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# Targeting neuropathic pain: Consider these alternatives

When patients with painful peripheral neuropathy fail to respond to—or are unable to tolerate—standard therapies, consider these lesser-known treatments.

**A**nticonvulsants, antidepressants, and opioids are the most frequently prescribed medications for neuropathic pain.<sup>1</sup> But some patients are unable to tolerate the adverse effects of these drugs, and others achieve only partial pain relief. What can you offer them?

Combinations of prescription medications are generally considered more effective than monotherapy for painful peripheral neuropathy,<sup>1</sup> but it is unclear which combinations are best. Alternative therapies—several of which have some evidence of safety and efficacy in treating peripheral neuropathy—are another option. Yet trials with alternative therapies, alone or in combination with prescription drugs, are rarely considered.

In fact, physicians are often unfamiliar with these therapies. Many are concerned about the absence of US Food and Drug Administration approval for alternative therapies and the variability in quality control associated with the lack of oversight, as well. Making recommendations about the duration of therapy also presents a challenge because most studies of supplements are relatively short. What's more, alternative treatments are rarely covered by third-party payers.

Nonetheless, the therapies detailed in the text and **TABLE**<sup>2-12</sup> that follow are generally well tolerated and appear to be safe. Adding them to your arsenal of therapeutic choices for patients with painful peripheral neuropathy may increase your ability to provide successful treatment.

## Acetyl-L-carnitine (ALC)

ALC occurs naturally in the body as L-carnitine and acetyl-carnitine esters, which are converted to carnitines by intracellular enzymes and cell membrane transporters.<sup>2</sup> ALC has been studied in patients with neuropathy associated with human immunodeficiency virus (HIV), cancer, and diabetes. Potential mechanisms of action include the correction of a deficiency that may be causing the neuropathy (which sometimes occurs in HIV-positive patients<sup>13</sup> or those taking anticonvulsants<sup>14</sup>), a direct antioxidant effect, or an enhanced response to nerve growth factor.<sup>13</sup>

ALC can be given intramuscularly (IM) or orally in doses of 2000 to 3000 mg/d. In one randomized placebo-controlled trial (N=333), patients with diabetic neuropathy received 1000 mg IM followed by an oral dose of 2000 mg every day for a year.<sup>6</sup> Mean pain scores decreased by 39%, with 67% of those receiving ALC vs 23% of those on placebo showing moderate to marked improvement.

In a pooled analysis (N=1257) of 2 randomized controlled trials (RCTs), patients with diabetes took 1000 mg ALC 3 times daily or placebo for a year.<sup>7</sup> Cohort pain scores improved by 40% from baseline in the ALC group compared with a 24% improvement for those in the placebo group.

**THE BOTTOM LINE** ALC is well tolerated, with minor adverse effects such as headache and nausea reported.<sup>6,7</sup> It should not be given to patients taking acenocouma-

## INSTANT POLL

**Which of the following alternative treatments (if any) have you prescribed for patients with painful peripheral neuropathy?**

- Acetyl-L-carnitine
- Alpha lipoic acid
- B vitamins
- Capsaicin
- Gamma linolenic acid
- Magnesium
- I have prescribed more than one
- I haven't prescribed any of these for this purpose

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Adding these generally well-tolerated therapies to your arsenal of therapeutic choices for patients may increase your ability to provide successful treatment.

rol or warfarin, however. A major interaction causing an elevated international normalized ratio has been found to occur when either agent is combined with L-carnitine<sup>2</sup> and could theoretically occur with ALC, as well. No other drug-drug interactions have been documented.<sup>2</sup>

### Alpha lipoic acid (ALA)

Both a fat- and a water-soluble vitamin that is usually obtained from the diet, ALA regenerates endogenous antioxidants like vitamins C and E and glutathione. It is this regenerative mechanism that it is believed to alleviate diabetic neuropathy.<sup>2</sup> ALA 600 mg/d appears to be effective, although studies suggest that intravenous (IV) use is more effective than oral administration.

A meta-analysis of 4 RCTs (N=653), 2 with ALA taken orally and 2 involving IV administration, is a case in point.<sup>3</sup> The pooled standardized mean difference estimated from all trials showed a reduction in total symptom scores of -2.26 (95% confidence interval [CI], -3.12 to

-1.41;  $P=.00001$ ), with 0 indicating no symptoms, 3 indicating severe symptoms, and a maximum score of 14.64 if all symptoms were severe and continuous. Subgroup analyses revealed a reduction of -1.78 (95% CI, -2.45 to -1.10;  $P=.00001$ ) for oral ALA and -2.81 (95% CI, -4.16 to -1.46;  $P=.0001$ ) for IV administration. Doses >600 mg/d did not improve efficacy, but did increase adverse effects such as nausea, vomiting, and dizziness.

In a multicenter RCT (N=460) of ALA 600 mg/d for 4 years, however, no improvement in the primary endpoint (a composite of neuropathy impairment scores and 7 neurophysiologic tests) was found.<sup>15</sup> Although there was a statistically significant improvement in symptoms of neuropathy (-0.68 with ALA compared with +0.61 with placebo), the change was too small to be considered clinically significant.

ALA did slow the progression of neuropathy, however, with 29% of patients in the treatment group experiencing worsening symptoms compared with 38% of those on placebo. There was no difference in tolerabil-

➤ **IV administration of alpha lipoic acid is more effective than oral administration, but patients run the risk of an allergic reaction at the injection site.**

ity or discontinuation of treatment between the 2 groups.

A recent observational study (N=101) compared the efficacy of pregabalin, carbamazepine, and ALA over a 21-month period.<sup>4</sup> Although those taking pregabalin had the best response rate, all 3 treatments led to significant improvement in the burning associated with neuropathic pain.

ALA 100 mg bid has been investigated as part of a 3-drug combination (with pregabalin 75 mg bid and methylcobalamin 750 mcg bid) compared with monotherapy (pregabalin 75 mg bid) in an open randomized study (N=30) for 12 weeks.<sup>16</sup> While there was a trend toward improvement in pain relief, sleep interference, and nerve function in the combination therapy group, no statistically significant difference between the 2 groups was found. Nonetheless, more than a third (36%) had a global assessment rating of “excellent” vs one in 5 (20%) of those on pregabalin alone.

**THE BOTTOM LINE** Overall, ALA is well tolerated; the most common adverse effects are nausea and skin rash. IV administration is more effective than oral administration, but may cause nausea, headache, and an allergic reaction at the injection site.<sup>2</sup> ALA does have the potential for an interaction with chemotherapy and thyroid hormone and may decrease the effectiveness of these therapies.<sup>2</sup>

### B vitamins

Deficiencies of vitamin B1 (thiamine), B6 (pyridoxine), B12 (cyanocobalamin), and folate are known causes of neuropathy, and correcting them often improves or eliminates the symptoms.<sup>13</sup> Vitamin B12 deficiency is commonly seen in patients taking metformin;<sup>14</sup> these patients may benefit from supplementation with B12 1000 mcg/d.

Many of the B vitamins have been studied for treatment of neuropathy, but benfotiamine (a lipid-soluble form of thiamine) is thought to be the best option because it is better absorbed across cell membranes than other B vitamins.<sup>9</sup> A Cochrane review found that benfotiamine alone may be effective for

both diabetic and alcoholic neuropathy and that short-term use of higher doses of vitamin B complex (25 mg B1 or 320 mg benfotiamine + 50-720 mg B6 + 1000 mcg B12 daily) may reduce neuropathic pain.<sup>9</sup>

A randomized multicenter trial (N=214) found that adding a supplement containing L-methylfolate 3 mg, pyridoxal 5-phosphate 35 mg, and methylcobalamin 2 mg twice daily to other medications (eg, pregabalin, gabapentin, or duloxetine) improved symptoms of diabetic neuropathy.<sup>10</sup> At 24 weeks, those receiving the combination therapy had a 26% decrease in pain symptoms compared with a 15% decrease for those on medication alone, with no significant adverse effects.

**THE BOTTOM LINE** Overall, vitamin B supplementation is well tolerated and appears to be more effective in relieving neuropathic pain than medication alone.<sup>9,14</sup> But larger studies are needed before its efficacy in treating patients who do not have a deficiency can be established.

### Capsaicin

Capsaicin, an ingredient found in peppers, works by binding to nociceptors to selectively stimulate afferent C fibers. This causes the release of substance P, a neurotransmitter that mediates pain, leading to its depletion and resulting in desensitization.<sup>2</sup> Several meta-analyses and systematic reviews have found that topical capsaicin can be very effective, both as an adjunctive treatment and as monotherapy for neuropathic pain.<sup>11,17,18</sup> The concentration used in the studies was 0.075% capsaicin cream, applied 3 to 4 times a day for 6 to 12 weeks, compared with placebo creams. In all categories studied, capsaicin was either statistically significant or trending in its favor, with the exception of adverse effects.

Capsaicin led to an improvement in daily activities and ability to sleep and a reduction in pain as measured with a visual analog scale and physician global evaluation.<sup>11,17,18</sup>

The most notable adverse effects were a burning sensation on the skin and coughing and sneezing caused by inhalation of dried cream. Although the adverse effects were expected to improve after 2 to 7 days of use, a

TABLE

Consider these alternatives for neuropathic pain<sup>2-12</sup>

Intervention	Dose	Adverse effects/special considerations
Acetyl-L-carnitine	2000-3000 mg/d	Nausea, vomiting; urine, breath, and sweat may have fishy odor Avoid use in patients taking warfarin
Alpha lipoic acid	600 mg/d	Nausea, vomiting, skin rash Possible injection site reaction with IV administration
ALA/Rx combination	ALA 100 mg bid + pregabalin 75 mg bid + methylcobalamin 750 mcg bid	Nausea, vomiting
B vitamins	Benfotiamine 100 mg qid OR B1 25 mg OR benfotiamine 320 mg + B6 50-720 mg + B12 1000 mcg/d OR L-methylfolate 3 mg + pyridoxal 5-phosphate 35 mg + methylcobalamin 2 mg bid	Nausea, vomiting
Capsaicin	Topical 0.075% cream, applied 3-4 times daily OR 8% patch worn 30-60 min/d	Burning, stinging, erythema, sneezing, coughing Pain may increase initially but diminish over time
Gamma linolenic acid	360-480 mg/d	Nausea, vomiting
Magnesium	Mg gluconate 300 mg/d	GI irritation, nausea, vomiting, diarrhea Monitor for hypermagnesemia and drug-drug interactions Avoid in patients with elevated Mg, renal dysfunction, or cardiac abnormalities

ALA, alpha lipoic acid; GI, gastrointestinal; IV, intravenous; Mg, magnesium.

significant number of participants withdrew from the study.

A 7-study meta-analysis showed the effectiveness of an 8% capsaicin patch for treatment of post-herpetic neuralgia and HIV-associated neuropathy.<sup>12</sup> The patch, available only by prescription, was worn every day for 4 weeks (60 minutes daily for post-herpetic neuralgia and 30 minutes a day for HIV-associated neuropathy). The pooled results were statistically significant, but the patch was less

effective for patients ages 18 to 40 years and for those of Asian descent. It can be used with other analgesics or as monotherapy, with few adverse reactions.<sup>12,19</sup>

**THE BOTTOM LINE** Since capsaicin is a topical medication, there are no relevant drug-drug interactions. Patients should be cautioned to wash their hands after application, however, and to avoid contact with eyes and open wounds.



Vitamin B12 deficiency is common in patients taking metformin; they may benefit from supplementation with B12 1000 mcg/d.

CONTINUED

➤ Patients with painful diabetic neuropathy may benefit from magnesium (Mg) gluconate 300 mg/d, but supplementation is unsafe for those with renal dysfunction, cardiac conduction abnormalities, or elevated Mg levels.

### Gamma linolenic acid (GLA)

Also known as evening primrose oil, GLA is an omega-6 fatty acid that's an important constituent of neuronal cell membranes—and believed to decrease neuropathic pain by having some anti-inflammatory effects.<sup>2</sup> This suggests that therapy with GLA has the potential to improve neuronal phospholipid structure and microcirculation.<sup>2</sup>

Two placebo-controlled trials (N=22,111) showed improvement in pain scores and multiple neurophysiologic assessments in patients with diabetes treated with GLA (360-480 mg/d).<sup>20,21</sup> The treatment was well tolerated, but the beneficial effect was more pronounced in those with less severe diabetes.

**THE BOTTOM LINE** The dose of GLA studied (8 to 12 capsules daily) could lead to problems with patient adherence. In addition, GLA should be used with caution in patients who are taking antiplatelet medication or have seizure disorders.<sup>2</sup>

### Magnesium (Mg)

Mg is highly involved in multiple enzyme systems throughout the body. Although it is very well absorbed from dietary sources,<sup>2</sup> patients with diabetes, liver disease, and hormonal imbalances, as well as the elderly, are often deficient in Mg. It is unclear how this affects peripheral neuropathy.<sup>13</sup>

Mg may have an antinociceptive effect by decreasing intracellular calcium influx and antagonizing N-methyl-D-aspartate receptors and associated nerve signaling.<sup>22</sup> A small RCT (N=80) showed Mg to decrease the severity of neuropathic back pain.<sup>22</sup> Patients received Mg sulfate 1 g IV, given over 4 hours, every day for 2 weeks. The infusion was then replaced with Mg oxide 400 mg plus Mg gluconate 100 mg, taken orally twice daily for 4 weeks. An improvement in mean pain score was seen as early as 2 weeks, and scores

had decreased by 2.8 points (on a 0-10-point scale) at 6 months.

Another small RCT (N=45) gave patients with neuropathy of postherpetic, traumatic, or surgical (but not diabetic) origin Mg chloride 838 mg orally 3 times a day for 4 weeks.<sup>23</sup> The supplement was taken with meals. Mean pain scores in the treatment group decreased by 3 points, but this was not significantly different from the improvement seen in those on placebo.

In a similar study, patients (N=110) with type 1 diabetes and a normal serum Mg but an insufficiency as measured by erythrocyte Mg were given Mg gluconate 300 mg or placebo daily for 5 years.<sup>8</sup> The supplement slowed the *progression* of peripheral neuropathy (only 12% of those receiving Mg gluconate experienced a significant worsening of symptoms over the course of the study, compared with 61% of those in the placebo group), but in most cases, it did not lead to an improvement.

No consistent approach to Mg supplementation has been studied, which makes recommending a particular route, dose, or formulation challenging. There is evidence that oral Mg, particularly in the form of Mg oxide, can cause diarrhea, especially in doses >350 mg/d. Mg gluconate and Mg chloride are better tolerated; Mg carbonate should be avoided due to poor oral absorption.<sup>2</sup>

**THE BOTTOM LINE** Mg supplementation appears to slow the progression of diabetic peripheral neuropathy, but is unsafe for patients with renal dysfunction, cardiac conduction abnormalities, or elevated Mg levels.<sup>2</sup> Caution is required, too, when considering Mg supplementation for patients taking anticoagulants, bisphosphonates, digoxin, potassium-sparing diuretics, or tetracycline antibiotics.<sup>2</sup> **JFP**

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#### References

1. Chaparro LE, Wiffen PJ, Moore RA, et al. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev*. 2012;(7): CD008943.
2. Natural Medicines Comprehensive Database. Natural Medi-

cines Comprehensive Database Web site. Available at: <http://naturaldatabase.therapeuticresearch.com>. Accessed January 4, 2015.

3. Mijnhout GS, Kollen BJ, Alkhalaf A, et al. Alpha lipoic acid for

symptomatic peripheral neuropathy in patients with diabetes: a meta-analysis of randomized controlled trials. *Int J Endocrinol.* 2012;2012:456279.

4. Patel N, Mishra V, Patel P, et al. A study of the use of carbamazepine, pregabalin and alpha lipoic acid in patients of diabetic neuropathy. *J Diabetes Metab Disord.* 2014;13:62.
5. Bertolotto F, Massone A. Combination of alpha lipoic acid and superoxide dismutase leads to physiological and symptomatic improvements in diabetic neuropathy. *Drugs R D.* 2012;12:29-34.
6. De Grandis D, Minardi C. Acetyl-L-carnitine (levacecarnine) in the treatment of diabetic neuropathy. A long-term, randomised, double-blind, placebo-controlled study. *Drugs R D.* 2002;3:223-231.
7. Sima AA, Calvani M, Mehra M, et al; Acetyl-L-Carnitine Study Group. Acetyl-L-carnitine improves pain, nerve regeneration, and vibratory perception in patients with chronic diabetic neuropathy: an analysis of two randomized placebo-controlled trials. *Diabetes Care.* 2005;28:89-94.
8. De Leeuw, Engelen W, De Block C, et al. Long term magnesium supplementation influences favourably the natural evolution of neuropathy in Mg-depleted type 1 diabetic patients (T1dm). *Magnes Res.* 2004;17:109-114.
9. Ang CD, Alviar MJM, Dans AL, et al. Vitamin B for treating peripheral neuropathy. *Cochrane Database Syst Rev.* 2008;(3):CD004573.
10. Fonseca VA, Lavery LA, Thethi TK, et al. Metaxin in type 2 diabetes with peripheral neuropathy: a randomized trial. *Am J Med.* 2013;126:141-149.
11. Mason L, Moore RA, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. *BMJ.* 2004;328:991.
12. Mou J, Paillard F, Turnbull B, et al. Efficacy of Qutenza® (capsaicin) 8% patch for neuropathic pain: a meta-analysis of the Qutenza Clinical Trials Database. *Pain.* 2013;154:1632-1639.
13. Head KA. Peripheral neuropathy: pathogenic mechanisms and alternative therapies. *Altern Med Rev.* 2006; 11:294-329.
14. Miranda-Massari JR, Gonzalez MJ, Jimenez FJ, et al. Metabolic correction in the management of diabetic peripheral neuropathy: improving clinical results beyond symptom control. *Curr Clin Pharmacol.* 2011; 6:260-273.
15. Ziegler D, Low PA, Litchy WJ, et al. Efficacy and safety of antioxidant treatment with α-lipoic acid over 4 years in diabetic polyneuropathy: the NATHAN 1 trial. *Diabetes Care.* 2011;34: 2054-2060.
16. Vasudevan D, Naik MM, Mukaddam QL. Efficacy and safety of methylcobalamin, alpha lipoic acid and pregabalin combination versus pregabalin monotherapy in improving pain and nerve conduction velocity in type 2 diabetes associated impaired peripheral neuropathic condition. [MAINTAIN]: Results of a pilot study. *Ann Indian Acad Neurol.* 2014;17:19-24.
17. Halat KM, Dennehy CE. Botanicals and dietary supplements in diabetic peripheral neuropathy. *J Am Board Fam Pract.* 2003;16:47-57.
18. Donofrio P, Walker F, Hunt V, et al. Treatment of painful diabetic neuropathy with topical capsaicin: A multicenter, double-blind, vehicle-controlled study. *Arch Int Med.* 1991;151:2225-2229.
19. Derry S, Rice ASC, Cole P, et al. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev.* 2013;(2):CD007393.
20. Keen H, Payan J, Allawi J, et al. Treatment of diabetic neuropathy with gamma-linolenic acid. The gamma-Linolenic Acid Multicenter Trial Group. *Diabetes Care.* 1993;16:8-15.
21. Jamal GA, Carmichael H. The effect of gamma linolenic acid on human diabetic peripheral neuropathy: a double blind placebo controlled trial. *Diabetic Med.* 1990;7:319-323.
22. Yousef AA, Al-deeb AE. A double-blinded randomised controlled study of the value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component. *Anaesthesia.* 2013;68:260-266.
23. Pickering G, Morel V, Simen E. Oral magnesium treatment in patients with neuropathic pain: a randomized clinical trial. *Magnes Res.* 2011;24:28-35.

## Treating pain in a patient with addiction

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## INSTANT POLL

Which alternative treatments have you prescribed for patients with painful peripheral neuropathy?

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