuropathic pain compared to first-line agents, alpha-lipoic acid (ALA), also known as thioctic acid, and acetyl-L-carnitine (ALC) have shown to be efficacious forms of treatment for diabetic neuropathy with less adverse side effects when compared to the traditional first-line treatment options.[11–22] The NNT for ALA is 2.7, which is comparable if not lower than most of the traditional first-line agents (Table 1). Furthermore, ALA and ALC overall cause less serious adverse side effects, when compared to first-line agents.

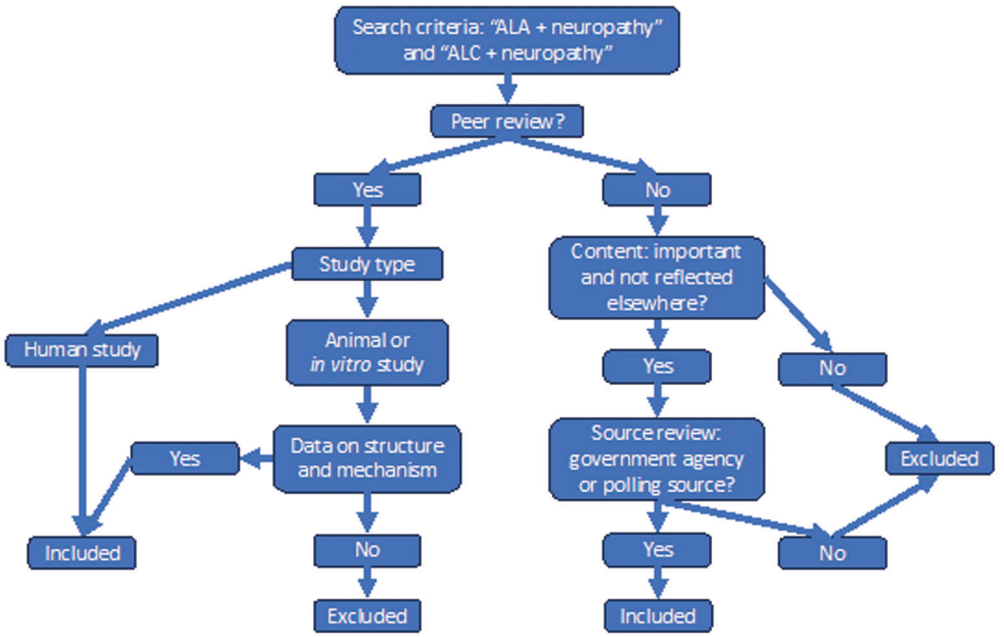
The most significant difference between these supplements and traditional medications is the monthly cost burden for the patients. On average, ALA costs $14.40 monthly, which equates to $0.24 per unit, and ALC costs $27.60 monthly, which equates to $0.23 per unit compared to a monthly cost of $29.43 to $844.87 with traditional medications. When comparing ALA and ALC with the current first-line agents to treat neuropathic pain, ALA and ALC are comparable in efficacy, present with fewer side effects, and place less of a financial burden on patients.

Here we present a review of the available literature on these supplements, including information on safety, efficacy, dosing, and cost to facilitate discussions with patients about alternatives to prescription medications in the treatment of neuropathic pain.

Methods

The purpose of this study is to evaluate the use of ALA and ALC for the treatment of neuropathy through a narrative review. Initial search criteria included "alpha-lipoic acid" + "neuropathy" and "acetyl-L-carnitine" + "neuropathy." Preference for full-text review of search

Figure 1. Methods Flowchart Indicating Process for Determining Source Inclusion Versus Exclusion



results was given to systematic reviews and randomized controlled trials, although other clinical trials and case reports were included, particularly if they contained relevant information for adverse reactions or contraindications to the use of either supplement. All sources cited are peer-reviewed journal articles, except for survey data from the consumer report network and the European Food Safety Authority, with exceptions made for these sources due to their clinical relevance.[7,23] Search engines used included PubMed and the Natural Medicines database. Further inclusion and exclusion criteria are outlined in Figure 1. Indications for the use of each supplement to be discussed in this review were based on approved indications as laid out in the Natural Medicines database. The clinical trials cited in the professional monographs for ALA and ALC were included in this review, with case reports, letters, and other reviews included only if the content contributed information unavailable in the cited clinical trials, such as additional adverse reactions.

Alpha-Lipoic Acid

Overview

ALA is a potent antioxidant with multiple trials demonstrating efficacy in the treatment of DPN.[12–21] In light of the therapeutic benefits of ALA in the treatment of DPN, ALA has been further investigated for the treatment of various other neuropathies including chemotherapy-induced peripheral neuropathy (CIPN), entrapment neuropathies such as carpal tunnel syndrome (CTS), radicular nerve pain (sciatica), and burning mouth syndrome (BMS) with mixed results regarding its efficacy.[24–32] Proposed mechanisms by which ALA may exert an anti-nociceptive effect focus on its anti-inflammatory properties, both through reduction of oxidative stress and modulation of cell signaling pathways that may affect gene expression.[33,34]

Mechanism of Action

ALA may alleviate neuropathic pain through the improvement of endothelial function and by acting as an antioxidant, which may mitigate pain responses.[35] ALA is an endogenous dithiol compound that has been shown to decrease oxidative stress.[34] In the mitochondria, it is involved in numerous bioenergetic reactions, including a critical step bridging glycolysis and the citric acid cycle.[33,34] It neutralizes reactive oxygen species, chelates metal ions, acts as an inducer of endogenous antioxidants, and reduces oxidized forms of other antioxidants, including vitamins C, E, and glutathione.[33,34]

ALA has also been found to exert an effect on gene modulation. By modifying intracellular thiol redox reactions, ALA may change the protein structures of signaling molecules, thereby altering transcription factor activities.[34] Cellular studies have suggested that ALA may induce nuclear localization of nuclear factor erythroid 2-related factor 2 (NRF2), the most important transcription factor regulating genes that contain the antioxidant response element, thereby modulating peroxisome proliferator-activated receptors-regulated genes.[34] Furthermore, ALA has been found to act as an inhibitor of nuclear factor-κB (NFκB), suggesting a mechanism for its anti-inflammatory properties.[34]

Notably, ALA is an enantiomer and occurs naturally in its R isoform, yet synthetic ALA is a racemic mixture of the R and S isoforms and the S-ALA has been found to increase bioavailability by preventing polymerization of R-ALA.[34]

Indications

Diabetic peripheral neuropathy (DPN): A majority of the published research has demonstrated the safety and efficacy of both IV and oral formulations of ALA in the treatment of neuropathic pain associated with DPN.[12–21] Earlier double-blind, placebo-controlled, randomized controlled trials (RCTs), mainly in Europe, evaluated the efficacy of ALA in IV formulation.[12–15] One of the earlier double-blind RCTs, ALADIN I, demonstrated significant improvement in neuropathic pain amongst 328 patients treated with 600-1200 mg/day of IV ALA.[12] This was followed by a smaller study (65 patients with DPN), ALADIN II, which evaluated IV therapy with ALA once daily for 5 days followed by oral therapy with either 1200 mg/day or 600 mg/day.[13] Researchers found improvements in sural nerve conduction velocity and amplitude, and improved neuropathic pain symptoms that were similar in both treatment groups and were significant when compared with placebo.[13] Multiple RCTs such as ALADIN I, ALADIN III, SYDNEY, and NATHAN II trials, were then pooled to perform a meta-analysis of 1258 patients with DPN.[16] This meta-analysis showed that 600 mg/day IV ALA significantly improved neuropathic pain.[16] Subsequent meta-analysis of 15 smaller RCTs with a total of 651 patients with DPN corroborated these results, emphasizing that the treatment with ALA (300-600 mg/day IV for 2-4 weeks) is safe and significantly improves neuropathic pain and nerve conduction velocity.[17]

Multiple trials have demonstrated comparable efficacy of oral ALA in the treatment of neuropathic pain from DPN.[18–21] This dispelled initial concerns about the inferiority of oral ALA suggested by the findings of an RCT comparing induction therapy with IV ALA followed by oral ALA (1200 mg/day or 600 mg/day).[13] This data was especially helpful as once-daily oral dosing is most feasible for patient compliance.

Chemotherapy-induced peripheral neuropathy (CIPN): There are mixed results regarding the efficacy of ALA in CIPN. A small, prospective study of 25 patients diagnosed with CIPN found that a combination herbal supplement containing 240 mg ALA in addition to methylsulfonylmethane, Boswellia, and bromelain reduced neuropathic pain over a course of 12 weeks.[25] Study results were limited by lack of a placebo control group and low dosing of ALA.[25] A larger, double-blind RCT of 243 cancer patients receiving cisplatin or oxaliplatin and diagnosed with CIPN showed no significant difference in peripheral neuropathic symptoms between oral ALA 600 mg/day orally and placebo but further studies are needed to conclusively determine if ALA could benefit this subset of patients.[26]

Entrapment Neuropathy: Several studies suggest that oral ALA may be a useful treatment in patients with carpal tunnel syndrome (CTS).[27–29] A randomized, controlled, open-label prospective study of 134 patients with mild to moderate CTS treated with oral ALA 600 mg/d for 2 months demonstrated significant pain reduction compared to controls.[27] Another study compared a combination oral supplement that included 600 mg/d ALA along with gamma-linolenic acid to a vitamin supplement containing vitamins B1, B6, and B12 over 3 months in 112 patients with moderate to severe CTS.28 Researchers found similar results, with significant pain reduction and improved function in the ALA treatment group with only slightly improved pain reduction in the vitamin B group but with worsened function. Finally, a double-blind RCT comprising 64 patients diagnosed with CTS requiring surgical decompression of the median nerve compared oral ALA 600 mg/d to placebo following surgery for CTS.[29] Researchers found no significant difference between ALA and placebo with respect to nerve conduction velocity or Boston CTS scores, yet did observe a significantly reduced incidence of pillar pain, i.e., pain at the base of the palm following carpal tunnel release, in the ALA group.

Radicular nerve pain: One double-blind RCT comprising 64 patients with lower extremity radicular nerve pain compared the use of oral ALC (1180 mg/d) to the use of ALA (600 mg/d) with respect to total symptom score and electromyography (EMG).[30] Researchers found that both treatments significantly improved both symptom score and EMG and there was no significant difference between the treatments. The study was limited by the absence of a placebo control group and small sample size.

Burning Mouth Syndrome (BMS): Although there is some evidence to suggest that ALA may benefit patients suffering from BMS, a majority of the data suggests no significant difference from placebo.[31] A double-blind RCT compared ALA and gabapentin to placebo in the treatment of 120 patients diagnosed with BMS.[32] After 2 months of treatment, the group of patients treated with a combination of oral ALA 600 mg/d and gabapentin 300 mg/d reported the greatest improvement in symptoms, with 70% of these patient reporting a reduction in pain.

Adverse Reactions, Contraindications, and Drug Interactions

Adverse reactions: Oral doses of ALA between 600-1800 mg/d have been shown to be safe and well tolerated.[20,21] Nausea is the most commonly experienced side effect, occurring in approximately 6% of patients at doses of 1200 mg/d.[21] Vomiting and vertigo are the next most frequently experienced symptoms and, like nausea, both illustrate a dose-dependent increase in frequency.[18] Headache has also been reported but is infrequent.[31] The upper limit for ALA consumption has not been established in humans.[34] In case reports, ALA supplementation has been suggested to be associated with insulin autoimmune syndrome.[36]

In a series of double-blind, placebo-controlled RCTs (ALADIN I, II, and III), ALA 600 mg/d administered both orally and IV was found to be safe with no significant difference in adverse reactions between treatment and

placebo groups.[12–14] Higher intravenous doses of ALA 1200 mg/d were found to have a higher incidence of adverse reactions than either ALA 600 mg/d or placebo.[12] This same effect was not observed with the administration of oral formulation of ALA, where the use of 1200 mg/d for 2 years was not found to have a significant difference in adverse reactions compared to placebo.[13]

Contraindications: A panel review of 49 case reports concluded that individuals with certain genetic polymorphisms might have an increased risk of developing insulin autoimmune syndrome with the consumption of ALA supplements.[23,36] However, even this risk remains low, with the highest reported incidence of insulin autoimmune syndrome at 0.017 per 100 000 in Japan. Caution should be used in individuals with a personal or family history of insulin autoimmune syndrome, or with genetic polymorphisms which increase the risk of developing insulin autoimmune syndrome.

Drug-interactions: ALA may interact with antiplatelet medications as indicated by *ex vivo* analysis which has shown that ALA inhibits both human and rabbit platelet aggregation.[37] Caution is advised in patients taking anticoagulants or antiplatelet therapies, although this is not a clear contraindication.

Dosing

Dosing recommendations were explored in a multicenter double-blind RCT conducted with 181 patients with DPN, comparing doses of 600-1800 mg/d oral ALA to placebo. Total symptom score decreased significantly compared to placebo across treatment groups of all doses 600-1800 mg/d oral ALA, yet there was a dose-dependent increase in nausea, vomiting, and vertigo, and therefore the lowest dose of oral ALA (600 mg/d) is recommended.[18]

Acetyl-L-carnitine

Overview

Acetyl-L-carnitine (ALC) has gained clinical attention for both prophylactic prevention and acute analgesic treatment of neuropathic pain.[11,22] Both *in vitro* and *in vivo* studies have demonstrated neuroprotective properties of ALC in DPN.[38] Further studies have investigated the utility of ALC in peripheral neuropathies of other causes, including HIV, CIPN, radicular nerve pain, and carpal tunnel syndrome, yet the benefits of ALC in neuropathies of causes other than DPN remain unclear.

Mechanism of Action

ALC may alleviate neuropathic pain by promoting a decrease in nerve pain through the expression of metabotropic glutamate in sensory neurons that have been injured and drive pain responses.[22] ALC serves a variety of functions in the nervous system, liver, and kidney, with an important role in mitochondrial energy homeostasis and detoxification.[38] It acts as an acetyl-group donor, most classically known for its role in the oxidation of fatty acids.[39] In addition, ALC ensures the availability of acetyl CoA for the elimination of toxic metabolic products, thereby reducing oxidative stress.[40] Beyond energy metabolism, ALC has been found to play a role in central nerve pathways by altering nerve growth factor receptors, activating cholinergic muscarinic M1 receptors in the central nervous system, up-regulating mGlu2 receptors in the dorsal root ganglion, and modulating transcriptional activity of NFκB.[41] Alterations in cholinergic nerve activity associated with the expression of the GRM2 gene may cause an increase in pain threshold.[42] These regulatory activities within the nervous system are likely to explain the anti-nociceptive properties of ALC.[41]

Indications

Diabetic peripheral neuropathy (DPN): A Cochrane meta-analysis in 2019 evaluating the use of ALC in patients with DPN demonstrated moderate reduction (approximately a 15-point decrease on a 100-point visual analog pain scale) in neuropathic pain amongst patients taking 2000-3000 mg/d of ALC orally. The effect of lower doses of 1,500 mg/d of ALC did not differ significantly from placebo.[11] A previous meta-analysis of 4 RTCs examining the efficacy of ALC versus placebo suggests that ALC effectively lowers visual analog pain scale ratings of neuropathic pain in DPN.[43] Additional reviews corroborate the superior efficacy of ALC in DPN than in other causes of neuropathy.[44,45] In two RTCs involving DPN, ALC has been shown to regenerate nerves and improve pain, and vibratory perception.[46] This effect was found to be most pronounced in the early stages of DPN. ALC was more effective at doses higher than 2000 mg/d than at doses lower than 1500 mg/d.[43,46,47]

Chemotherapy-induced peripheral neuropathy (CIPN): Several small studies have investigated the efficacy of ALC in the treatment of CIPN in the following patient populations: breast cancer patients receiving taxane-based chemotherapy[48]; patients with ovarian or prostate cancer receiving sagopilone[49]; and multiple myeloma patients receiving bortezomib and doxorubicin.[50] These studies yielded mixed results with the RCT amongst breast cancer patients demonstrating harm from ALC administration,[48] the RCT of ovarian and prostate cancer patients demonstrating benefit,[49] and the RCT amongst multiple myeloma patients demonstrating no significant difference between ALC and placebo.[50] Based on the review of these 3 RCTs, in addition to the review of another 84 manuscripts of smaller studies, the American Society of Clinical Oncology discourages the use of ALC amongst cancer patients, due to concerns of the risks outweighing the benefits.[51]

Results from the study involving ovarian or prostate cancer patients treated with sagopilone were slightly more promising.[49] In this study, patients treated with a low dose of oral ALC (1000 mg every 3 days) were compared to

placebo in the prevention of CIPN development. Although there was no significant difference with respect to the overall incidence of CIPN between the treatment and control groups, CIPN was found to be less severe in the low-dose ALC group than in the control group. It is to be noted that this study was limited by the low dose of ALC used.

Antiretroviral toxic neuropathy: Results from several small studies investigating the utility of ALC amongst patients with antiretroviral toxic neuropathy are unclear.

One RCT amongst 90 HIV-positive patients evaluated the efficacy of ALC (1000 mg/d IM) in reducing pain from HIV-associated neuropathy.[52] Researchers found no significant difference in treatment versus placebo groups when analyzed via intention to treat. It is to be noted that the dosing used in this trial (1000 mg/d) was lower than doses used in trials where significant differences were seen.[43] When this trial was analyzed via efficacy-evaluable population, the ALC treatment group with HIV-associated neuropathy did show a significant reduction in visual analog pain scale ratings compared to placebo.[52]

A small clinical trial amongst 21 HIV-positive patients diagnosed with antiretroviral toxic neuropathy evaluated symptoms and skin biopsies before and 33 months following treatment with oral ALC (3000 mg/d).[53] Researchers found that ALC treatment significantly increased the area for small sensory fibers compared with controls and improved neuropathic grade in 76% of the patients. Another small clinical trial amongst 16 HIV-positive patients evaluated IM and IV ALC with a dose of 500-1000 mg/d over 3 weeks and found that the treatment improved symptoms in 62.5% of patients.[54]

Radicular nerve pain: One double-blind RCT amongst 64 patients with lower extremity radicular nerve pain compared the use of different doses of oral ALC (1180 mg/d versus 600 mg/d) with respect to total symptom score and EMG.[30] Researchers found that both treatments significantly improved the symptom score and EMG, and there was no significant difference between the treatments. The study was limited by the absence of a placebo control group and small sample size.

Carpal Tunnel Syndrome (CTS): The utility of ALC for entrapment neuropathies such as CTS is unclear. One double-blind RCT has evaluated the utility of oral ALC (3000 mg/d) for use in 20 patients with median neuropathy following carpal tunnel release surgery.[55] While ALC was well tolerated, it did not improve nerve regeneration or functional recovery compared with placebo, so it is not recommended.

Adverse Reactions, Contraindications, and Drug Interactions

Adverse reactions: Meta-analysis has shown that ALC is generally well tolerated without significant differences in adverse reactions between the ALC treatment and placebo groups.[43] Reported adverse reactions in one RTC include headache, facial paresthesia, nausea, biliary colic, vomiting, epigastric pain, and GI disorders, yet they did not differ significantly between placebo and treatment groups.[47] In another RTC, adverse reactions were more commonly reported in the placebo group than the treatment group and included paresthesia, pain, anorexia, dry mouth, and neuropathy.[52]

Contraindications: The American Society of Clinical Oncology recommends discouraging the use of ALC amongst cancer patients, due to concerns that the risks of potentially worsening the patient's pain outweigh the benefits of potentially reducing the pain.[51]

Drug-interactions: In animal models, ALC appears to play a role in the modulation of neurotransmitters and may lead to an increase in serotonin levels in the cerebral cortex.[56] This provides a plausible mechanism via which ALC could theoretically interact with other medications that increase serotonin levels.

Dosing

Meta-analysis suggests that dosages higher than 2000 mg/d total show more benefit to patients than lower doses (1500 mg/d).[43,46,47] A dosage of 1000 mg/d has not shown a significant difference from placebo when evaluated via intention to treat.[52]

One RCT found that the group of cancer patients receiving a dose of ALC 3000 mg/d demonstrated an increase in CIPN at 24 weeks relative to placebo.[48] Considering these studies, our recommendation from a practical clinical perspective is the oral administration of 2000 mg/d ALC, divided BID.

Summary

ALA and ALC have demonstrated safe and significant improvement in neuropathic pain management in RCTs, with favorable side effect profiles primarily when used for DPN.[18–21,43,46,47] There is a larger body of evidence to support the use of ALA for neuropathic pain than to support the use of ALC, although both have demonstrated efficacy in clinical trials.

Oral use of ALA has been shown to improve neuropathic pain in DPN,[18–21] CIPN,[25] and entrapment neuropathy in CTS.[27–29] The currently available data do not demonstrate the benefit of ALA use in radicular nerve pain30 or BMS.[31]

Oral use of ALC has been shown to improve neuropathic pain in DPN,[43,46,47] with some studies demonstrating its efficacy for antiretroviral toxic neuropathy.[54] Available data do not demonstrate the benefit of ALC use for radicular nerve pain[30] or CTS.[55] Conflicting results have been reported regarding the efficacy of ALC for CIPN, with one study reporting worsening of neuropathic pain in CIPN patients with ALC; therefore, the use of ALC in such patient population is not recommended.[51]

Given the case reports associating the use of ALA with insulin autoimmune syndrome, caution should be

used in individuals with a personal or family history of insulin autoimmune syndrome.[23,36] Due to the worsening of CIPN with the use of ALC in one trial,[51] the use of ALC is discouraged amongst cancer patients, although this is not a clear contraindication.

Overall, adult patients with DPN are ideal candidates for ALA and ALC supplementation.

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